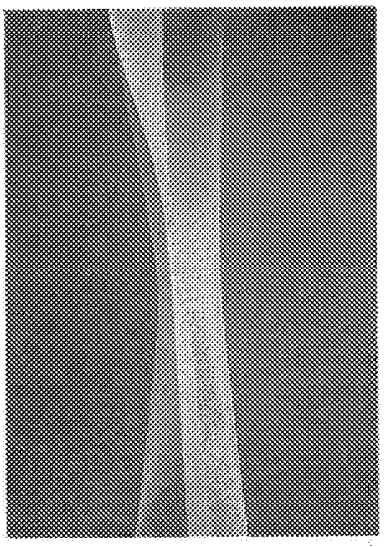
EXHIBIT 12

Steven S. Zumdahl
UNIVERSITY OF ILLINOIS

Chemistry



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To my parents and to Eunice, Whitney, and Leslie.

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GLOSSARY

Accuracy the agreement of a particular value with the true value. (1.3)

Acid a substance that produces hydrogen ions in solution; a proton donor. (4.2)

Acid-base indicator a substance that marks the end point of an acid-base titration by changing color. (15.4)

Acid rain a result of air pollution by sulfur dioxide. (5.9)

Acid dissociation constant (K_a) the equilibrium constant for a reaction in which a proton is removed from an acid by H_2O to form the conjugate base and H_3O^+. (14.1)

Acidic oxide a covalent oxide that dissolves in water to give an acidic solution. (14.10)

Actinide series a group of fourteen elements following actinium in the periodic table, in which the *5f* orbitals are being filled. (7.11; 18.1)

Activated complex (transition state) the arrangement of atoms found at the top of the potential energy barrier as a reaction proceeds from reactants to products. (12.5)

Activation energy the threshold energy that must be overcome to produce a chemical reaction. (12.5)

Addition polymerization a type of polymerization in which the monomers simply add together to form the polymer, with no other products. (22.5)

Addition reaction a reaction in which atoms add to a carbon-carbon multiple bond. (22.2)

Adsorption the collection of one substance on the surface of another. (12.6)

Air pollution contamination of the atmosphere, mainly by the gaseous products of transportation and production of electricity. (5.9)

Alcohol an organic compound in which the hydroxyl group is a substituent on a hydrocarbon. (22.4)

Aldehyde an organic compound containing the carbonyl group bonded to at least one hydrogen atom. (22.4)

Alkali metal a Group 1A metal. (2.7; 18.2)

Alkaline earth metal a Group 2A metal. (2.7; 18.4)

Alkane a saturated hydrocarbon with the general formula C_nH_{2n+2}. (22.1)

Alkene an unsaturated hydrocarbon containing a carbon-carbon double bond. The general formula is C_nH_{2n}. (22.2)

Alkyne an unsaturated hydrocarbon containing a triple carbon-carbon bond. The general formula is C_nH_{2n-2}. (22.2)

Alloy a substance that contains a mixture of elements and has metallic properties. (10.4)

Alloy steel a form of steel containing carbon plus other metals such as chromium, cobalt, manganese, and molybdenum. (24.4)

Alpha (α) particle a helium nucleus. (21.1)

Alpha particle production a common mode of decay for radioactive nuclides in which the mass number changes. (21.1)

Amine an organic base derived from ammonia in which one or more of the hydrogen atoms are replaced by organic groups. (14.6; 22.4)

α-Amino acid an organic acid in which an amino group and an R group are attached to the carbon atom next to the carboxyl group. (23.1)

Amorphous solid a solid with considerable disorder in its structure. (10.3)

Ampere the unit of electrical current equal to one coulomb of charge per second. (17.7)

Amphoteric substance a substance that can behave either as an acid or as a base. (14.2)

Anion a negative ion. (2.6)

Anode the electrode in a galvanic cell at which oxidation occurs. (17.1)

Antibonding molecular orbital an orbital higher in energy than the atomic orbitals of which it is composed. (9.2)

Aromatic hydrocarbon one of a special class of cyclic unsaturated hydrocarbons, the simplest of which is benzene. (22.3)

Arrhenius concept a concept postulating that acids produce hydrogen ions in aqueous solution, while bases produce hydroxide ions. (14.1)

Arrhenius equation the equation representing the rate constant as $k = Ae^{-E_a/RT}$ where A represents the product of the collision frequency and the steric factor, and $e^{-E_a/RT}$ is the fraction of collisions with sufficient energy to produce a reaction. (12.5)

Aqueous solution a solution in which water is the dissolving medium or solvent. (4.0)

Atactic chain a polymer chain in which the substituent groups such as CH_3 are randomly distributed along the chain. (24.2)

Atmosphere the mixture of gases that surrounds the earth's surface. (5.9)

Atomic number the number of protons in the nucleus of an atom. (2.5; 21)

particle is formed having the same mass as an electron but opposite charge. The net effect is to change a proton to a neutron. (21.1)

Potential energy energy due to position or composition. (6.1)

Precipitation reaction a reaction in which an insoluble substance forms and separates from the solution. (4.5)

Precision the degree of agreement among several measurements of the same quantity; the reproducibility of a measurement. (1.3)

Primary structure (of a protein) the order (sequence) of amino acids in the protein chain. (23.1)

Principal quantum number the quantum number relating to the size and energy of an orbital; it can have any positive integer value. (7.6)

Probability distribution the square of the wave function indicating the probability of finding an electron at a particular point in space. (7.5)

Product a substance resulting from a chemical reaction. It is shown to the right of the arrow in a chemical equation. (3.6)

Protein a natural high-molecular-weight polymer formed by condensation reactions between amino acids. (23.1)

Proton a positively charged particle in an atomic nucleus. (2.5; 21)

Pure substance a substance with constant composition. (1.8)

Pyrometallurgy recovery of a metal from its ore by treatment at high temperatures. (24.4)

Qualitative analysis the separation and identification of individual ions from a mixture. (4.6)

Quantitative analysis a process in which the amounts of the components of a mixture are determined. (4.7)

Quantization the fact that energy can occur only in discrete units called quanta. (7.2)

Rad a unit of radiation dosage corresponding to 10^{-2} J of energy deposited per kilogram of tissue (from *r*adiation *a*bsorbed *d*ose). (21.7)

Radioactive decay (radioactivity) the spontaneous decomposition of a nucleus to form a different nucleus. (21.1)

Radiocarbon dating (carbon-14 dating) a method for dating ancient wood or cloth based on the rate of radioactive decay of the nuclide $^{14}_{6}C$. (21.4)

Radiotracer a radioactive nuclide, introduced into an organism for diagnostic purposes, whose pathway can be traced by monitoring its radioactivity. (21.4)

Random error an error that has an equal probability of being high or low. (1.3)

Raoult's law the vapor pressure of a solution is directly proportional to the mole fraction of solvent present. (11.4)

Rate constant the proportionality constant in the relationship between reaction rate and reactant concentrations. (12.2)

Rate of decay the change in the number of radioactive nuclides in a sample per unit time. (21.2)

Rate-determining step the slowest step in a reaction mechanism, the one determining the overall rate. (12.4)

Rate law an expression that shows how the rate of reaction depends on the concentration of reactants. (12.2)

Reactant a starting substance in a chemical reaction. It appears to the left of the arrow in a chemical equation. (3.6)

Reaction mechanism the series of elementary steps involved in a chemical reaction. (12.4)

Reaction quotient a quotient obtained by applying the law of mass action to initial concentrations rather than to equilibrium concentrations. (13.5)

Reaction rate the change in concentration of a reactant or product per unit time. (12.1)

Reactor core the part of a nuclear reactor where the fission reaction takes place. (21.6)

Reducing agent (electron donor) a reactant that donates electrons to another substance to reduce the oxidation state of one of its atoms. (4.9; 17.1)

Reduction a decrease in oxidation state (a gain of electrons). (4.9; 17.1)

Rem a unit of radiation dosage that accounts for both the energy of the dose and its effectiveness in causing biological damage (from *r*oentgen *e*quivalent for *m*an). The number of rems = (number of rads) × RBE, where RBE represents the relative effectiveness of the radiation in causing biological damage. (21.7)

Resonance a condition occurring when more than one valid Lewis structure can be written for a particular molecule. The actual electronic structure is not represented by any one of the Lewis structures but by the average of all of them. (8.12)

Reverse osmosis the process occurring when the external pressure on a solution causes a net flow of solvent through a semipermeable membrane from the solution to the solvent. (11.6)

Reversible process a cyclic process carried out by a hypothetical pathway, which leaves the universe exactly the same as it was before the process. No real process is reversible. (16.9)

Ribonucleic acid (RNA) a nucleotide polymer that transmits the genetic information stored in DNA to the ribosomes for protein synthesis. (23.3)

Roasting a process of converting sulfide minerals to oxides by heating in air at temperatures below their melting points. (24.4)

Root mean square velocity the square root of the average of the squares of the individual velocities of gas particles. (5.6)

Salt an ionic compound. (14.8)

Salt bridge a U-tube containing an electrolyte that connects the two compartments of a galvanic cell, allowing ion flow without extensive mixing of the different solutions. (17.1)

EXHIBIT 13

Chemistry

The Central Science

Ninth Edition

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becquerel The SI unit of radioactivity. It corresponds to one nuclear disintegration per second. (Section 21.4)

Beer's law The light absorbed by a substance (A) equals the product of its molar absorptivity constant (a), the path length through which the light passes (b), and the molar concentration of the substance (c): $A = abc$. (Section 14.2)

beta particles Energetic electrons emitted from the nucleus, symbol $_{-1}^{0}e$. (Section 21.1)

bidentate ligand A ligand in which two coordinating atoms are bound to a metal. (Section 24.2)

bimolecular reaction An elementary reaction that involves two molecules. (Section 14.6)

biochemistry The study of the chemistry of living systems. (Chapter 25: Introduction)

biocompatible Any substance or material that is compatible with living systems. (Section 12.3)

biodegradable Organic material that bacteria are able to oxidize. (Section 18.6)

biomaterial Any material that has a biomedical application. (Section 12.3)

biopolymer A polymeric molecule of high molecular weight found in living systems. The three major classes of biopolymer are proteins, carbohydrates, and nucleic acids. (Section 25.8)

body-centered cubic cell A cubic unit cell in which the lattice points occur at the corners and at the center. (Section 11.7)

bomb calorimeter A device for measuring the heat evolved in the combustion of a substance under constant-volume conditions. (Section 5.5)

bond angles The angles made by the lines joining the nuclei of the atoms in a molecule. (Section 9.1)

bond dipole The dipole moment due to the two atoms of a covalent bond. (Section 9.3)

bond enthalpy The enthalpy change, ΔH, required to break a particular bond when the substance is in the gas phase. (Section 8.8)

bonding atomic radius The radius of an atom as defined by the distances separating it from other atoms to which it is chemically bonded. (Section 7.3)

bonding molecular orbital A molecular orbital in which the electron density is concentrated in the internuclear region. The energy of a bonding molecular orbital is lower than the energy of the separate atomic orbitals from which it forms. (Section 9.7)

bonding pair In a Lewis structure a pair of electrons that is shared by two atoms. (Section 9.2)

bond length The distance between the centers of two bonded atoms. (Section 8.8)

bond order The number of bonding electron pairs shared between two atoms, less the number of antibonding electron pairs: bond order = (number of bonding electrons − number of antibonding electrons). (Section 9.7)

bond polarity A measure of how equally the electrons are shared between the two atoms in a chemical bond. (Section 8.4)

boranes Covalent hydrides of boron. (Section 22.11)

Born–Haber cycle A thermodynamic cycle based on Hess's law that relates the lattice energy of an ionic substance to its enthalpy of formation and to other measurable quantities. (Section 8.2)

Boyle's law A law stating that at constant temperature, the product of the volume and pressure of a given amount of gas is a constant. (Section 10.3)

Brønsted–Lowry acid A substance (molecule or ion) that acts as a proton donor. (Section 16.2)

Brønsted–Lowry base A substance (molecule or ion) that acts as a proton acceptor. (Section 16.2)

buffer capacity The amount of acid or base a buffer can neutralize before the pH begins to change appreciably. (Section 17.2)

buffered solution (buffer) A solution that undergoes a limited change in pH upon addition of a small amount of acid or base. (Section 17.2)

calcination The heating of an ore to bring about its decomposition and the elimination of a volatile product. For example, a carbonate ore might be calcined to drive off CO_2. (Section 23.2)

caloric A unit of energy, it is the amount of energy needed to raise the temperature of 1 g of water by 1°C, from 14.5°C to 15.5°C. A related unit is the joule: 1 cal = 4.184 J. (Section 5.1)

calorimeter An apparatus that measures the evolution of heat. (Section 5.5)

calorimetry The experimental measurement of heat produced in chemical and physical processes. (Section 5.5)

capillary action The process by which a liquid rises in a tube because of a combination of adhesion to the walls of the tube and cohesion between liquid particles. (Section 11.3)

carbide A binary compound of carbon with a metal or metalloid. (Section 22.9)

carbohydrates A class of substances formed from polyhydroxy aldehydes or ketones. (Section 25.10)

carbon black A microcrystalline form of carbon. (Section 22.9)

carbonyl group The C=O double bond, a characteristic feature of several organic functional groups, such as ketones and aldehydes. (Section 25.6)

carboxylic acid A compound that contains the —COOH functional group. (Sections 16.10 and 25.6)

catalyst A substance that changes the speed of a chemical reaction without itself undergoing a permanent chemical change in the process. (Section 14.7)

cathode An electrode at which reduction occurs. (Section 20.3)

cathode rays Streams of electrons that are produced when a high voltage is applied to electrodes in an evacuated tube. (Section 2.2)

cathodic protection A means of protecting a metal against corrosion by making it the cathode in a voltaic cell. This can be achieved by attaching a more easily oxidized metal, which serves as an anode, to the metal to be protected. (Section 20.8)

cation A positively charged ion. (Section 2.7)

cell potential A measure of the driving force or "electrical pressure," for an electrochemical reaction; it is measured in volts: 1 V = 1 J/C. Also called electromotive force. (Section 20.4)

cellulose A polysaccharide of glucose; it is the major structural element in plant matter. (Section 25.10)

Celsius scale A temperature scale on which water freezes at 0° and boils at 100° at sea level. (Section 1.4)

ceramic A solid inorganic material, either crystalline (oxides, carbides, silicates) or amorphous (glasses). Most ceramics melt at high temperatures. (Section 12.4)

chain reaction A series of reactions in which one reaction initiates the next. (Section 21.7)

changes of state Transformations of matter from one state to a different one, for example, from a gas to a liquid. (Section 1.3)

charcoal A form of carbon produced when wood is heated strongly in a deficiency of air. (Section 22.9)

Charles's law A law stating that at constant pressure, the volume of a given quantity of gas is proportional to absolute temperature. (Section 10.3)

chelate effect The generally larger formation constants for polydentate ligands as compared with the corresponding monodentate ligands. (Section 24.2)

chelating agent A polydentate ligand that is capable of occupying two or more sites in the coordination sphere. (Section 24.2)

chemical bond A strong attractive force that exists between atoms in a molecule. (Section 8.1)

chemical changes Processes in which one or more substances are converted into other substances; also called **chemical reactions**. (Section 1.3)

chemical equation A representation of a chemical reaction using the chemical formulas of the reactants and products; a balanced chemical equation contains equal numbers of atoms of each element on both sides of the equation. (Section 3.1)

chemical equilibrium A state of dynamic balance in which the rate of formation of the products of a reaction from the reactants equals the rate of formation of the reactants from the products; at equilibrium the concentrations of the reactants and products remain constant. (Section 4.1; Chapter 15: Introduction.)

chemical formula A notation that uses chemical symbols with numerical subscripts to convey the relative proportions of atoms of the different elements in a substance. (Section 2.6)

product A substance produced in a chemical reaction; it appears to the right of the arrow in a chemical equation. (Section 3.1)

protein A biopolymer formed from amino acids. (Section 25.9)

protium The most common isotope of hydrogen. (Section 22.2)

proton A positively charged subatomic particle found in the nucleus of an atom. (Section 2.3)

pure substance Matter that has a fixed composition and distinct properties. (Section 1.2)

pyrometallurgy A process in which heat converts a mineral in an ore from one chemical form to another and eventually to the free metal. (Section 23.2)

qualitative analysis The determination of the presence or absence of a particular substance in a mixture. (Section 17.7)

quantitative analysis The determination of the amount of a given substance that is present in a sample. (Section 17.7)

quantum The smallest increment of radiant energy that may be absorbed or emitted; the magnitude of radiant energy is $h\nu$. (Section 6.2)

racemic mixture A mixture of equal amounts of the dextrorotatory and levorotatory forms of a chiral molecule. A racemic mixture will not rotate polarized light. (Section 24.4)

rad A measure of the energy absorbed from radiation by tissue or other biological material; 1 rad = transfer of 1×10^{-2} J of energy per kilogram of material. (Section 21.9)

radioactive series A series of nuclear reactions that begins with an unstable nucleus and terminates with a stable one. Also called **nuclear disintegration series**. (Section 21.2)

radioactivity The spontaneous disintegration of an unstable atomic nucleus with accompanying emission of radiation. (Section 2.2; Chapter 21: Introduction)

radioisotope An isotope that is radioactive; that is, it is undergoing nuclear changes with emission of radiation. (Section 21.1)

radionuclide A radioactive nuclide. (Section 21.1)

radiotracer A radioisotope that can be used to trace the path of an element. (Section 21.5)

Raoult's law A law stating that the partial pressure of a solvent over a solution, P_A, is given by the vapor pressure of the pure solvent, P_A°, times the mole fraction of a solvent in the solution, $X_A : P_A = X_A P_A^\circ$. (Section 13.5)

rate constant A constant of proportionality between the reaction rate and the concentrations of reactants that appear in the rate law. (Section 14.3)

rate-determining step The slowest elementary step in a reaction mechanism. (Section 14.6)

rate law An equation that relates the reaction rate to the concentrations of reactants (and sometimes of products also). (Section 14.3)

reactant A starting substance in a chemical reaction; it appears to the left of the arrow in a chemical equation. (Section 3.1)

reaction mechanism A detailed picture, or model, of how the reaction occurs; that is, the order in which bonds are broken and formed, and the changes in relative positions of the atoms as the reaction proceeds. (Section 14.6)

reaction order The power to which the concentration of a reactant is raised in a rate law. (Section 14.3)

reaction quotient (Q) The value that is obtained when concentrations of reactants and products are inserted into the equilibrium expression. If the concentrations are equilibrium concentrations, $Q = K$; otherwise, $Q \neq K$. (Section 15.5)

reaction rate The decrease in concentration of a reactant or the increase in concentration of a product with time. (Section 14.2)

redox (oxidation-reduction) reaction A reaction in which certain atoms undergo changes in oxidation states. The substance increasing in oxidation state is oxidized; the substance decreasing in oxidation state is reduced. (Chapter 20; Introduction)

reducing agent, or **reductant** The substance that is oxidized and thereby causes the reduction of some other substance in an oxidation-reduction reaction. (Section 20.1)

reduction A process in which a substance gains one or more electrons. (Section 4.4)

refining The process of converting an impure form of a metal into a more usable substance of well-defined composition. For example, crude pig iron from the blast furnace is refined in a converter to produce steels of desired compositions. (Section 23.2)

rem A measure of the biological damage caused by radiation; rems = rads × RBE. (Section 21.9)

renewable energy Energy such as solar energy, wind energy, and hydroelectric energy that is from essentially inexhaustible sources. (Section 5.8)

representative (main-group) element Element in which the s and p orbitals are partially occupied. (Section 6.9)

resonance structures (resonance forms) Individual Lewis structures in cases where two or more Lewis structures are equally good descriptions of a single molecule. The resonance structures in such an instance are "averaged" to give a correct description of the real molecule. (Section 8.6)

reverse osmosis The process by which water molecules move under high pressure through a semipermeable membrane from the more concentrated to the less concentrated solution. (Section 18.5)

reversible process A process that can go back and forth between states along exactly the same path; a system at equilibrium is reversible because it can be reversed by an infinitesimal modification of a variable such as temperature. (Section 19.1)

ribonucleic acid (RNA) A polynucleotide in which ribose is the sugar component. (Section 25.11)

roasting Thermal treatment of an ore to bring about chemical reactions involving the furnace atmosphere. For example, a sulfide ore might be roasted in air to form a metal oxide and SO_2. (Section 23.2)

root-mean-square (rms) speed (u) The square root of the average of the squared speeds of the gas molecules in a gas sample. (Section 10.7)

rotational motion Movement of a molecule as though it is spinning like a top. (Section 19.3)

salinity A measure of the salt content of seawater, brine, or brackish water. It is equal to the mass in grams of dissolved salts present in 1 kg of seawater. (Section 18.5)

salt An ionic compound formed by replacing one or more H^+ of an acid by other cations. (Section 4.3)

saponification Hydrolysis of an ester in the presence of a base. (Section 25.6)

saturated solution A solution in which undissolved solute and dissolved solute are in equilibrium. (Section 13.2)

scientific law A concise verbal statement or a mathematical equation that summarizes a broad variety of observations and experiences. (Section 1.3)

scientific method The general process of advancing scientific knowledge by making experimental observations and by formulating laws, hypotheses, and theories. (Section 1.3)

scintillation counter An instrument that is used to detect and measure radiation by the fluorescence it produces in a fluorescing medium. (Section 21.5)

secondary structure The manner in which a protein is coiled or stretched. (Section 25.9)

second law of thermodynamics A statement of our experience that there is a direction to the way events occur in nature. When a process occurs spontaneously in one direction, it is nonspontaneous in the reverse direction. It is possible to state the second law in many different forms, but they all relate back to the same idea about spontaneity. One of the most common statements found in chemical contexts is that in any spontaneous process the entropy of the universe increases. (Section 19.2)

second-order reaction A reaction in which the overall reaction order (the sum of the concentration-term exponents) in the rate law is 2. (Section 14.4)

sigma (σ) bond A covalent bond in which electron density is concentrated along the internuclear axis. (Section 9.6)

sigma (σ) molecular orbital A molecular orbital that centers the electron density about an imaginary line passing through two nuclei. (Section 9.7)

significant figures The digits that indicate the precision with which a measurement is made; all digits of a measured quantity are significant, including the last digit, which is uncertain. (Section 1.5)

silicates Compounds containing silicon and oxygen, structurally based on SiO_4 tetrahedra. (Section 22.10)

EXHIBIT 14

WEBSTER'S New Collegiate Dictionary

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or briskness 5 : marked by much life, animation, or activity : SWARMING 6 — used as an intensive following the noun ⟨the proudest boy ~⟩ *syn* 1 see LIVING *ant* dead, defunct 2 see AWARE *ant* blind (to) — **alive·ness** *n*

ali·yah \ˌä-lē-ˈ(y)ä\ *n* [NHeb *'aliyāh*, fr. Heb, ascent] 1 : the action of going up or of being called to the reading desk of the synagogue to read from the Scriptures 2 : the immigration of Jews to Israel

ali·za·rin \ə-ˈliz-ə-rən\ *n* [prob. fr. F *alizarine*] 1 : an orange or red crystalline compound $C_{14}H_8O_4$ formerly prepared from madder and now made synthetically and used esp. to dye Turkey reds and in making red pigments 2 : any of various acid, mordant, and solvent dyes derived like alizarin proper from anthraquinone

alk *abbr* alkaline

al·ka·hest \ˈal-kə-ˌhest\ *n* [NL *alchahest*] : the universal solvent believed by the alchemists to exist — **al·ka·hes·tic** \ˌal-kə-ˈhes-tik\ *adj*

al·ka·les·cence \ˌal-kə-ˈles-ᵊn(t)s\ *n* : the property or degree of being alkaline — **al·ka·les·cent** \-ᵊnt\ *adj*

al·ka·li \ˈal-kə-ˌlī\ *n, pl* **-lies** *or* **-lis** [ME, fr. ML, fr. Ar *al-qili* the ashes of the plant saltwort] 1 : a soluble salt obtained from the ashes of plants and consisting largely of potassium or sodium carbonate; *broadly* : a substance (as a hydroxide or carbonate of an alkali metal) having marked basic properties — compare BASE 7 2 : ALKALI METAL 3 : a soluble salt or a mixture of soluble salts present in some soils of arid regions in quantity detrimental to agriculture

al·ka·li·fy \ˌal-ˈkal-ə-ˌfī, ˈal-kə-lə-\ *vb* **-fied; -fy·ing** *vt* : to convert or change into an alkali : make alkaline ~ *vi* : to become alkaline

alkali metal *n* : any of the univalent mostly basic metals of group I of the periodic table comprising lithium, sodium, potassium, rubidium, cesium, and francium

al·ka·lim·e·ter \ˌal-kə-ˈlim-ət-ər\ *n* [F *alcalimètre*, fr. *alcali* alkali + *-mètre* -meter] : an apparatus for measuring the strength or the amount of alkali in a mixture or solution — **al·ka·lim·e·try** \-ˈlim-ə-trē\ *n*

al·ka·line \ˈal-kə-lən, -ˌlīn\ *adj* : of, relating to, or having the properties of an alkali; *esp* : having a pH of more than 7 — **al·ka·lin·i·ty** \ˌal-kə-ˈlin-ət-ē\ *n*

alkaline earth *n* 1 : an oxide of any of several bivalent strongly basic metals comprising calcium, strontium, and barium and sometimes also magnesium, radium, or less often beryllium 2 : ALKALINE-EARTH METAL

alkaline-earth metal *n* : any of the metals whose oxides are the alkaline earths

alkaline phosphatase *n* : a phosphatase (as the phosphomonoesterase from blood plasma or milk) active in alkaline medium

al·ka·lin·ize \ˈal-kə-lə-ˌnīz\ *vt* **-ized; -iz·ing** : to make alkaline — **al·ka·lin·iz·ation** \ˌal-kə-ˌlin-ə-ˈzā-shən, -lə-nə-\ *n*

al·ka·loid \ˈal-kə-ˌloid\ *n* : any of numerous usu. colorless, complex, and bitter organic bases (as morphine or codeine) containing nitrogen and usu. oxygen that occur esp. in seed plants — **al·ka·loi·dal** \ˌal-kə-ˈloid-ᵊl\ *adj*

al·ka·lo·sis \ˌal-kə-ˈlō-səs\ *n* : a condition of increased alkalinity of the blood and tissues

al·ka·net \ˈal-kə-ˌnet\ *n* [ME, fr. OSp *alcaneta*, dim. of *alcana* henna shrub, fr. ML *alchanna*, fr. Ar *al-ḥinnā'* the henna] 1 a : a European plant (*Alkanna tinctoria*) of the borage family; *also* : its root b : a red dyestuff prepared from the root 2 : BUGLOSS

alk·oxy \ˈal-ˌkäk-sē\ *adj* [ISV *alkyl* + *oxygen*] : of, relating to, or containing a univalent radical composed of an alkyl group united with oxygen

alky *abbr* alkalinity

al·kyd \ˈal-kəd\ *n* [blend of *alkyl* and *acid*] : any of numerous thermoplastic or thermosetting synthetic resins made by heating polyhydroxy alcohols with polybasic acids or their anhydrides and used esp. for protective coatings

al·kyl \ˈal-kəl\ *n* [prob. fr. G, fr. *alkohol* alcohol, fr. ML *alcohol*] 1 a : a univalent aliphatic radical C_nH_{2n+1} (as methyl) b : any univalent aliphatic, aromatic-aliphatic, or alicyclic hydrocarbon radical 2 : a compound of alkyl radicals with a metal — **al·kyl·ic** \al-ˈkil-ik\ *adj*

al·kyl·ate \ˈal-kə-ˌlāt\ *vt* **-at·ed; -at·ing** : to introduce one or more alkyl groups into (a compound)

al·kyl·ation \ˌal-kə-ˈlā-shən\ *n* : the act or process of alkylating esp. for producing high-octane fuel

all \ˈȯl\ *adj* [ME *all*, *al*, fr. OE *eall*; akin to OHG *al* all] 1 a : the whole amount or quantity of (sat up ~ night) b : as much as possible (spoke in ~ seriousness) 2 a : every member or individual component of (~ men will go) (~ five children were present) b — used in logic as a verbalized equivalent of the universal quantifier 3 : the whole number or sum of (~ the angles of a triangle are equal to two right angles) 4 : EVERY (~ manner of hardship) 5 : any whatever (beyond ~ doubt) 6 : nothing but : ONLY: a : completely taken up with, given to, or absorbed by (became ~ attention) b : having or seeming to have (some physical feature) in conspicuous excess or prominence (~ thumbs) c : paying full attention with (~ ears) 7 *dial* : used up : entirely consumed — used esp. of food and drink 8 : being more than one person or thing — **all the** : as much of . . . as : as much of a . . . as ⟨*all the* home I ever had⟩

²all *adv* 1 : WHOLLY, ALTOGETHER ⟨sat ~ alone⟩ — often used as an intensive ⟨~ out of proportion⟩ 2 *obs* : EXCLUSIVELY, ONLY 3 *archaic* : JUST 4 : so much ⟨~ the better for it⟩ 5 : for each side : APIECE ⟨the score is two ~⟩

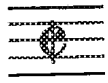
³all *pron* 1 : the whole number, quantity, or amount : TOTALITY ⟨~ that I have⟩ ⟨~ of us⟩ ⟨~ of the books⟩ 2 : EVERYBODY, EVERYTHING ⟨sacrificed ~ for love⟩ — **all in all** : on the whole : generally ⟨*all in all*, things might have been worse⟩ — **at all** : in any way — usu. used with a negative ⟨no good *at all*⟩

⁴all *n* : the whole of one's possessions or of what one prizes ⟨gave his ~ for the cause⟩

all- *or* **allo-** *comb form* [Gk, fr. *allos* other — more at ELSE] 1 : other : different : atypical ⟨*allo*gamous⟩ ⟨*allo*merism⟩ 2 *allo-* : isomeric form or variety of (a specified chemical compound) 3 *allo-* : being one of a group whose members together constitute a structural unit esp. of a language ⟨*allo*phone⟩

¹al·la breve \ˌal-ə-ˈbrev, ˌäl-ə-ˈbrev-(ˌ)ā\ *adv or adj* [It, lit., according to the breve] : in duple or quadruple time with the beat represented by the half note

²alla breve *n* : the sign marking a piece or passage to be played alla breve; *also* : a passage so marked



alla breve

Al·lah \ˈal-ə, ä-ˈlä\ *n* [Ar *allāh*] : the Supreme Being of the Muslims

¹all-Amer·i·can \ˌȯ-lə-ˈmer-ə-kən\ *adj* 1 : composed wholly of American elements 2 : representative of the ideals of the U.S. ⟨an ~ boy⟩ 3 a : selected (as by a poll of journalists) as one of the best in the U.S. in a particular category at a particular time ⟨an ~ quarterback⟩ b : made up of all-American participants ⟨an ~ basketball team⟩ 4 : of or relating to the American nations as a group

²all-American *n* : one (as an athlete) that is voted all-American

al·lan·to·is \ə-ˈlant-ə-wəs\ *n, pl* **al·lan·to·ides** \ˌal-ən-ˈtō-ə-ˌdēz, ˌal-ˌan-\ [NL, deriv. of Gk *allant-, allas* sausage] : a vascular fetal membrane of reptiles, birds, or mammals that is formed as a pouch from the hindgut and that in placental mammals is intimately associated with the chorion in formation of the placenta — **al·lan·to·ic** \ˌal-ən-ˈtō-ik, ˌal-ˌan-\ *adj*

al·lar·gan·do \ˌäl-är-ˈgän-(ˌ)dō\ *adj or adv* [It, widening, verbal of *allargare* to widen, fr. *al-* (fr. L *ad-*) + *largare* to widen] : becoming gradually broader with the same or greater volume — used as a direction in music

all-around \ˌȯ-lə-ˈraund\ *adj* 1 : competent in many fields ⟨an ~ man of letters⟩ 2 : having general utility 3 : considered in or encompassing all aspects : INCLUSIVE ⟨the best ~ recording of the work to date⟩ ⟨good nature and ~ competence —G. H. Soule⟩ *syn* see VERSATILE

al·lay \ə-ˈlā\ *vb* [ME *alayen*, fr. OE *ālecgan*, fr. *ā-* (perfective prefix) + *lecgan* to lay — more at ABIDE, LAY] *vt* 1 : to subdue or reduce in intensity or severity : ALLEVIATE ⟨wishing for a breeze to ~ the summer heat⟩ 2 : to make quiet : CALM ~ *vi, obs* : to diminish in strength : SUBSIDE *syn* see RELIEVE *ant* intensify

all but *adv* : very nearly : ALMOST ⟨he *all but* disappeared from public notice⟩

all clear *n* : a signal that a danger has passed

all-day \ˌȯl-ˌdā\ *adj* : lasting for, occupying, or appearing throughout an entire day ⟨an ~ trip⟩

al·le·ga·tion \ˌal-i-ˈgā-shən\ *n* 1 : the act of alleging 2 : a positive assertion; *specif* : a statement by a party to a legal action of what he undertakes to prove 3 : an assertion unsupported and by implication regarded as unsupportable ⟨vague ~s of misconduct⟩

al·lege \ə-ˈlej\ *vt* **al·leged; al·leg·ing** [ME *alleggen*, fr. OF *alleguer*, fr. L *allegare* to depute — more at LEGATE] 1 : to assert without proof or before proving ⟨the newspaper ~s the mayor's guilt⟩ 2 *archaic* : to adduce or bring forward as a source or authority 3 : to bring forward as a reason or excuse *syn* see ADDUCE *ant* contravene, traverse

al·leged \ə-ˈlejd, -ˈlej-əd\ *adj* 1 : asserted to be true or to exist : AVOWED ⟨an ~ miracle⟩ 2 : questionably true or of a specified kind : SO-CALLED ⟨bought an ~ antique vase⟩ — **al·leg·ed·ly** \-ˈlej-əd-lē\ *adv*

Al·le·ghe·ny spurge \ˌal-ə-ˌgā-nē- *also* ˌgen-ē\ *n* [*Alleghany* mts., U.S.A.] : a low herb or subshrub (*Pachysandra procumbens*) of the box family widely grown as a ground cover

al·le·giance \ə-ˈlē-jən(t)s\ *n* [ME *allegeaunce*, modif. of MF *ligeance*, fr. OF, fr. *lige* liege] 1 a : the obligation of a feudal vassal to his liege lord b (1) : the fidelity owed by a subject or citizen to his sovereign or government (2) : the obligation of an alien to the government under which he resides 2 : devotion or loyalty to a person, group, or cause *syn* see FIDELITY *ant* treachery, treason

al·le·giant \-jənt\ *adj* : giving allegiance : LOYAL

al·le·gor·i·cal \ˌal-ə-ˈgȯr-i-kəl, -ˈgär-\ *adj* 1 : of, relating to, or having the characteristics of allegory 2 : having hidden spiritual meaning that transcends the literal sense of a sacred text — **al·le·gor·i·cal·ly** \-k(ə-)lē\ *adv* — **al·le·gor·i·cal·ness** \-kəl-nəs\ *n*

al·le·go·rist \ˈal-ə-ˌgȯr-əst, -ˌgȯr-\ *n* : a writer of allegory

al·le·go·ri·za·tion \ˌal-ə-ˌgȯr-ə-ˈzā-shən, -ˌgȯr-, -gər-\ *n* : allegorical representation or interpretation

al·le·go·rize \ˈal-ə-ˌgȯr-ˌīz, -ˌgȯr-, -gər-\ *vb* **-rized; -riz·ing** *vt* 1 : to make into allegory 2 : to treat or explain as allegory ~ *vi* 1 : to give allegorical explanations 2 : to compose or use allegory — **al·le·go·riz·er** *n*

al·le·go·ry \ˈal-ə-ˌgȯr-ē, -ˌgȯr-\ *n, pl* **-ries** [ME *allegorie*, fr. L *allegoria*, fr. Gk *allēgoria*, fr. *allēgorein* to speak figuratively, fr. *allos* other + *-agorein* to speak publicly, fr. *agora* assembly — more at ELSE, GREGARIOUS] 1 a : the expression by means of symbolic fictional figures and actions of truths or generalizations about human existence b : an instance (as in a story or painting) of such expression 2 : a symbolic representation : EMBLEM

¹al·le·gret·to \ˌal-ə-ˈgret-(ˌ)ō, ˌäl-\ *adv or adj* [It, fr. *allegro*] : faster than andante but not so fast as allegro — used as a direction in music

²allegretto *n, pl* **-tos** : a musical composition or movement in allegretto tempo

¹al·le·gro \ə-ˈleg-(ˌ)rō, -ˈlā-(ˌ)grō\ *adv or adj* [It, merry, fr. (assumed) VL *alecrus* lively, alter. of L *alacr-, alacer* — more at ALACRITY] : in a brisk lively manner — used as a direction in music

²allegro *n, pl* **-gros** : a musical composition or movement in allegro tempo

pre-med-i-cal \(ˌ)prē-ˈmed-i-kəl\ *adj* : preceding and preparing for the professional study of medicine

pre-med-i-tate \prē-ˈmed-ə-ˌtāt, ˈprē-\ *vb* [L *praemeditatus*, pp. of *praemeditari*, fr. *prae-* + *meditari* to meditate] *vt* : to think about and revolve in the mind beforehand ~ *vi* : to think, consider, or deliberate beforehand — **pre-med-i-ta-tor** \-ˌtāt-ər\ *n*

pre-med-i-tat-ed *adj* : characterized by fully conscious willful intent and a measure of forethought and planning ⟨~ murder⟩ — **pre-med-i-tat-ed-ly** *adv*

pre-med-i-ta-tion \prē-ˌmed-ə-ˈtā-shən, ˌprē-\ *n* : an act or instance of premeditating; *specif* : consideration or planning of an act beforehand that shows intent to commit that act

pre-med-i-ta-tive \prē-ˈmed-ə-ˌtāt-iv, ˈprē-\ *adj* : given to or characterized by premeditation

pre-meio-tic \ˌprē-mī-ˈät-ik\ *adj* : of, occurring in, or typical of a stage prior to meiosis ⟨~ DNA synthesis⟩ ⟨~ tissue⟩

pre-men-stru-al \(ˌ)prē-ˈmen(t)-strəl, -ˈmen-\ *adj* : of, relating to, or occurring in the period just preceding menstruation — **pre-men-stru-al-ly** \-ᵊl-ē\ *adv*

pre-mie *var of* PREEMIE

¹pre-mier \pri-ˈmi(y)ir, ˈprē-mē-ər, ˈprem-ē-\ *adj* [ME *primier*, fr. MF *premier* first, chief, fr. L *primarius* of the first rank — more at PRIMARY] 1 : first in position, rank, or importance : PRINCIPAL 2 : first in time : EARLIEST

²premier *n* [F, fr. *premier*, *adj.*] : PRIME MINISTER

pre-mier dan-seuse \prə-myā-dän-ˈsəz\ *n* [F] : the principal male dancer in a ballet company

¹pre-miere \pri-ˈmyer(ə)r, -ˈmi(ə)r; ˌprim-ə-ˈ(e)ə(r)\ *n* [F *première*, fr. fem. of *premier* first] 1 : a first performance or exhibition ⟨the ~ of a play⟩ 2 : the leading lady of a group; *esp* : the chief actress of a theatrical cast

²premiere *or* **pre-mier** *like* ¹PREMIERE\ *vb* **pre-mi-ered; pre-mier-ing** *vt* : to give a first public performance of ~ *vi* 1 : to have a first public performance 2 : to appear for the first time as a star performer

³premiere *adj* [alter. of ¹*premier*] : OUTSTANDING, CHIEF

pre-miere dan-seuse \prə-myer-dän-ˈsəz\ *n* [F *première danseuse*] : the principal female dancer in a ballet company

pre-mier-ship \pri-ˈmi(y)ir-ˌship; ˈprē-mē-ər-, ˈprem-ē-\ *n* : the position or office of a premier

pre-mil-le-nar-i-an-ism \ˈprē-mil-ə-ˈner-ē-ə-ˌni-zəm\ *n* : PREMILLENNIALISM — **pre-mil-le-nar-i-an** \-ē-ən\ *adj or n*

pre-mil-len-ni-al \ˌprē-mə-ˈlen-ē-əl\ *adj* [*pre-* + *millennium*] 1 : coming before a millennium 2 : holding or relating to premillennialism — **pre-mil-len-ni-al-ly** \-ē-ə-lē\ *adv*

pre-mil-len-ni-al-ism \-ē-ə-ˌli-zəm\ *n* : the view that Christ's return will precede and usher in a future millennium of Messianic rule mentioned in Revelation — **pre-mil-len-ni-al-ist** \-ē-ə-list\ *n*

¹prem-ise \ˈprem-əs\ *n* [in sense 1, fr. ME *premise*, fr. MF, fr. ML *praemissa*, fr. L, fem. of *praemissus*, pp. of *praemittere* to place ahead, fr. *prae-* pre- + *mittere* to send; in other senses, fr. ME *premisses*, fr. ML *praemissa*, fr. L, neut. pl. of *praemissus* — more at SMITE] 1 *a* : a proposition antecedently supposed or proved as a basis of argument or inference; *specif* : either of the first two propositions of a syllogism from which the conclusion is drawn *b* : something assumed or taken for granted : PRESUPPOSITION 2 *pl* : matters previously stated; *specif* : the preliminary and explanatory part of a deed or of a bill in equity 3 *pl* [fr. its being identified in the premises of the deed] *a* : a tract of land with the buildings thereon *b* : a building or part of a building usu. with its appurtenances (as grounds)

²pre-mise \ˈprem-əs *also* pri-ˈmīz\ *vt* **pre-mised; pre-mis-ing** 1 *a* : to set forth beforehand as an introduction or a postulate *b* : to offer as a premise in an argument 2 : to presuppose or imply as preexistent : POSTULATE

¹pre-mi-um \ˈprē-mē-əm\ *n* [L *praemium* booty, profit, reward, fr. *prae-* + *emere* to take, buy — more at REDEEM] 1 *a* : a reward or recompense for a particular act *b* : a sum over and above a regular price paid chiefly as an inducement or incentive ⟨willing to pay a ~ for immediate delivery⟩ *c* : a sum in advance of or in addition to the nominal value of something ⟨bonds callable at a ~ of six percent⟩ *d* : something given free or at a reduced price with the purchase of a product or service 2 : the consideration paid for a contract of insurance 3 : a high value or a value in excess of that normally or usu. expected ⟨put a ~ on accuracy⟩

²premium *adj* : of exceptional quality or amount

¹pre-mix \(ˌ)prē-ˈmiks\ *vt* : to mix far in advance of use

²pre-mix \ˈprē-ˌmiks\ *n* : a mixture of ingredients (as the dry materials for a cake batter) prepared beforehand and designed to be later mixed with other ingredients (as liquids)

pre-molar \(ˌ)prē-ˈmō-lər\ *adj* : situated in front of or preceding the molar teeth; *esp* : being or relating to those teeth of a mammal in front of the true molars and behind the canines when the latter are present — **premolar** *n*

pre-mon-ish \-ˈmän-ish\ *vt, archaic* : FOREWARN ~ *vi, archaic* : to give warning in advance

pre-mon-i-tion \ˌprē-mə-ˈnish-ən, ˌprem-ə-\ *n* [ME, fr. LL *praemonition-*, *praemonitio*, fr. L *praemonitus*, pp. of *praemonēre* to warn in advance, fr. *prae-* + *monēre* to warn — more at MIND] 1 : previous notice or warning : FOREWARNING 2 : anticipation of an event without conscious reason : PRESENTIMENT

pre-mon-i-to-ry \pri-ˈmän-ə-ˌtōr-ē, -ˌtȯr-\ *adj* : giving warning ⟨a ~ symptom⟩ — **pre-mon-i-to-ri-ly** \-ˌmän-ə-ˈtōr-ə-lē, -ˈtȯr-\ *adv*

Pre-mon-stra-ten-sian \ˌprē-ˌmän(t)-strə-ˈten-chən\ *n* [ML *praemonstratensis*, fr. *praemonstratus* of Prémontré, fr. *Praemonstratus* Prémontré] : a member of an order of canons regular founded by St. Norbert at Prémontré near Laon, France, in 1120

pre-morse \pri-ˈmȯ(ə)rs\ *adj* [L *praemorsus*, fr. pp. of *praemordere* to bite off in front, fr. *prae-* + *mordēre* to bite — more at SMART] : terminated abruptly but irregularly as if bitten off ⟨a ~ root⟩

pre-mune \(ˌ)prē-ˈmyün\ *adj* [back-formation fr. *premunition*] : exhibiting premunition

pre-mu-ni-tion \ˌprē-myü-ˈnish-ən\ *n* [L *praemunition-*, *praemunitio* advance fortification, fr. *praemunitus*, pp. of *praemunire* to fortify in advance, fr. *prae-* + *munire* to fortify — more at MUNITION] 1 *archaic* : an advance provision of protection 2 *a* : resistance to a disease due to the existence of its causative agent in a state of physiological equilibrium in the host *b* : immunity to a particular infection due to previous presence of the causative agent

pre-name \ˈprē-ˌnām\ *n* : FORENAME

pre-na-tal \(ˌ)prē-ˈnāt-ᵊl\ *adj* : occurring, existing, or being in a stage before birth — **pre-na-tal-ly** \-ᵊl-ē\ *adv*

¹pre-nom-i-nate \(ˌ)prē-ˈnäm-ə-ˌnāt\ *adj* [L *praenominatus*, pp. of *praenominare* to name before, fr. L *prae-* + *nominare* to name — more at NOMINATE] *obs* : previously mentioned

²pre-nom-i-nate \-ˌnāt\ *vt, obs* : to mention previously — **pre-nom-i-na-tion** \(ˌ)prē-ˌnäm-ə-ˈnā-shən\ *n, obs*

pre-no-tion \(ˌ)prē-ˈnō-shən, ˈprē-\ *n* [L *praenotion-*, *praenotio* preconception, fr. *prae-* + *notio* idea, conception — more at NOTION] 1 : PRESENTIMENT, PREMONITION 2 : PRECONCEPTION

¹pren-tice \ˈprent-əs\ *n* [ME *prentis*, short for *apprentis*] : APPRENTICE 1, LEARNER

²prentice *adj* 1 : of, relating to, or characteristic of a prentice 2 : not fully skilled; *also* : lacking in finish or polish

³prentice *vt* **pren-ticed; pren-tic-ing** : APPRENTICE

pre-oc-cu-pan-cy \(ˌ)prē-ˈäk-yə-pən-sē\ *n* 1 : an act or the right of taking possession before another 2 : the condition of being completely busied or preoccupied

pre-oc-cu-pa-tion \(ˌ)prē-ˌäk-yə-ˈpā-shən\ *n* [L *praeoccupation-*, *praeoccupatio* act of seizing beforehand, fr. *praeoccupatus*, pp. of *praeoccupare* to seize beforehand, fr. *prae-* + *occupare* to seize, occupy] 1 : an act of preoccupying : the state of being preoccupied 2 *a* : complete absorption of the mind or interests *b* : something that causes such absorption

pre-oc-cu-pied \(ˌ)prē-ˈäk-yə-ˌpīd\ *adj* 1 *a* : lost in thought : ENGROSSED *b* : already occupied 2 : previously applied to another group and unavailable for use in a new sense — used of a biological generic or specific name

pre-oc-cu-py \-ˌpī\ *vt* [*pre-* + *occupy*] 1 : to engage or engross the interest or attention of beforehand or preferentially 2 : to take possession of or fill beforehand or before another

pre-oper-a-tive \(ˌ)prē-ˈäp-(ə-)rət-iv, -ˈäp-ə-ˌrāt-\ *adj* : occurring during the period preceding a surgical operation — **pre-oper-a-tive-ly** *adv*

pre-or-bit-al \-ˈȯr-bət-ᵊl\ *adj* : occurring before going into orbit

pre-or-dain \ˌprē-ȯr-ˈdān\ *vt* : to decree or ordain in advance : FOREORDAIN — **pre-or-dain-ment** \-mənt\ *n* — **pre-or-di-na-tion** \(ˌ)prē-ˌȯrd-ᵊn-ˈā-shən\ *n*

pre-ovi-po-si-tion \ˌprē-ˌō-və-pə-ˈzish-ən\ *adj* : of, relating to, or being the period before oviposition of the first eggs by an adult female (as of an insect)

pre-ovu-la-to-ry \(ˌ)prē-ˈäv-yə-lə-ˌtōr-ē, -ˌtȯr-, -ˈōv-\ *adj* : occurring in or typical of the period immediately preceding ovulation

¹prep \ˈprep\ *n* 1 *Brit* : preparation of lessons : HOMEWORK 2 : PREPARATORY SCHOOL 3 : a trial run in horse racing

²prep *vb* **prepped; prep-ping** *vi* : to attend preparatory school or engage in preparatory study or training ~ *vt* : to prepare for operation or examination

³prep *abbr* 1 preparatory 2 preposition

pre-pack-age \(ˌ)prē-ˈpak-ij\ *vt* : to package (as food or a manufactured article) before offering for sale to the consumer

prep-a-ra-tion \ˌprep-ə-ˈrā-shən\ *n* [ME *preparacion*, fr. MF *preparation*, fr. L *praeparation-*, *praeparatio*, fr. *praeparatus*, pp. of *praeparare*] 1 : the action or process of making something ready for use or service or of getting ready for some occasion, test, or duty 2 : a state of being prepared : READINESS 3 : a preparatory act or measure 4 : something that is prepared; *specif* : a medicinal substance made ready for use ⟨a ~ for colds⟩

¹pre-par-a-tive \pri-ˈpar-ət-iv\ *n* : something that prepares the way for or serves as a preliminary to something else : PREPARATION

²preparative *adj* : PREPARATORY — **pre-par-a-tive-ly** *adv*

pre-par-a-tor \pri-ˈpar-ət-ər\ *n* : one that prepares; *specif* : one that prepares scientific specimens

¹pre-par-a-to-ry \pri-ˈpar-ə-ˌtōr-ē, -ˌtȯr- *also* ˈprep-(ə-)rə-\ *adj* : preparing or serving to prepare for something : INTRODUCTORY *syn* see PRELIMINARY — **pre-par-a-to-ri-ly** \pri-ˌpar-ə-ˈtōr-ə-lē, -ˈtȯr- *also* ˌprep-(ə-)rə-\ *adv*

²preparatory *adv* : by way of preparation : in a preparatory manner — usu. used with *to* ⟨took a deep breath ~ to drinking⟩

preparatory school *n* 1 : a usu. private school preparing students primarily for college 2 *Brit* : a private elementary school preparing students primarily for public schools

pre-pare \pri-ˈpa(ə)r, -ˈpe(ə)r\ *vb* **pre-pared; pre-par-ing** [ME *preparen*, fr. MF *preparer*, fr. L *praeparare*, fr. *prae-* pre- + *parare* to procure, prepare — more at PARE] *vt* 1 : to make ready beforehand for some purpose, use, or activity ⟨~ food for dinner⟩ ⟨~ children for school⟩ 2 : to work out the details of : plan in advance ⟨*preparing* his strategy for the coming campaign⟩ 3 *a* : to put together : COMPOUND ⟨~ a prescription⟩ *b* : to put into written form ⟨~ a report⟩ ~ *vi* : to get ready ⟨*preparing* for a career in teaching⟩ — **pre-par-er** *n*

syn PREPARE, FIT, QUALIFY, CONDITION, READY *shared meaning element* : to make someone or something ready (as for a use or an activity)

pre-pared \-ˈpa(ə)rd, -ˈpe(ə)rd\ *adj* : subjected to a special process or treatment — **pre-par-ed-ly** \-ˈper-əd-lē, -ˈpar-\ *adv*

pre-pared-ness \pri-ˈper-əd-nəs, -ˈpar- *also* -ˈpa(ə)rd-nəs *or* -ˈpe(ə)rd-nəs\ *n* : the quality or state of being prepared; *specif* : a state of adequate preparation in case of war

pro·ba·tion·er \-shə-nər\ *n* **1** : one (as a newly admitted student nurse) whose fitness is being tested during a trial period **2** : a convicted offender on probation

probation officer *n* : an officer appointed to investigate, report on, and supervise the conduct of convicted offenders on probation

pro·ba·tive \'prō-bət-iv\ *adj* **1** : serving to test or try : EXPLORATORY **2** : serving to prove : SUBSTANTIATING

pro·ba·to·ry \'prō-bə-ˌtōr-ē, -ˌtȯr-\ *adj* : PROBATIVE

¹probe \'prōb\ *n* [ML *probe* examination, fr. L *probare*] **1** : a slender surgical instrument for examining a cavity **2** *a* : a pointed metal tip for making electrical contact with a circuit element being checked *b* : a device used to penetrate or send back information esp. from outer space *c* : a pipe on the receiving airplane thrust into the drogue of the delivering airplane in air refueling **3** *a* : the action of probing *b* : a penetrating or critical investigation : INQUIRY *c* : a tentative exploratory advance or survey

²probe *vb* **probed; prob·ing** *vt* **1** : to examine with or as if with a probe **2** : to investigate thoroughly ~ *vi* : to make an exploratory investigation *syn* see ENTER — **prob·er** *n*

pro·ben·e·cid \prō-'ben-ə-səd\ *n* [irreg. fr. *propyl* + *benzoic acid*] : a drug $C_{13}H_{19}NO_4S$ that acts on renal tubular function and is used to inhibit the excretion of some drugs (as penicillin) and to increase the excretion of urates in gout

pro·bit \'prō-ˌbit\ *n* [*probability unit*] : a unit of measurement of statistical probability based on deviations from the mean of a normal distribution

pro·bi·ty \'prō-bət-ē\ *n* [MF *probité*, fr. L *probitas*, *probitas*, fr. *probus* honest — more at PROVE] : adherence to the highest principles and ideals : UPRIGHTNESS *syn* see HONESTY

¹problem \'prä-ləm, 'präb-ˌlem, -ləm\ *n* [ME *probleme*, fr. MF, fr. L *problema*, fr. Gk *problēma*, lit., something thrown forward, fr. *probeballein* to throw forward, fr. *pro-* forward + *ballein* to throw — more at PRO-, DEVIL] **1** *a* : a question raised for inquiry, consideration, or solution *b* : a proposition in mathematics or physics stating something to be done **2** *a* : an intricate unsettled question *b* : a source of perplexity, distress, or vexation *syn* see MYSTERY

²problem *adj* **1** : dealing with a problem of human conduct or social relationship (a ~ play) **2** : difficult to deal with (a ~ child)

prob·lem·at·ic \ˌprä-blə-'mat-ik\ *or* **prob·lem·at·i·cal** \-i-kəl\ *adj* **1** *a* : difficult to solve or decide : PUZZLING *b* : not definite or settled (their future remains ~) *c* : open to question or debate : QUESTIONABLE **2** : expressing or supporting a possibility *syn* see DOUBTFUL — **prob·lem·at·i·cal·ly** \-i-k(ə-)lē\ *adv*

pro·bos·ci·de·an \ˌprō-ˌbäs-ə-'dē-ən\ *or* **pro·bos·ci·di·an** \-'si-dē-ən, -'sid-ē-\ *n* [deriv. of L *proboscid-*, *proboscis*] : any of an order (Proboscidea) of large mammals comprising the elephants and extinct related forms — **proboscidean** *adj*

pro·bos·cis \prə-'bäs-əs\ *n, pl* **-bos·cis·es** *also* **-bos·ci·des** \-'bäs-ə-ˌdēz\ [L, fr. Gk *proboskis*, fr. *pro-* + *boskein* to feed; akin to Lith *gaujа* herd] **1** *a* : the trunk of an elephant; *also* : any long flexible snout *b* : the human nose esp. when prominent **2** : any of various elongated or extensible tubular processes (as the sucking organ of a butterfly) of the oral region of an invertebrate

press able proceedings

pro·caine \'prō-ˌkān\ *n* [ISV ²*pro-* + *cocaine*] : a basic ester $C_{13}H_{20}N_2O_2$ of para-aminobenzoic acid; *also* : its crystalline hydrochloride used as a local anesthetic

pro·cam·bi·um \(ˌ)prō-'kam-bē-əm\ *n* [NL] : the part of a plant meristem that forms cambium and primary vascular tissues — **procambial** \-bē-əl\ *adj*

pro·car·yote \(ˌ)prō-'kar-ē-ˌōt\ *n* [*pro-* + Gk *karyon* provided with nuts — more at EUCARYOTE] : a cellular organism (as a bacterium or a blue-green alga) that does not have a distinct nucleus — compare EUCARYOTE — **pro·car·y·ot·ic** \-ˌkar-ē-'ät-ik\ *adj*

pro-cathedral \prō-kə-'thē-drəl\ *n* : a parish church used as a cathedral

pro·ce·dur·al \prə-'sē-jə-rəl\ *adj* : of or relating to procedure esp. of courts or other bodies administering substantive law — **pro·ce·dur·al·ly** \-ē\ *adv*

pro·ce·dure \prə-'sē-jər\ *n* [F *procédure*, fr. MF, fr. *procéder*] **1** *a* : a particular way of accomplishing something or of acting *b* : a step in a procedure **2** : a series of steps followed in a regular definite order (legal ~) **3** *a* : a traditional or established way of doing things *b* : PROTOCOL

pro·ceed \prō-'sēd, prə-\ *vi* [ME *proceden*, fr. MF *procéder*, fr. L *procedere*, fr. *pro-* forward + *cedere* to go — more at PRO-, CEDE] **1** : to come forth from a source : ISSUE **2** *a* : to continue after a pause or interruption *b* : to go on in an orderly regulated way **3** *a* : to begin and carry on an action, process, or movement *b* : to be in the process of being accomplished *c* : to move along a course : ADVANCE *syn* see SPRING

pro·ceed·ing *n* **1** : PROCEDURE **2** *pl* : EVENTS, HAPPENINGS **3** *pl* : legal action (divorce ~s) **4** : AFFAIR, TRANSACTION **5** *pl* : an official record of things said or done

pro·ceeds \'prō-ˌsēdz\ *n pl* **1** : the total amount brought in (the ~ of a sale) **2** : the net amount received (as for a check or from an insurance settlement) after deduction of any discount or charges

pro·ce·phal·ic \ˌprō-sə-'fal-ik\ *adj* : relating to, forming, or situated on or near the front of the head

pro·cer·coid \(ˌ)prō-'sər-ˌkȯid\ *n* [*pro-* + Gk *kerkos* tail] : the solid first parasitic larva of some tapeworms that develops usu. in the body cavity of a copepod

¹pro·cess \'prä-ˌses, 'prō-ˌ, -səs\ *n, pl* **pro·cess·es** \-ə-səz, -ə-ˌsēz\ [ME *proces*, fr. MF, fr. L *processus*, fr. *processus*, pp. of *procedere*] **1** *a* : PROGRESS, ADVANCE *b* : something going on : HAPPENING **2** *a* : a natural phenomenon marked by gradual changes that lead toward a particular result (the ~ of growth) *b* : a series of actions or operations conducing to an end; esp : a continuous operation or treatment esp. in manufacture **3** *a* : the whole course of proceedings in a legal action *b* : the summons, mandate, or writ used by a court to compel the appearance of the defendant in a legal action or compliance with its orders **4** : a prominent or projecting part of an organism or organic structure (a bone ~) **5** : CONK

²process *vt* **1** *a* : to proceed against by law : prosecute *b* (1) : to take out a summons against (2) : to serve a summons on **2** *a* : to subject to a special process or treatment (as in the course of manufacture) *b* : to work (hair) into a conk

³process *adj* **1** : treated or made by a special process esp. when involving synthesis or artificial modification **2** : made by or used in a mechanical or photomechanical duplicating process **3** : of or involving illusory effects usu. introduced during processing of the film (a ~ motion-picture scene)

⁴process \'prō-ˌses\ *vi* [back-formation fr. *procession*] *chiefly Brit* : to move in a procession

process cheese \'prä-ˌses-, 'prō-ˌ, -zes-\ *n* : a cheese made by blending several lots of cheese

pro·cess·i·ble *or* **pro·cess·a·ble** \'prä-ˌse-sə-bəl, 'prō-\ *adj* : suitable for processing : capable of being processed — **pro·cess·i·bil·i·ty** *or* **pro·cess·a·bil·i·ty** \ˌprä-ˌse-sə-'bil-ət-ē, ˌprō-\ *n*

¹pro·ces·sion \prə-'sesh-ən\ *n* **1** *a* : continuous forward movement : PROGRESSION *b* : EMANATION (the Holy Ghost's ~ from the Father) **2** *a* : a group of individuals moving along in an orderly often ceremonial way *b* : SUCCESSION, SEQUENCE

²procession *vi, archaic* : to go in procession

¹pro·ces·sion·al \prə-'sesh-nəl, -ən-ᵊl\ *n* **1** : a book containing material for a procession **2** : a musical composition (as a hymn) designed for a procession **3** : a ceremonial procession

²processional *adj* : of, relating to, or moving in a procession — **pro·ces·sion·al·ly** \-ē\ *adv*

pro·ces·sor \'prä-ˌse-sər, 'prō-\ *n* **1** : one that processes (food ~) **2** *a* (1) : COMPUTER (2) : the part of a computer system that operates on data — called also *central processing unit* *b* : a computer program (as a compiler) that puts another program into a form acceptable to the computer

process printing *n* : a method of printing from halftone plates in use, three or more colors so that nearly any hue may be reproduced

pro·cès-ver·bal \prō-ˌsā-ver-'bäl, -ˌver-\ *n, pl* **pro·cès-ver·baux** \-'bō\ [F, lit., verbal trial] : an official written record

pro·claim \prō-'klām, prə-\ *vt* [ME *proclamen*, fr. MF or L; MF *proclamer*, fr. L *proclamare*, fr. *pro-* before + *clamare* to cry out — more at PRO-, CLAIM] **1** *a* : to declare publicly, typically insistently, proudly, or defiantly and in either speech or writing : ANNOUNCE *b* : to give outward indication of : SHOW **2** : to declare or declare to be solemnly, officially, or formally (~ an amnesty) (~ the country a republic) **3** : to praise or glorify openly or publicly : EXTOL *syn* see DECLARE — **pro·claim·er** *n*

proc·la·ma·tion \ˌpräk-lə-'mā-shən\ *n* [ME *proclamacion*, fr. MF *proclamation*, fr. L *proclamation-*, *proclamatio*, fr. *proclamare*, pp. of *proclamare*] **1** : the action of proclaiming : the state of being proclaimed **2** : something proclaimed; *specif* : an official formal public announcement

pro·cli·max \(ˌ)prō-'klī-ˌmaks\ *n* : an ecological community that suggests a climax in stability and permanence but is not primarily the product of climate

pro·clit·ic \prō-'klit-ik\ *adj* [NL *procliticus*, fr. Gk *pro-* + LL *-clitikos* (as in *enclitikos* enclitic)] : of, relating to, or constituting a word or particle without sentence stress that is accentually dependent upon a following stressed word and is pronounced with it as a phonetic unit — **proclitic** *n*

pro·cliv·i·ty \prō-'kliv-ət-ē\ *n, pl* **-ties** [L *proclivitas*, fr. *proclivis* sloping, prone, fr. *pro-* forward + *clivus* hill — more at PRO-, DECLIVITY] : an inclination or predisposition toward something; esp : a strong inherent inclination toward something objectionable *syn* see LEANING

Pro·cne \'präk-nē\ *n* [L, fr. Gk *Prokne*] : the wife of Tereus changed into a swallow while fleeing with her sister from Tereus

pro·con·sul \(ˌ)prō-'kän(t)-səl\ *n* [ME, fr. L, fr. *pro consule* for a consul] **1** : a governor or military commander of an ancient Roman province **2** : an administrator in a modern colony, dependency, or occupied area usu. with wide powers — **pro·con·su·lar** \-sə-lər\ *adj* — **pro·con·su·late** \-sə-lət\ *n* — **pro·con·sul·ship** \-səl-ˌship\ *n*

pro·cras·ti·nate \prō-'kras-tə-ˌnāt, prə-\ *vb* **-nat·ed; -nat·ing** [L, *procrastinatus*, pp. of *procrastinare*, fr. *pro-* forward + *crastinus* of tomorrow, fr. *cras* tomorrow] *vt* : to put off intentionally and habitually ~ *vi* : to put off intentionally and reprehensibly the doing of something that should be done — **pro·cras·ti·na·tion** \-ˌkras-tə-'nā-shən\ *n* — **pro·cras·ti·na·tor** \-'kras-tə-ˌnāt-ər\ *n*

pro·cre·ant \'prō-krē-ənt\ *adj* **1** : producing offspring **2** *archaic* : of or relating to procreation

pro·cre·ate \-ət\ *vb* **-at·ed; -at·ing** [L *procreatus*, pp. of *procreare*, fr. *pro-* forth + *creare* to create — more at PRO-, CREATE] *vt* : to beget or bring forth (offspring) : PROPAGATE ~ *vi* : to beget or bring forth offspring : REPRODUCE — **pro·cre·a·tion** \ˌprō-krē-'ā-shən\ *n* — **pro·cre·a·tive** \'prō-krē-ˌāt-iv\ *adj* — **pro·cre·a·tor** \-ət-ər\ *n*

pro·crus·te·an \prō-'krəs-tē-ən, prə-\ *adj often cap* **1** : of, relating to, or typical of Procrustes **2** : marked by arbitrary often ruthless disregard of individual differences or special circumstances

procrustean bed *n, often cap P* : a scheme or pattern into which someone or something is arbitrarily forced

Pro·crus·tes \prō-'krəs-(ˌ)tēz, prə-\ *n* [L, fr. Gk *Prokroustēs*] : a giant of Eleusis who forced travelers to fit one of two unequally long beds by stretching their bodies or cutting off their legs

pro·cryp·tic \(ˌ)prō-'krip-tik\ *adj* [*pro-* (as in *protect*) + *cryptic*] : of, relating to, or being a concealing pattern or shade of coloring esp. in insects

proc·to·de·um \ˌpräk-tə-'dē-əm\ *n, pl* **-de·a** \-'dē-ə\ *or* **-de·ums** [NL, fr. Gk *prōktos* anus + *hodos* way — more at CHART] : the posterior ectodermal part of the alimentary canal formed in the embryo by invagination of the outer body wall

proc·tol·o·gy \präk-'täl-ə-jē\ *n* [Gk *prōktos* anus + E *-logy*] : a branch of medicine dealing with the structure and diseases of the anus, rectum, and sigmoid colon — **proc·to·log·ic** \ˌpräk-tə-'läj-

ik\ or proto-to-log-i-cal \-i-kəl\ *adj* ---- pro-to-to-gist \prō-'tä-ə-jəst\ *n*

pro-tor \'prō-tər\ *n* [ME *prouctour procurator*, proctor, alter. of *procuratour*] : SUPERVISOR, MONITOR; *specif* : one appointed to supervise students (as at an examination) ---- **proctor** *vb* ---- **pro-to-ri-al** \prō-'tōr-ē-əl, -'tȯr-\ *adj* ---- **pro-tor-ship** \'prō-tər-,ship\ *n*

pro-cum-bent \prō-'kəm-bənt\ *adj* [L *procumbent-, procumbens*, pp. of *procumbere* to fall or lean forward, fr. *pro-* forward + *-cumbere* to lie down] ---- more at HP] 1 : being or having stems that trail along the ground without rooting 2 : lying face down

pro-cu-re-ment \prō-'kyu̇r-mənt\ *n* [ME *procurement*, fr. MF *procuration*, fr. L *procuration-, procuratio*, fr. *procuratus*, pp. of *procurare*] 1 *a* : the act of appointing another as one's agent or attorney *b* : the authority vested in one so appointed 2 : the action of obtaining something (as supplies) : PROCUREMENT

pro-cu-ra-tor \'prōk-yə-,rā-tər\ *n* 1 : one that manages another's affairs : AGENT 2 : an officer of the Roman empire entrusted with management of the financial affairs of a province and often having administrative powers as agent of the emperor ---- **pro-cu-ra-to-ri-al** \,prōk-yə-rə-'tōr-ē-əl, -'tȯr-\ *adj*

pro-cure \prə-'kyu̇(ə)r, prō-\ *vb* **pro-cured; pro-cur-ing** [ME *procuren*, fr. L *procurare*, fr. L, to take care of, fr. *pro-* for + *curare* care] *vt* 1 *a* : to get possession of : obtain by particular care and effort *b* : to get and make available for promiscuous sexual intercourse 2 : to bring about : ACHIEVE ~ *vi* : to procure women *syn* see GET ---- **pro-cur-able** \-'kyu̇r-ə-bəl\ *adj* ---- **pro-cur-ance** \-ən(t)s\ *n* ---- **pro-cure-ment** \-'kyu̇(ə)r-mənt\ *n*

pro-cur-er \-'kyu̇r-ər\ *n* : one that procures; *esp* : PANDER ---- **pro-cur-ess** \-ər\ *n*

Pro-cy-on \'prō-sē-,än, -ən\ *n* [L, fr. Gk *Prokyōn*, lit., fore dog; fr. its rising before the Dog Star] : a first-magnitude star in Canis Minor

1prod \'präd\ *vt* **prod-ded; prod-ding** [origin unknown] 1 *a* : to thrust a pointed instrument into : PRICK *b* : to incite to action : GOAD 2 : to poke or stir as if with a prod ---- **prod-der** *n*

2prod *n* 1 : a pointed instrument used to prod 2 : an incitement to act

3prod *abbr* production

prod-i-gal \'präd-i-gəl\ *adj* [L *prodigus*, fr. *prodigere* to drive away, squander, fr. *pro-* forth + *agere* to drive ---- more at PRO-, AGENT] 1 : recklessly extravagant 2 : characterized by wasteful expenditure : LAVISH 3 : yielding abundantly : LUXURIANT *syn* see PROFUSE and parsimonious, frugal ---- **prod-i-gal-i-ty** \,präd-ə-'gal-ət-ē\ *n* ---- **prod-i-gal-ly** \'präd-i-gə-lē\ *adv*

2prodigal *n* : one who spends or gives lavishly and foolishly *syn* see SPENDTHRIFT

pro-di-gious \prə-'dij-əs\ *adj* 1 *a* *obs* : being an omen : PORTENTOUS *b archaic* : resembling or befitting a prodigy : STRANGE, UNUSUAL 2 : exciting amazement or wonder 3 : extraordinary in bulk, quantity, or degree : ENORMOUS *syn* see MONSTROUS ---- **pro-di-gious-ly** *adv* ---- **pro-di-gious-ness** *n*

prod-i-gy \'präd-ə-jē\ *n, pl* **-gies** [L *prodigium* omen, monster, fr. *pro-* prob. + *-igium* (akin to *ais* I say)] ---- more at ADAGE] 1 *a* : a portentous event : OMEN *b* : something extraordinary or inexplicable 2 *a* : an extraordinary, marvelous, or unusual accomplishment, deed, or event *b* : a highly talented child

pro-dro-mal \'prō-'drō-məl\ *or* **pro-drom-ic** \-'dräm-ik\ *adj* : PRECURSORY; *esp* : marked by prodromes

pro-dro-me \'prō-,drōm\ *n, pl* **pro-dro-ma-ta** \(')prō-'drō-mət-ə\ *or* **pro-dromes** \'prō-,drōmz\ [F, lit., precursor, fr. Gk *prodromos*, fr. *pro-* before + *dromos* running ---- more at PRO-, DROMEDARY] : a premonitory symptom of disease

1pro-duce \prə-'dü̇s, prō-\ *vb* **pro-duced; pro-duc-ing** [ME (3b) *producen*, fr. L *producere*, fr. *pro-* forward + *ducere* to lead ---- more at TOW] *vt* 1 : to offer to view or notice : EXHIBIT 2 : to give birth or rise to : YIELD 3 : to extend in length, area, or volume (~ a side of a triangle) 4 : to present to the public on the stage or screen or over radio or television 5 : to give being, form, or shape to : MAKE *esp* : MANUFACTURE 6 : to accrue or cause to accrue ~ *vi* : to bear, make, or yield something ---- **pro-duc-ible** \-'dü̇-sə-bəl\ *adj*

2pro-duce \'prōd-,ü̇s, 'prōd- *also* -,ü̇z\ *n* 1 *a* : something produced *b* : the amount produced : YIELD 2 : agricultural products and esp. fresh fruits and vegetables as distinguished from grain and other staple crops 3 : the progeny usu. of a female animal

pro-duced \prə-'d(y)üst, prō-\ *adj* : disproportionately elongated (a ~ foot)

pro-duc-er \prə-'d(y)ü-sər, prō-\ *n* 1 : one that produces; *esp* : one that grows agricultural products or manufactures crude materials into articles of use 2 : a furnace or apparatus that produces combustible gas to be used for fuel by circulating air or a mixture of air and steam through a layer of incandescent fuel 3 : a person who supervises or finances the production of a stage or screen production or radio or television program 4 : an organism (as a green plant) which produces its own organic compounds from simple precursors (as carbon dioxide and inorganic nitrogen) and many of which are food sources for other organisms ---- compare CONSUMER *b*

producer gas *n* : gas made in a producer and consisting chiefly of carbon monoxide, hydrogen, and nitrogen

producer goods *n pl* : goods (as tools and raw materials) that are used to produce other goods and satisfy human wants only indirectly

prod-uct \'präd-(,)əkt\ *n* [in sense 1, fr. ME, fr. ML *productum*, fr. L, something produced, fr. neut. of *productus*, pp. of *producere* in other senses, fr. L *producere*] 1 : the number or expression resulting from the multiplication together of two or more numbers or expressions 2 : something produced 3 : the amount, quantity, or total produced 4 : CONJUNCTION 5

pro-duc-tion \prə-'dək-shən, prō-\ *n* 1 *a* : something produced : PRODUCT *b* (1) : a literary or artistic work (2) : a work presented on the stage or screen or over the air *c* : an exaggerated action 2 *a* : the act or process of producing *b* : the creation of utility; *esp* : the making of goods available for human wants 3 : total output esp. of a commodity or an industry ---- **pro-duc-tion-al** \-shnəl, -shən-ᵊl\ *adj*

production control *n* : systematic planning, coordinating, and directing of all manufacturing activities and influences to insure having goods made on time, of adequate quality, and at reasonable cost

production line *n* : LINE 6j

pro-duc-tive \prə-'dək-tiv, prō-\ *adj* 1 : having the quality or power of producing esp. in abundance (~ fishing waters) 2 : effective in bringing about : ORIGINATIVE (investigating committees have been ~ of much good ---R. K. Carr) 3 *a* : yielding or furnishing results, benefits, or profits *b* : yielding or devoted to the satisfaction of wants or the creation of utilities 4 : continuing to be used in the formation of new words or constructions (*un-* is a ~ prefix) 5 : raising mucus or sputum (as from the bronchi) (a ~ cough) ---- **pro-duc-tive-ly** *adv* ---- **pro-duc-tive-ness** *n*

pro-duc-tiv-i-ty \(,)prō-,dək-'tiv-ət-ē, ,prōd-(,)ək-, prə-,dək-\ *n* 1 : the quality or state of being productive 2 : rate of production esp. of food by fixation of solar energy by producer organisms

pro-em \'prō-,em\ *n* [ME *proheme*, fr. MF, fr. L *prooemium*, fr. Gk *prooimion*, fr. *pro-* + *oimē* song] 1 : preliminary comment : PREFACE 2 : PRELUDE ---- **pro-em-i-al** \prō-'ē-mē-əl, -'em-ē-\ *adj*

pro-en-zyme \(')prō-'en-,zīm\ *n* [ISV] : ZYMOGEN

pro-es-trus \(')prō-'es-trəs\ *n* [NL] : a period immediately preceding estrus characterized by preparatory physiological changes

1prof \'präf\ *n, slang* : PROFESSOR

2prof *abbr* professor; professional

pro-fa-na-tion \,präf-ə-'nā-shən, ,prō-fə-\ *n* : the act or an instance of profaning
syn PROFANATION, DESECRATION, SACRILEGE *shared meaning element* : a violation or misuse of something normally held sacred

pro-fa-na-to-ry \prō-'fan-ə-,tōr-ē, prə-, -'fā-nə-, -,tȯr-\ *adj* : tending to profane : DESECRATING

1pro-fane \prō-'fān, prə-\ *vt* **pro-faned; pro-fan-ing** 1 : to treat (something sacred) with abuse, irreverence, or contempt : DESECRATE, VIOLATE 2 : to debase by a wrong, unworthy, or vulgar use ---- **pro-fan-er** *n*

2profane *adj* [ME *prophane*, fr. MF, fr. L *profanus*, fr. *pro-* before + *fanum* temple ---- more at PRO-, FEAST] 1 : not concerned with religion or religious purposes : SECULAR 2 : not holy because unconsecrated, impure, or defiled : UNSANCTIFIED 3 : serving to debase or defile what is holy : IRREVERENT 4 *a* : not among the initiated *b* : not possessing esoteric or expert knowledge ---- **pro-fane-ly** *adv* ---- **pro-fane-ness** \-'fān-nəs\ *n*

pro-fan-i-ty \prō-'fan-ət-ē, prə-\ *n, pl* **-ties** 1 *a* : the quality or state of being profane *b* : the use of profane language 2 *a* : profane language *b* : an utterance of profane language

pro-fess \prə-'fes, prō-\ *vb* [in sense 1, fr. ME *professen*, fr. *professe*, adj., having professed one's vows, fr. Off, fr. L *professus*, fr. L, pp. of *profiteri* to profess, confess, fr. *pro-* before + *fatēri* to acknowledge] in other senses, fr. L *professus*, pp. ---- more at CONFESS] *vt* 1 : to receive formally into a religious community following a novitiate by acceptance of the required vows 2 *a* : to declare or admit openly or freely : AFFIRM *b* : to declare in words or appearances only : PRETEND 3 : to confess one's faith in or allegiance to 4 : to practice or claim to be versed in (a calling or profession) ~ *vi* 1 : to make a profession or avowal 2 *obs* : to profess friendship

pro-fessed \-'fest\ *adj* 1 : openly and freely declared or acknowledged : AFFIRMED 2 : professing to be qualified; *also* : EXPERT

pro-fessed-ly \prə-'fes-əd-lē, -'fest-lē\ *adv* 1 : by profession or declaration : AVOWEDLY 2 : with pretense : ALLEGEDLY

pro-fession \prə-'fesh-ən\ *n* 1 : the act of taking the vows of a religious community 2 : an act of openly declaring or publicly claiming a belief, faith, or opinion : PROFESSATION 3 : an avowal religious faith 4 *a* : a calling requiring specialized knowledge and often long and intensive academic preparation *b* : a principal calling, vocation, or employment *c* : the whole body of persons engaged in a calling

pro-fes-sion-al \prə-'fesh-nəl, -ən-ᵊl\ *adj* 1 *a* : of, relating to, or characteristic of a profession *b* : engaged in one of the learned professions *c* : characterized by or conforming to the technical or ethical standards of a profession 2 *a* : participating for gain or livelihood in an activity or field of endeavor often engaged in by amateurs *b* : engaged in by persons receiving financial return (~ football) 3 : following a line of conduct as though it were a profession (a ~ patriot) ---- **pro-fes-sion-al-ly** \-ē\ *adv*

2professional *n* : one that engages in a pursuit or activity professionally

pro-fes-sion-al-ism \-ə-,niz-əm\ *n* 1 : the conduct, aims, or qualities that characterize or mark a profession or a professional person 2 : the following of a profession (as athletics) for gain or livelihood

pro-fes-sion-al-ize \-,īz\ *vt* **-ized, -iz-ing** : to give a professional character to ---- **pro-fes-sion-al-i-za-tion** \-,fesh-nə-lə-'zā-shən, -ən-ᵊl-ə-\ *n*

pro-fes-sor \prə-'fes-ər\ *n* 1 : one that professes, avows, or declares 2 *a* : a faculty member of the highest academic rank at an institution of higher education *b* : a teacher at a university, college, or sometimes secondary school *c* : one that teaches or professes special knowledge of an art, sport, or occupation requiring skill ---- **pro-fes-so-ri-al** \,prō-fə-'sōr-ē-əl, ,präf-ə-, -'sȯr-\ *adj* ---- **pro-fes-so-ri-al-ly** \-ə-lē\ *adv*

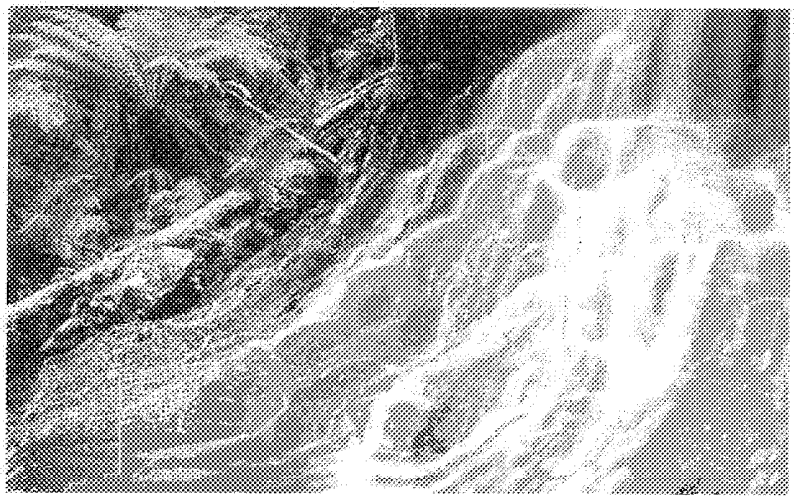
pro-fes-sor-ate \prə-'fes-ə-rət\ *n* : the office, term of office, or position of a professor

EXHIBIT 15

Conceptual Chemistry

Understanding Our World of Atoms and Molecules

John Suchocki
Leeward Community College



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physical dependence A dependence characterized by the need to continue taking a drug to avoid withdrawal symptoms.

physical model A representation of a system that helps us predict how the system behaves.

physical property Any physical attribute of a substance, such as color, density, or hardness.

point source A specific, well-defined location where pollutants enter a body of water.

polar bond A chemical bond having a dipole.

polymer A long organic molecule made of many repeating units.

potential energy Stored energy.

power The rate at which energy is expended.

precipitate A solute that has come out of solution.

principal quantum number *n* An integer that specifies the quantized energy level of an atomic orbital.

probability cloud The pattern of electron positions plotted over time to show the likelihood of an electron being at a given position at a given time.

producer An organism at the bottom of a trophic structure.

product A new material formed in a chemical reaction, appearing after the arrow in a chemical equation.

protein A polymer of amino acids, also known as a polypeptide.

proton A positively charged subatomic particle of the atomic nucleus.

psychoactive Said of a drug that affects the mind or behavior.

psychological dependence A deep-rooted craving for a drug.

pure The state of a material that consists of a single element or compound.

quantum hypothesis The idea that light energy is contained in discrete packets called quanta.

quantum A small, discrete packet of light energy.

rad A unit for measuring radiation dosage, equal to 0.01 joule of radiant energy absorbed per kilogram of tissue.

radioactivity The tendency of some elements, such as uranium, to emit radiation as a result of changes in the atomic nucleus.

reactant A starting material in a chemical reaction, appearing before the arrow in a chemical equation.

reaction rate A measure of how quickly the concentration of products in a chemical reaction increases or the concentration of reactants decreases.

recombinant DNA A hybrid DNA composed of DNA strands from different organisms.

reduction The process whereby a reactant gains one or more electrons.

rem A unit for measuring radiation dosage, obtained by multiplying the number of rads by a factor that allows for the different health effects of different types of radiation.

replication The process by which DNA strands are duplicated.

reverse osmosis A technique for purifying water by forcing it through a semipermeable membrane.

ribonucleic acid A nucleic acid containing a fully oxygenated ribose sugar.

saccharide Another term for carbohydrate. The prefixes *mono-*, *di-*, and *poly-* are used before this term to indicate the length of the carbohydrate.

salinization The process whereby irrigated land becomes more salty.

salt An ionic compound formed from the reaction between an acid and a base.

saturated hydrocarbon A hydrocarbon containing no multiple covalent bonds, with each carbon atom bonded to four other atoms.

saturated solution A solution containing the maximum amount of solute that will dissolve.

scientific hypothesis A testable assumption often used to explain an observed phenomenon.

scientific law Any scientific hypothesis that has been tested over and over again and has not been contradicted. Also known as a scientific principle.

semipermeable membrane A membrane that allows water molecules to pass through its submicroscopic pores but not solute molecules.

sensory neuron A peripheral neuron that transmits electrical signals from the senses to the central nervous system.

soil horizon A layer of soil.

solid Matter that has a definite volume and a definite shape.

solubility The ability of a solute to dissolve in a given solvent.

soluble Capable of dissolving to an appreciable extent in a given solvent.

solute Any component in a solution that is not the solvent.

solution A homogeneous mixture in which all components are in the same phase.

solvent The component in a solution present in the largest amount.

specific heat capacity The quantity of heat required to change the temperature of 1 gram of a substance by 1 Celsius degree.

EXHIBIT 16

J|A|C|S
ARTICLES
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Asymmetric, Stereocontrolled Total Synthesis of Paraherquamide A

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Abstract: The first total synthesis of paraherquamide A, a potent anthelmintic agent isolated from various *Penicillium* sp. with promising activity against drug-resistant intestinal parasites, is reported. Key steps in this asymmetric, stereocontrolled total synthesis include a new enantioselective synthesis of α-alkylated-β-hydroxyproline derivatives to access the substituted proline nucleus and a highly diastereoselective intramolecular S_N2' cyclization to generate the core bicyclo[2.2.2]diazaoctane ring system.

Introduction

The paraherquamides[1−4] are an unusual family of fungal natural products which contain a bicyclo[2.2.2]diazaoctane core structure, a *spiro*-oxindole, and a substituted proline moiety. The parent member, paraherquamide A (**1**), was first isolated from cultures of *Penicillium paraherquei* by Yamazaki and co-workers in 1981.[1] Since then, paraherquamides B−G,[2] VM55595, VM55596, and VM55597,[3] SB203105 and SB200437,[4] and sclerotamide[5] have been isolated from various *Penicillium* and *Aspergillus* species. Marcfortines A−C are structurally similar, containing a pipecolic acid unit in place of proline.[6] Also closely related are VM55599,[3] aspergamides A and B,[7] avrainvillamide (CJ-17,665),[8] and the most recently isolated members of this family, stephacidins A and B .[9] These last six compounds contain a 2,3-disubstituted indole in place of the *spiro*-oxindole. Brevianamides A and B,[10] which contain a *spiro*-indoxyl rather than a *spiro*-oxindole, and the asperparalines, which contain a *spiro*-succinimide,[11] are also structurally comparable (Figure 1).

The paraherquamides have attracted considerable attention due to their molecular complexity, intriguing biogenesis,[12,13] and biological activity. Some members, most notably paraherquamide A, display potent anthelmintic activity and antinematodal properties.[14] Due to the appearance of drug resistance developed by helminths, broad spectrum anthelmintic agents such as the macrolide endectocides, benzimidazoles, tetrahydropyrimidines, and imidazothiazoles are beginning to lose efficacy and there has arisen an urgent need to discover new families of antiparasitic agents. The paraherquamides represent an entirely new structural class of anthelmintic compounds, and as such, they hold great potential as drugs for the treatment of intestinal parasites in animals.[15] The mode of action of the paraherquamides is, as yet, incompletely characterized, but recent work suggests that they are selective competitive cholinergic antagonists.[16]

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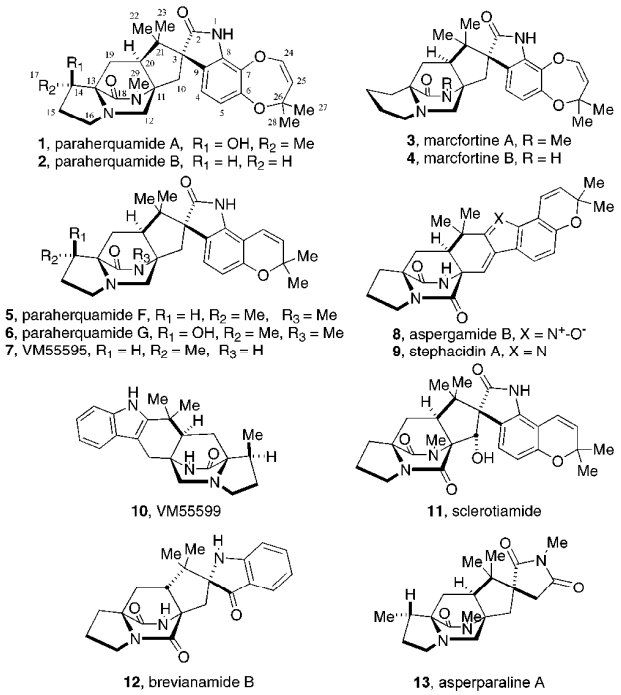
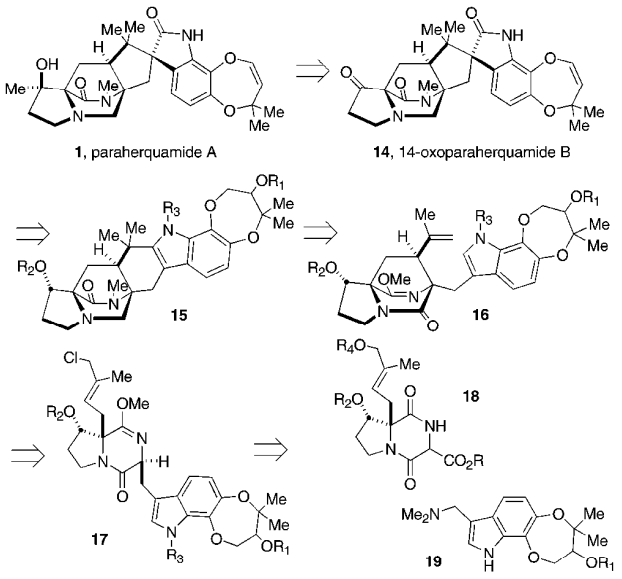


Figure 1. Structures of some paraherquamides and related compounds.

The small quantities of paraherquamide A that can be isolated from cultures for biological study have slowed the development of these agents. Recently, Lee and Clothier reported the interesting semisynthetic conversion of marcfortine A (**3**), a metabolite more readily available by fermentation, into paraherquamide A via paraherquamide B (**2**).[17] Following synthetic studies on brevianamide B (**12**),[18] our laboratory reported the first total synthesis of a member of the paraherquamide family, *ent*-paraherquamide B, in 1993, in which a diastereoselective intramolecular S_N2' cyclization reaction was used to construct the core bicyclo[2.2.2]diazaoctane ring system.[19] We have further exploited this reaction strategy, and we described the first total synthesis of paraherquamide A in 2000.[20] Herein, we detail a full account of this work.

Scheme 1. Retrosynthetic Plan for Paraherquamide A



Synthesis of an α-Alkylated-β-Hydroxyproline

Despite the apparent similarity in the structures of paraherquamides A and B, synthesis of the former turned out to be a significantly more challenging endeavor owing to the presence of the unusual β-hydroxy-β-methyl proline residue. In the semisynthesis of paraherquamide A from marcfortine A (**3**), the final step was addition of methylmagnesium bromide to 14-oxoparaherquamide B (**14**).[17] We planned to use this same methodology to complete our total synthesis and to construct **14** using a similar strategy to that used for paraherquamide B, that is, coupling of suitably functionalized indole (**19**) and diketopiperazine (**18**) units and then an intramolecular S_N2' cyclization followed by palladium-mediated closure of the seventh ring, and finally oxidation and rearrangement of the 2,3-disubstituted indole to the *spiro*-oxindole of 14-oxoparaherquamide B[19] (Scheme 1).

New methodology was now required to prepare a suitably functionalized α-alkylated-β-hydroxyproline residue. A variety of methods were investigated for the asymmetric construction of this class of compound, leading to the development of a potentially general synthetic method which uses dianion alkylation of the readily available *N*-*t*-BOC-β-hydroxyproline ethyl ester derivative **12** with net retention of stereochemistry.[21] This methodology has now successfully been applied to a concise asymmetric and stereocontrolled total synthesis of paraherquamide A.

Epoxide **20**, which is commercially available or made by epoxidation of isoprene with *m*CPBA, was treated with *n*-Bu_4NI and TBSCl to provide iodide **21** as a mixture of geometrical isomers (*E*:*Z* ≈ 6:1) in 58% overall yield. Diester **22** was prepared in two steps from ethyl glycinate and ethyl acrylate, and then a Dieckmann cyclization was conducted, using a slight modification of the procedure described by Rapoport,[22]

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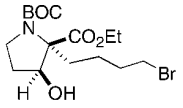
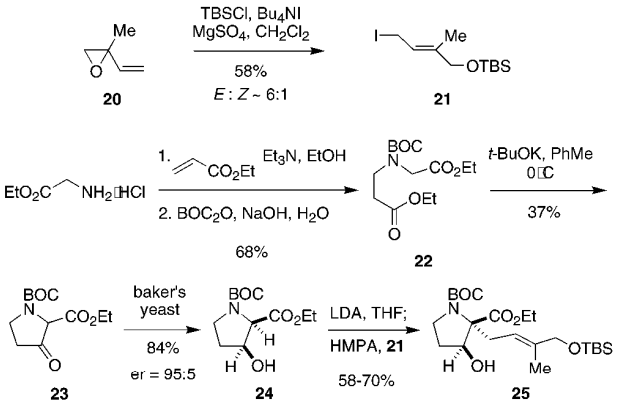


26

Figure 2. Assignment of relative stereochemistry of **25**.

Scheme 2. Synthesis of α-Alkylated-β-Hydroxyproline **25**



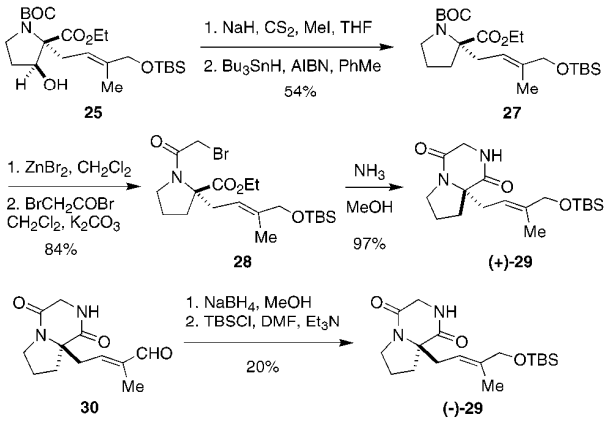
to yield racemic β-ketoester **23** (Scheme 2). Baker's yeast reduction afforded the optically active β-hydroxyester **24** with an enantiomeric ratio of ca. 95:5 as described by Knight et al.[23] Alkylation of the dianion of **24** with substituted allyl iodide **21** proceeded with retention of stereochemistry and excellent diastereoselectivity under the conditions previously developed.[21] The desired α-alkylated product **25** was obtained in 58−70% isolated yield with little or no *O*-monoalkylation or *O*-,*C*-dialkylation taking place. It was interesting to note during large scale synthesis of **25** that the amount of HMPA required in the alkylation reaction ranged from 1.4 to 13.6 equiv depending on the batch of **24** that was used, despite the batches being apparently identical by ^{1}H NMR, IR, TLC, and optical rotation. The reasons for this phenomenon are presently unclear.[24]

The assignment of the relative stereochemistry of **25** was obtained by comparison of the ^{1}H NMR and optical rotation data of **25** to those of **26**, which was obtained by alkylation of **24** with 1,4-dibromobutane. The relative stereochemistry of **26** was assigned unambiguously through single-crystal X-ray analysis (Figure 2).[21] The absolute stereochemistry of **25** was confirmed by Barton deoxygenation and conversion to diketopiperazine **(+)-29** as illustrated in Scheme 3. This same diketopiperazine could be obtained, as the enantiomer, from **30**. This compound has previously been converted to (+)-paraherquamide B, a substance whose absolute stereochemistry has been confirmed.[19]

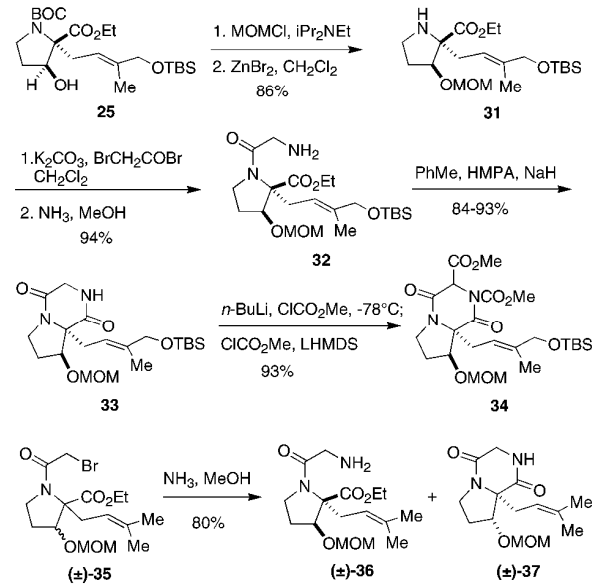
Synthesis of a Functionalized Diketopiperazine

It was necessary to convert the substituted proline (**25**) into a suitably functionalized diketopiperazine for a similar Somei−Kametani coupling reaction to that used in our total synthesis of paraherquamide B. Initial studies on this system were carried out with the secondary alcohol protected as a benzyl ether.

Scheme 3. Assignment of Absolute Chemistry of **25**



Scheme 4. Preparation of the Diketopiperazine **34**



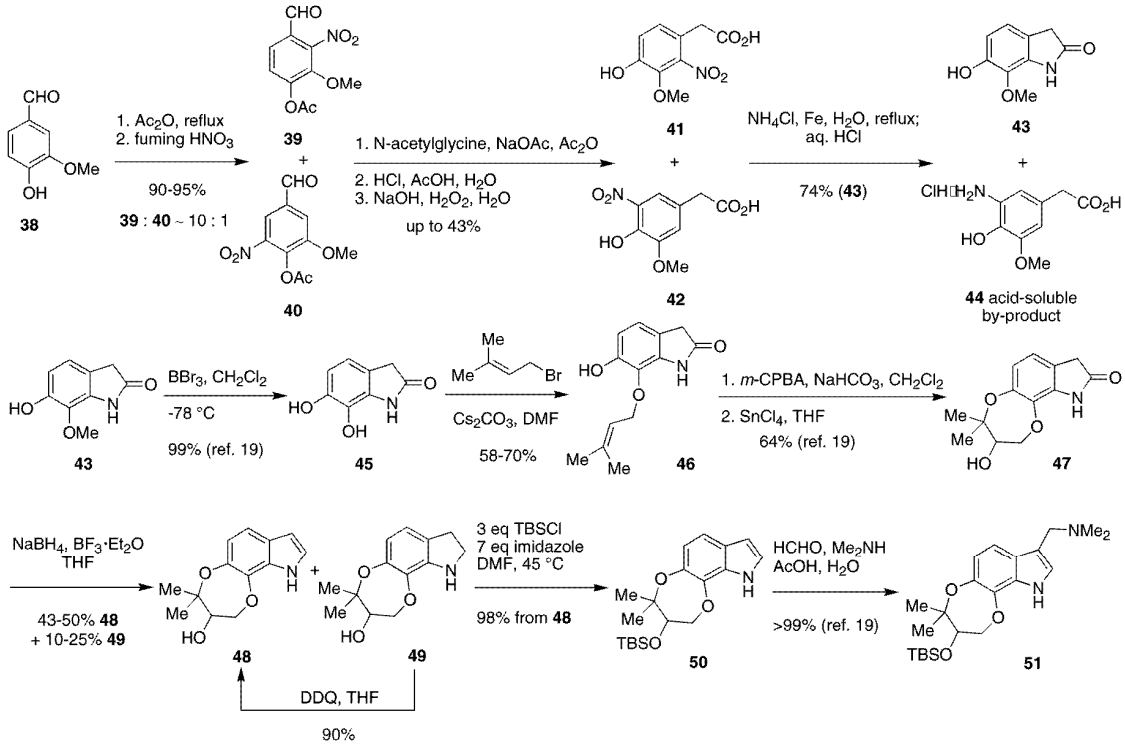
However, because of problems with selectivity and purification later in the synthesis, the less bulky and more polar methoxymethyl (MOM) protecting group was used in the final synthetic route. After MOM protection of the alcohol, the *N*-*t*-BOC group was smoothly removed with $ZnBr_2$ in dichloromethane[25] and the exposed secondary amine (**31**) was acetylated with bromoacetyl bromide under Schotten−Baumann conditions (Scheme 4). Treatment of the bromoacetamide with methanolic ammonia afforded the corresponding glycinamide (**32**) which was directly subjected to cyclization in the presence of sodium hydride in toluene/HMPA to afford the bicyclic compound **33** in 75% overall yield from **25**. An interesting observation about the ease of closure of hydroxylated diketopiperazines was made during this study. When there is no hydroxyl substituent (e.g., in **28**) or the protected hydroxyl group is *trans* to the ester, the diketopiperazine typically forms spontaneously from the aminoester in methanol at room temperature. On the other hand, a *cis*-isomer such as **31** can be isolated as the aminoester from the amination reaction, and formation of the diketopiperazine requires much more forcing conditions. On amination of a

(23) (a) Cooper, J.; Gallagher, P. T.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1313−1317. For alternative baker's yeast reductions, see: (b) Sibi, M. P.; Christensen, J. W. *Tetrahedron Lett.* **1990**, *31*, 5689−5692. (c) Bhide, R.; Mortezaei, R.; Scilimati, A.; Sih, C. J. *Tetrahedron Lett.* **1990**, *31*, 4827−4830.

(24) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654.

(25) Nigam, S. C.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Synth. Commun.* **1989**, *19*, 3139−3142.

Scheme 5. Preparation of the Gramine Derivative **51**



mixture of diastereomeric bromoacetamides **35**, the aminoester **36** and the diketopiperazine **37** are produced. This is presumably because the *cis*-diketopiperazine is significantly more sterically hindered. After diketopiperazine formation, a one-pot double carbomethoxylation reaction was performed by the sequential addition of *n*-BuLi in THF followed by addition of methylchloroformate, which carbomethoxylates the amide nitrogen. Subsequent addition of more methylchloroformate followed by LHMDS afforded **34** in 93% yield as an ~6:1 mixture of *E* and *Z* isomers, with the newly created stereogenic center as a single stereoisomer (relative configuration was not assigned).

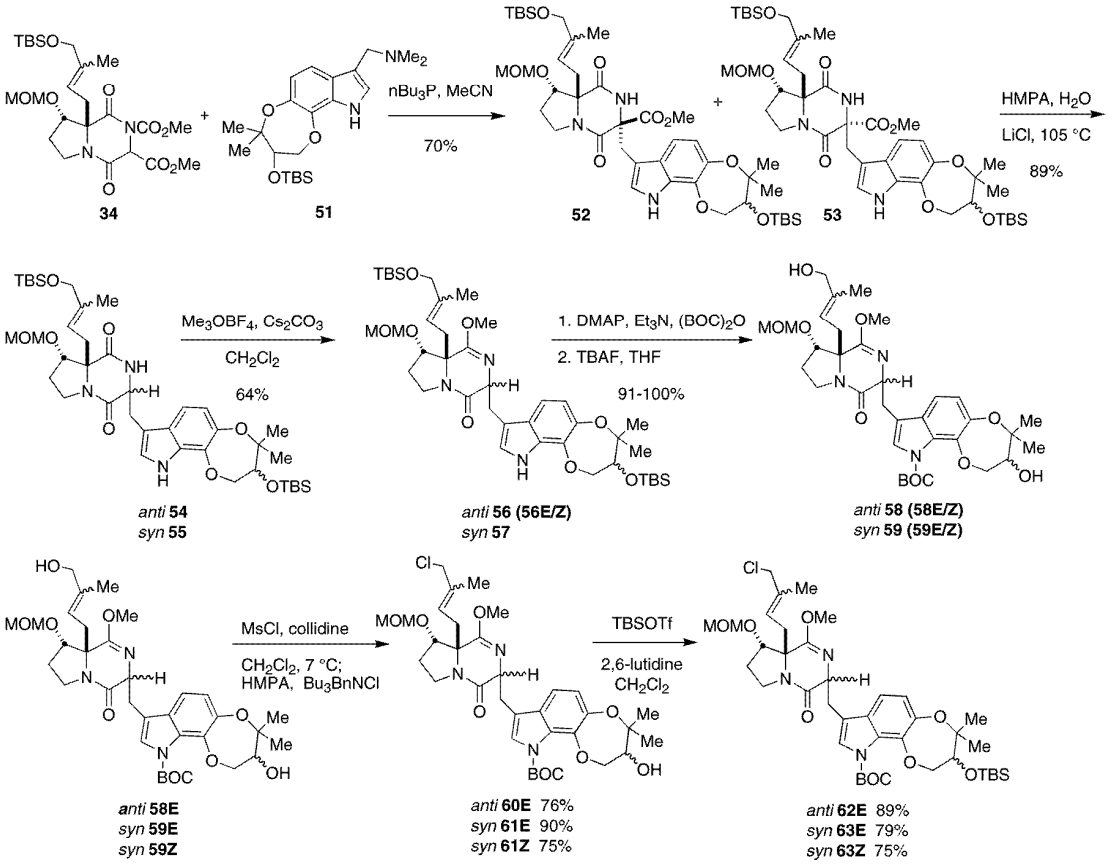
Improved Synthesis of the Gramine Derivative

With this functionalized diketopiperazine in hand, we turned our attention to improvement of the synthesis of the dioxepin-containing indole fragment that we originally described in 1990.[26] The original route provides compound **51** in 14 steps with no chromatography required until the ninth step. However, further optimization was necessary to achieve a more rapid and efficient large-scale synthesis. The route we have developed is illustrated in Scheme 5. Vanillin (**38**) was acetylated with acetic anhydride and then treated with fuming nitric acid to afford **39**, the desired regioisomer, and **40**, the undesired isomer, in an ~10:1 ratio. Initially, these regioisomers were separated by hydrolysis of the acetate group and isolation of the desired phenol isomer by crystallization.[27] Analysis of the product mixture by TLC revealed that **39** had a lower R_f and **40** had exactly the same R_f as that of the starting material, and it was possible to isolate **39** by flash chromatography. However, neither purification method proved optimal for a large-scale protocol. The new approach circumvents these problems. Instead, we directly used the mixture of nitrobenzaldehydes **39** and **40**. After a three-step transformation,[28] **39** provided the desired acid **41**, and **40** provided the undesired acid **42**. Reduction of the nitro group was originally carried out in 95% yield by hydrogenation over palladium on carbon at 40 psi and 80 °C. However, this protocol could prove awkward on a large scale, so an alternative approach was developed using iron and NH_4Cl[29] which, while the yield (74%) is more moderate, proved easier to scale-up. On reduction to the corresponding amines, the amine intermediate from **41** cyclized to oxindole **43**, but **42** was simply reduced to amino acid **44**, which cannot undergo an intramolecular cyclization reaction due to geometric restriction. On extraction of the reaction mixture, the amino acid (**44**) was removed with aqueous acid leaving the oxindole (**43**) in the organic phase. Demethylation then proceeded smoothly as already described to give **45**.[30]

Prenylation of **45** is partially selective for the 7-hydroxy position due to the greater acidity of this hydroxyl group. However, under the prenylation conditions originally developed for paraherquamide B, small amounts of the 6-prenyloxy and 6,7-diprenyloxy isomers were also formed, and the three compounds are difficult to separate by flash chromatography. In this modification of our original route, replacement of the base with Cs_2CO_3 improves the selectivity and yield of **46**.

(26) Williams, R. M.; Cushing, T. D. *Tetrahedron Lett.* **1990**, *31*, 6325−6328.
(27) Raiford, L. C.; Stocsser, W. C. *J. Am. Chem. Soc.* **1928**, *50*, 2556−2563.
(28) (a) MacDonald, S. F. *J. Chem. Soc.* **1948**, 376−378. (b) Beer, R. J. S.; Clarke, K.; Davenport, H. F.; Robertson, A. *J. Chem. Soc.* **1951**, 2029−2032.
(29) Wissner, A.; Berger, D. M.; Boschelli, D. H.; Floyd, M. B., Jr.; Greenberger, L. M.; Gruber, B. C.; Johnson, B. D.; Mamuya, N.; Nilakantan, R.; Reich, M. F.; Shen, R.; Tsou, H.-R.; Upeslacis, E.; Wang, Y. F.; Wu, B.; Ye, F.; Zhang, N. *J. Med. Chem.* **2000**, *43*, 3244−3256.
(30) Since this route was developed, McWhorter and Savall have published a route to **45** which is shorter and higher yielding, but the applicability of their synthesis on a large scale has not yet been demonstrated. Savall, B. M.; McWhorter, W. W. *J. Org. Chem.* **1996**, *61*, 8696−8697.

Scheme 6. Coupling of the Indole and Diketopiperazine



Extraction into base during the workup procedure also removes the diprenylated byproduct which allowed for easier purification.

A major problem in our first generation synthesis of the gramine derivative was during reduction of the oxindole to the indole, when over-reduction to the indoline occurred in variable quantities giving a ratio of 4:1 to 2:1 of indole/indoline. Attempts were made, without success, to effect a more selective reduction of the oxindole. However, the problem was solved in an indirect fashion as it proved possible to oxidize the indoline byproduct to the indole with DDQ[31] in greater than 90% yield.

Formation of TBS ethers on hindered alcohols is known to be very sensitive to the concentration of the reaction mixture. The silylation reaction was optimized by concentrating the reaction mixture to give an improved yield of 95% from 82%. Finally indole **50** was converted to the gramine derivative **51** under standard conditions. The advantages of this new approach are significant in terms of increased yield, lower cost, and faster synthesis on a large scale.

Coupling of the Indole and Diketopiperazine

Somei−Kametani coupling[32] of diketopiperazine **34** with the gramine derivative **51** in the presence of tri-*n*-butylphosphine gave a separable mixture of two diastereomers **52** and **53** in a 3:1 ratio, each as a mixture of four diastereomers (Scheme 6).[33] Decarbomethoxylation was effected by treatment of **52** and **53** individually with LiCl in hot, aqueous HMPA to provide, in both cases, a mixture of **54** (*anti*-isomer) and **55** (*syn*-isomer), which could now be separated into the *E* and *Z* isomers, each of which as a mixture of two diastereomers (epimeric at the dioxepin secondary alcohol). However, as separation of the geometric isomers proved to be difficult, the compounds were usually carried through the synthetic sequence as a mixture and separated only for analytical purposes. Protection of the secondary amide as the corresponding methyl lactim ether was accomplished by treating **54** and **55** with trimethyloxonium tetrafluoroborate and Cs_2CO_3 in dichloromethane. Model studies had shown that Cs_2CO_3 was a more efficient base than Na_2CO_3 for this reaction, as it leads to a lower incidence of TBS cleavage and *N*-methylation. Next, the indole nitrogen was protected as the corresponding *N*-*t*-BOC derivative by treatment with di-*tert*-butyl dicarbonate in the presence of DMAP, and then the silyl ethers were removed with tetrabutylammonium fluoride (TBAF) to provide **58** (*anti*) and **59** (*syn*). From this point onward, the *E* and *Z* isomers were utilized separately. Unfortunately, the Corey procedure,[34] which had been successful

(31) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417−6418.
(32) (a) Somei, M.; Karasawa, Y.; Kaneko, C. *Heterocycles* **1981**, *16*, 941−949. (b) Kametani, T.; Kanaya, N.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 959−963.
(33) The stereochemistry at the newly formed stereogenic centers in **52** and **53**, and in all subsequent compounds, was assigned on the basis of ^{1}H NMR data. In compounds where the indole substituent is on the same face of the diketopiperazine as the MOM ether, the signal for the methoxy group is at significantly higher field than in the situation where these two substituents are on opposite faces. This is due to the proximity of the methoxy group to the shielding effects of the aromatic system.
(34) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 4339−4342.

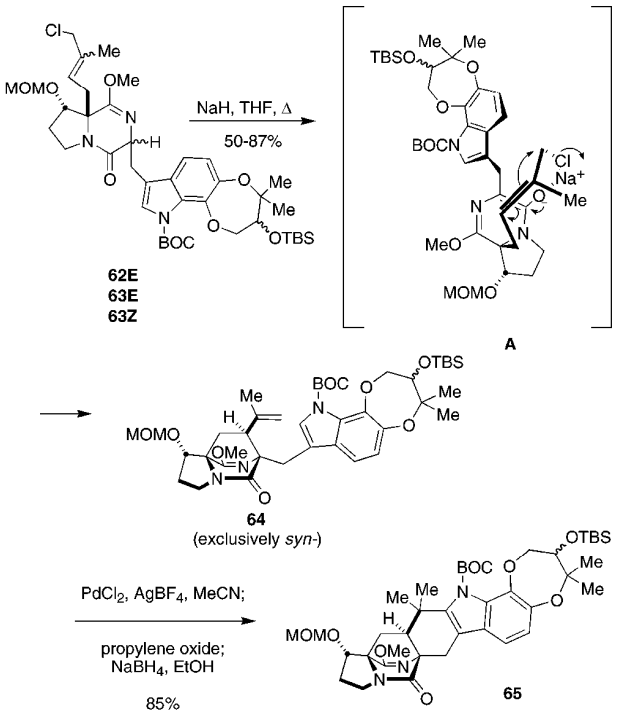
in the synthesis of paraherquamide B for conversion of an allylic alcohol to the corresponding chloride, proved unreliable when applied to the paraherquamide A system. Under the conditions used previously, cleavage of the lactim ether and chlorination at the 2-position of the indole were observed. Extensive investigation into suitable conditions was carried out, and it was eventually found that selective conversion of the primary alcohols **58** and **59** to the corresponding mesylates was possible in the presence of the hindered base collidine. Displacement of mesylate by a chloride ion under these reaction conditions was very slow so Bu_3BnNCl (as an external chloride source) and a polar solvent were added to accelerate the reaction, allowing formation of the allylic chlorides (**60** and **61**) in up to 90% yield. This is a simple, practical, and reproducible method for preparing allylic chlorides in molecules bearing labile functional groups. Finally, careful reprotection of the secondary alcohols with *tert*-butyldimethylsilyl triflate in the presence of 2,6-lutidine afforded the key allylic chlorides **62** and **63**.

S_N2' Cyclization and Closure of the Seventh Ring

The stage was now set for the critical intramolecular S_N2' cyclization, that sets the relative stereochemistry at C-20 during formation of the bicyclo[2.2.2]diazaoctane ring nucleus. Based on precedent from the paraherquamide B synthesis,[19] **63E** was treated with NaH in refluxing benzene. However, the reaction was very slow and gave the desired cyclization product **64** in only 25% yield, accompanied by products from competing pathways. The acidic proton in **63E** is more sterically hindered than in the corresponding substrate for the paraherquamide B synthesis, due to the presence of the MOM ether. Since NaH likely exists as heterogeneous clusters in benzene, it was expected that use of a more coordinating solvent may break up the clusters and render deprotonation more facile. Conveniently, use of NaH in refluxing THF afforded the desired S_N2' cyclization product **64** in 87% yield from **63E** exclusively as the desired *syn*-isomer.[35] This remarkably diastereoselective intramolecular S_N2' cyclization reaction proceeds, in a nonpolar solvent like THF, via a tight, intramolecular ion-pair driven cyclization ("closed" transition state)[36] as shown in Scheme 7. Compound **62E** also underwent the same transformation to give **64** in 82% yield. In both cases, the product was sometimes accompanied by a small amount of Boc-deprotected cyclized product which could be reprotected under standard conditions. In addition, it was interesting to note that the *Z*-isomer, **63Z**, provides the same cyclization product, again with exclusive *syn* selectivity, in 50% yield.

Closure of the seventh ring was attempted using $PdCl_2$ and $AgBF_4$ in acetonitrile followed by $NaBH_4$ to reduce the incipient heptacyclic σ-palladium adduct,[37] reaction conditions which had been successful in the paraherquamide B synthesis.[19] However, the only products isolated under the same conditions with **64** were those appearing to arise from removal of the *N*-*t*-BOC, MOM and lactim ether protecting groups, presumably by HBF_4 generated in situ. To buffer the reaction mixture, propylene oxide was added as an acid scavenger and the reaction now proceeded to give the desired 2,3-disubstituted indole (**65**) in 85% yield.

Scheme 7. Formation of the Heptacycle

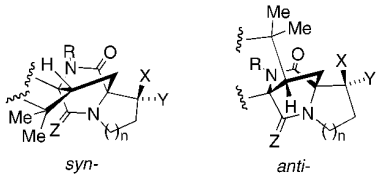


Completion of the Synthesis

Conditions could not be found which would allow direct and high-yielding conversion of the lactim ether (**65**) to the amide. However, use of 0.1 M aqueous HCl in THF gave the corresponding ring-opened amine methyl ester (**66**) which was recyclized to the bicyclo[2.2.2]diazaoctane (**67**) by treatment of **66** with catalytic 2-hydroxypyridine in hot toluene. Chemoselective reduction of the tertiary amide in the presence of the secondary amide to give **68** could be effected by treatment of the diamide **67** with the AlH_3-Me_2NEt complex followed by quenching with sodium cyanoborohydride, methanol, and acetic acid, as used in the synthesis of paraherquamide B. However, use of excess diisobutylaluminum hydride (DIBAL-H) in dichloromethane was a simpler experimental procedure and gave improved yields of **68**.[38] *N*-Methylation of the secondary amide proceeded smoothly and was followed by cleavage of the MOM ether with bromocatecholborane.[39] Oxidation of the secondary alcohol with Dess–Martin periodinane[40] and concomitant removal of the *N*-*t*-BOC group and TBS ether with TFA gave ketone **70** (Scheme 8).

The final critical oxidative spirocyclization of the 2,3-disubstituted indole was effected by a two-step procedure.

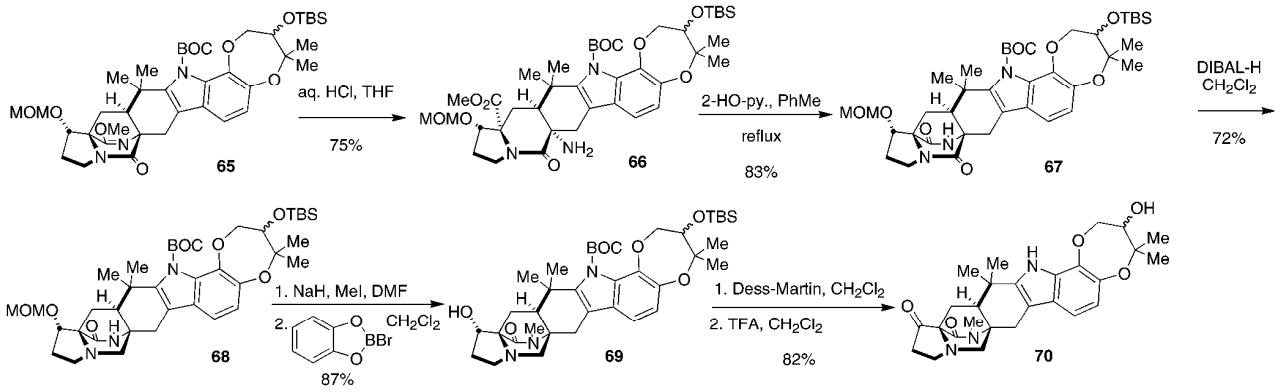
(35) The *syn*/*anti* relationship in this case refers to the relative stereochemistry between the C-20 stereogenic center (see paraherquamide numbering) and the proline residue.



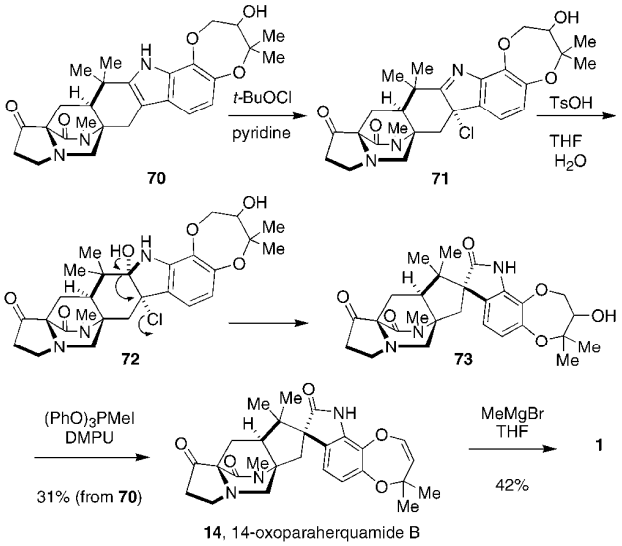
(36) (a) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 8032–8034. (b) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 2177–2194.

(37) Trost, B. M.; Fortunak, J. M. D. *Organometallics* **1982**, *1*, 7–13.
(38) Fukuyama, T.; Liu, G. *Pure Appl. Chem.* **1997**, *69*, 501–505.
(39) Boeckman, R. K., Jr.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411–1414.
(40) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

Scheme 8. Manipulation of the Heptacycle



Scheme 9. Spirocyclization and Completion of the Synthesis



Treatment of **70** with *tert*-butyl hypochlorite in pyridine provided a labile 3-chloroindolenine, from which it was found necessary to rigorously remove, by azeotroping with benzene, all of the pyridine prior to the next step. Pinacol-type rearrangement with TsOH in aqueous THF then generated the desired *spiro*-oxindole (**73**). From our investigations during the paraherquamide B synthesis, it was found that use of a sterically demanding amine such as pyridine gives the best stereoselectivity during the chlorination reaction. It is assumed that addition of chlorine to **70** proceeds from the least hindered face of the indole giving the α-chloroindolenine **71**. Hydration of the imine functionality, interestingly, must also occur from the same α-face, that is, *syn*-to the relatively large chlorine atom, to furnish the *syn*-chlorohydrin **72** which subsequently rearranges stereospecifically to the desired *spiro*-oxindole **73** (Scheme 9).

Dehydration of the seven-membered ring in **73** with methyl triphenoxyphosphonium iodide (MTPI) in DMPU afforded 14-oxoparaherquamide B (**14**) in moderate yield.[17] This intermediate has been previously obtained semisynthetically from marcfortine A by a group from Pharmacia−Upjohn, and comparison of the authentic and synthetic materials confirmed the identity of this substance. Addition of methylmagnesium bromide to the ketone group of **14** has been previously described to give paraherquamide A along with the corresponding C-14 epimer in around 50% yield.[17a] Employment of this protocol using MeMgBr with our synthetic ketone gave (−)-paraherquamide A (**1**) as the exclusive product (the C-14 epimer was not detected) in 42% yield. This product was identical to a natural sample of paraherquamide A by ^{1}H NMR, ^{13}C NMR, IR, exact mass, and mobility on TLC (R_f). A synthetic sample was recrystallized from ether and had mp 250 °C (dec), $[\alpha]_D^{25}$= −22 (c = 0.2, MeOH). Natural paraherquamide A recrystallized from ether under the same conditions yielded a sample with mp 250 °C (dec) and $[\alpha]_D^{25}$ = −21 (c = 0.2, MeOH). All intermediates up to the final product have an enantiomeric ratio of approximately 97.5:2.5; the final synthetic paraherquamide A upon recrystallization from ether is approximately optically pure.

We have reported here the first total synthesis of paraherquamide A, the most biologically potent member of this family of compounds. This asymmetric synthesis proceeds in 46 steps from commercially available materials, with the longest linear sequence being 34 steps.

The approach developed in this study makes it feasible to examine the design and synthesis of other members of the paraherquamide family and should also permit access to structurally unique paraherquamides that may have significant biological properties. The application of this methodology to the asymmetric, stereocontrolled total synthesis of other members of the paraherquamide family, and evaluation of their properties is currently under study in these laboratories.

Acknowledgment. This work was supported by the NIH (Grant CA 70375). The Japanese Society for the Promotion of Science (JSPS) is acknowledged for providing fellowship support to H.T. Mass spectra were obtained on instruments supported by the NIH Shared Instrumentation Grant GM49631. We also wish to thank Dr. Timothy Blizzard of Merck & Co. for providing an authentic sample of natural paraherquamide A. We also wish to acknowledge Dr. Byung H. Lee of the Pharmacia−Upjohn Co. (now Pfizer) for providing NMR spectra and an authentic specimen of 14-oxoparaherquamide B. We also wish to thank Dr. Alfredo Vazquez for assistance with purification and characterization of synthetic paraherquamide A.

Supporting Information Available: Complete experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA036713+

EXHIBIT 17

J. Am. Chem. Soc. 1996, *118*, 557−579 557

Stereocontrolled Total Synthesis of (+)-Paraherquamide B[⊥]

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Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received August 7, 1995[⊗]

Abstract: The convergent stereocontrolled, asymmetric total synthesis of (+)-paraherquamide B is described. Key features of this synthesis include (1) an improved procedure to effect reduction of unprotected oxindoles to indoles; (2) a complex application of the Somei/Kametani coupling reaction; (3) a high-yielding and entirely stereocontrolled intramolecular S_N2' cyclization reaction that constructs the core bicyclo[2.2.2] ring system; (4) a mild Pd(II)-mediated cyclization reaction that constructs a complex tetrahydrocarbazole; and (5) the chemoselective reduction of a highly hindered tertiary lactam in the presence of an unhindered secondary lactam, utilizing precoordination of the more reactive secondary lactam to triethylaluminum.

Introduction

The paraherquamides are complex, heptacyclic, toxic mold metabolites with potent anthelmintic activity isolated from various *Penicillium* sp. The parent and most potent derivative, paraherquamide A (**1**), was first isolated from *Penicillium parherquei* in 1980 by Yamazaki.[1] The simplest member, paraherquamide B (**2**), plus five other structurally related paraherquamides C−G (**3**−**9**) were isolated from *Penicillium charlesii* (*fellutanum*) (ATCC 20841) in 1990 at Merck & Co.[2,3] and concomitantly at SmithKline Beecham.[4] More recently three additional related compounds were discovered by the same group at SmithKline.[5] Interest in the paraherquamides has come from the finding that this class of alkaloids displays potent anthelmintic and antinematodal properties.[6,7]

There are essentially three classes of broad-spectrum anthelmintics currently in use: the benzimidazoles, the levamisoles/morantels, and the avermectins/milbemycins. Unfortunately, the first two groups have lost much of their utility due to the recent appearance of drug resistance built up by the helminths.[7a,8] More recently drug resistance to the avermectins has been observed in various parasites.[9] The paraherquamides represent an entirely new structural class of antiparasitic agents, which promise to play a significant role in the near future. The relatively low culture yields of paraherquamide obtained for biological study have slowed the development and potential commercialization of these agents (Figure 1).

As part of our ongoing efforts to elucidate the biosynthesis of the core bicyclo[2.2.2] ring system of the related alkaloids the brevianamides,[10] we have applied methodology originally developed for the stereocontrolled total synthesis of (−)-brevianamide B[11] to complete the first stereocontrolled total synthesis of (+)-paraherquamide B (**12**);[12] the results of this study are described in full herein.

The paraherquamides are structurally very similar to brevianamides A and B (**17** and **16**)[13] and marcfortines A−C (**13**−**15**)[14] with respect to the common core bicyclo[2.2.2] ring system that is derived from the cycloaddition of an isoprene unit across the amino acid α-carbons. This close structural similarity might imply a related biogenesis, and the structural features of these substances shall be described briefly from this standpoint. The paraherquamides and brevianamides A and B (**17** and **16**) appear to be derived from the condensation of tryptophan and proline, while the marcfortines are formed from the condensation of tryptophan and pipecolic acid. The origin of the methyl group in the pyrrolidine ring of paraherquamides A and C−E and VM55595-7 could in principle come from the methylation of proline, but it seems more likely that this amino acid residue is derived from isoleucine. The very low fermentation yield of paraherquamide B may be a manifestation of poor incorporation of cyclo-L-trp-L-pro into the subsequent biosynthetic machinery

[⊥] Dedicated to Professor Ei-ichi Negishi on the occasion of his 60th birthday.

[†] On leave from the Department of Organic Chemistry of the University of Valencia, Spain.

[‡] Present address: Tularik Inc., 270 East Grand Ave., South San Francisco, CA 94080.

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1995.

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(9) (a) Van Wyk, J. A.; Malan, F. S. *Vet. Rec.* **1988**, *123*, 226. (b) Echevarria, F. A. M.; Trindade, N. P. *Vet. Rec.* **1989**, *124*, 147.

(10) (a) Sanz-Cervera, J. F.; Glinka, T.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 347. (b) Sanz-Cervera, J. F.; Glinka, T.; Williams, R. M. *Tetrahedron* **1993**, *49*, 8471.

(11) (a) Williams, R. M.; Glinka, T.; Kwast, E. *J. Am. Chem. Soc.* **1988**, *110*, 5927. (b) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 808. (c) Williams, R. M.; Glinka, T.; Kwast, E. *Tetrahedron Lett.* **1989**, *30*, 5575.

(12) A preliminary account of this work has appeared: Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 9323.

(13) (a) Birch, A. J.; Wright, J. J. *J. Chem. Soc., Chem. Commun.* **1969**, 644. (b) Birch, A. J.; Wright, J. J.; *Tetrahedron* **1970**, *26*, 2339. (c) Birch, A. J.; Russell, R. A. *Tetrahedron* **1972**, *28*, 2999. (d) Baldas J.; Birch, A. J.; Russell, R. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 50.

(14) (a) Polonsky, J.; Merrien, M. A.; Prange, T; Pascard, C. *J. Chem Soc., Chem Commun.* **1980**, 601. (b) Prange, T.; Billion, M.-A.; Vuilhorgne, M.; Pascard, C.; Polonsky, J. *Tetrahedron Lett.* **1981**, *22*, 1977.

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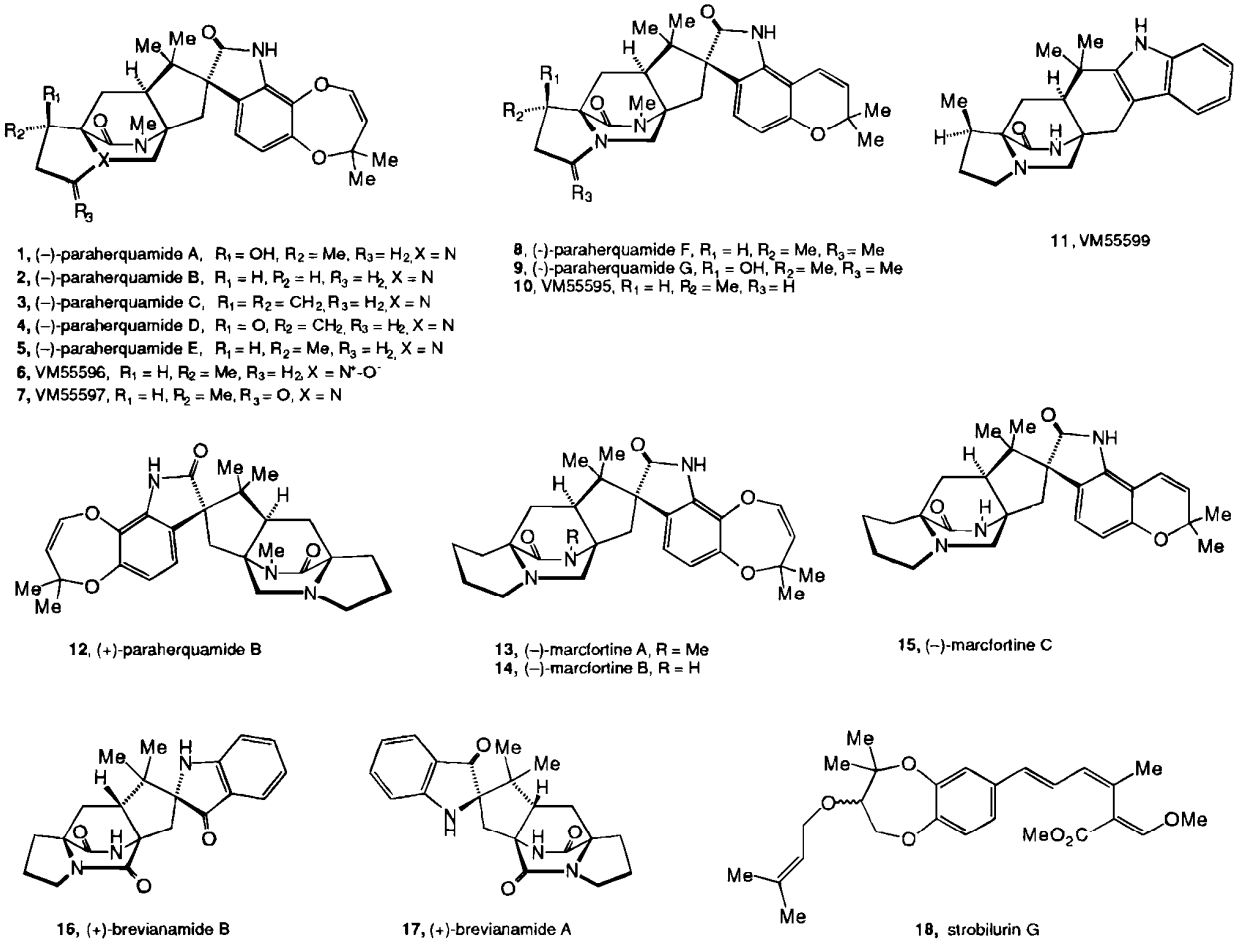


Figure 1.

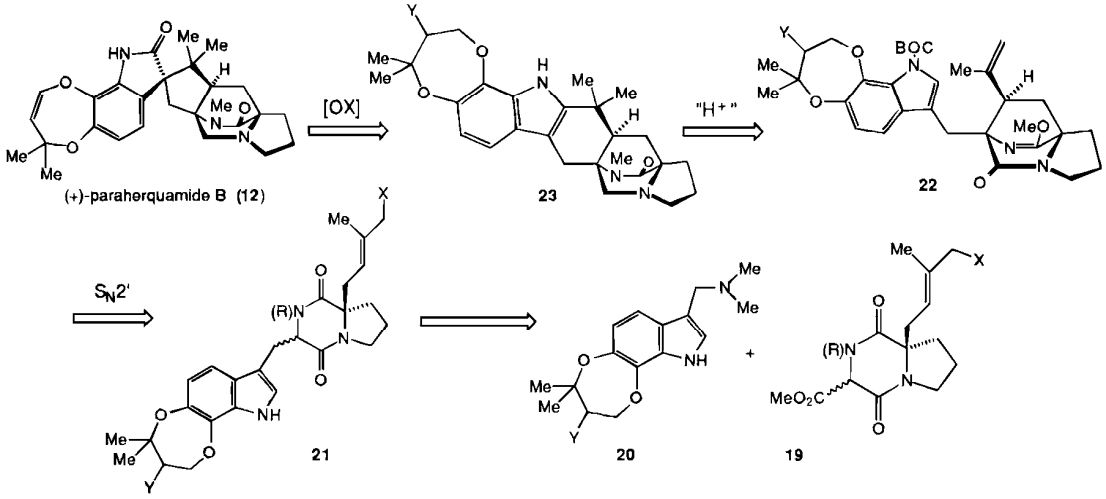
or may be the result of inefficient demethylation of the isoleucine-derived amino acid precursor.

The oxidation state of the amino acid-derived dioxopiperazine moiety remains unchanged in the case of the brevianamides, but for the paraherquamides and the marcfortines the tertiary amide residue is enzymatically reduced to a monooxopiperazine, a process that is known.[15] The tryptophan-derived indolyl side chain of the paraherquamides and marcfortines is oxidized to spiro-oxindoles while the indolyl side chain of the brevianamides oxidize to spiro-indoxyls. The paraherquamides, marcfortines, and brevianamides all incorporate one isoprene unit that forms the bridging bicyclo[2.2.2] ring structure. The paraherquamides and marcfortines differ from the brevianamides in that a second isoprene unit coupled with an oxidized form of tryptophan gives the dioxepin (or pyran) moiety. This is one of the most interesting and unique features of these compounds. The *gem*-dimethyl dioxepin ring found in paraherquamides A–E (**1**–**5**) and marcfortines A and B (**13** and **14**) is a unique ring system among natural products. A similar structural feature was discovered in the antifungal natural product strobilurin G (**18**),[16] but this dioxepin moiety lacks the double bond found in the other metabolites (Figure 1).

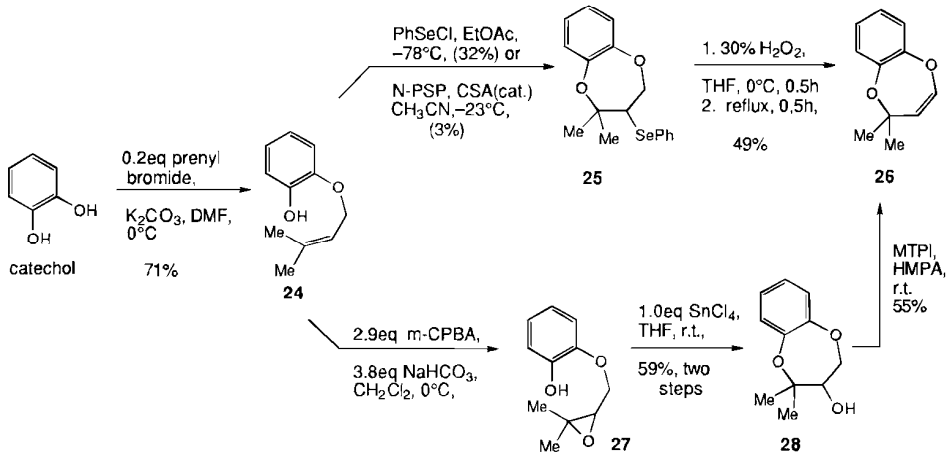
As outlined in Scheme 1, a convergent synthesis of the enantiomer of paraherquamide B (**12**)[17] was envisioned to contain four key carbon–carbon bond-forming reactions. The first task would involve the construction of a suitably α-alkylated proline derivative.[11] The second important coupling would be the Somei/Kametani-type alkylation[18] of a suitably protected gramine derivative (**20**) and the requisite piperazinedione (**19**). The third and perhaps most crucial C–C bond-forming reaction, providing the core bicyclo[2.2.2] ring system, was a stereofacially controlled intramolecular S_N2' cyclization reaction that sets the stereochemistry at C-20 (paraherquamide numbering) and concomitantly installs the isopropenyl group that will be utilized in the fourth C–C bond-forming reaction. This isopropenyl group, in turn, would be conscripted for an olefin–cation cyclization to provide the heptacyclic tetrahydrocarbazole. Standard procedures to effect this transformation involve strong protic acids,[11,19] and there was reason for concern about the reactivity of the more highly oxygenated indole (**22**) as a practical synthetic precursor to **23**. The penultimate step, a regio- and stereofacially controlled oxidative spirocyclization reaction, must be accomplished to construct the desired spirooxindole. A number of these transformations were explored during the course of the investigations on the synthesis of (–)-brevianamide B,[11] including a simple oxindole model study,[11c] which set a firm foundation for addressing some of the

(15) Bond, R. F.; Boeyens, J. C. A.; Holzapfel, C. V.; Steyn, P. S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1751.
(16) Fredenhagen, A.; Hug, P.; Peter, H. H. *J. Antibiot.* **1990**, *48*, 661.
(17) The enantiomer of the natural product was selected as the target due to the large relative cost difference between (*S*)- and (*R*)-proline.
(18) (a) Somei, M.; Karasawa, Y.; Kaneko, C. *Heterocycles* **1981**, *16*, 941. (b) Kametani, T.; Kanaya, N.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 3974.
(19) (a) Stoermer, D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 564. (b) Guller, R.; Dobler, M.; Borschberg, H.-J. *Helv. Chim. Acta* **1991**, *74*, 1636. (c) Darbre, T.; Nussbaumer, C.; Borschberg, H.-J. *Helv. Chim. Acta* **1984**, *67*, 1040. (d) Delpech, B.; Khuong-Huu, Q. *J. Org. Chem.* **1978**, *43*, 4898.

Scheme 1



Scheme 2



stereochemical and regiochemical issues that would be faced in attacking the paraherquamide ring system.

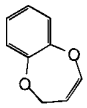
Results and Discussion

Construction of the Dioxepinooxindole Ring System. The prenylated catechol ring system of the paraherquamides is an unusual oxidative cyclization product that previously has not been observed to occur in metabolites of mixed biogenetic origin. Although the parent 2*H*-1,5-benzodioxepin has been synthesized previously,[20] to the best of our knowledge there has been no reported synthesis of the corresponding isoprenyl dioxepin ring system of paraherquamide. The synthesis of this ring system was explored in a simple model study employing prenylated catechol **24** (Scheme 2).[21] It was speculated that the requisite 7-*endo-tet* cyclization reaction would be facilitated by a stabilized tertiary carbocation provided by the prenyl substituent.

The first attempt at effecting this cyclization reaction employed a phenylselenoetherification.[22] Following a procedure of Clive,[23] **24** cyclized to **25** with either PhSeCl or *N*-phenylselenophthalimide (N-PSP),[24] although in very low yield. The main byproducts came from the electrophilic addition across the double bond, electrophilic aromatic substitution of the phenyl ring by the phenyl selenide, and phenolic attack at the methylene producing the six-membered-ring product. The selenide **25** was treated with H_2O_2 and the resulting selenoxide thermally eliminated providing the unique dioxepin **26** in 49% yield.

Due to the low yield of the phenylselenoetherification, an alternative procedure involving epoxidation followed by a Lewis acid-mediated ring closure was investigated.[25] The prenylated catechol **24** was epoxidized with buffered *m*-CPBA to provide epoxide **27**, which was treated with stannic chloride to give the dioxepin **28**. A major side product in this reaction was a ketone,

(20) Guillaumet, G.; Coudert, G.; Loubinnoux, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 64.



2H-1,5-benzodioxepin

(21) Williams, R. M.; Cushing, T. D. *Tetrahedron Lett.* **1990**, *31*, 6325.

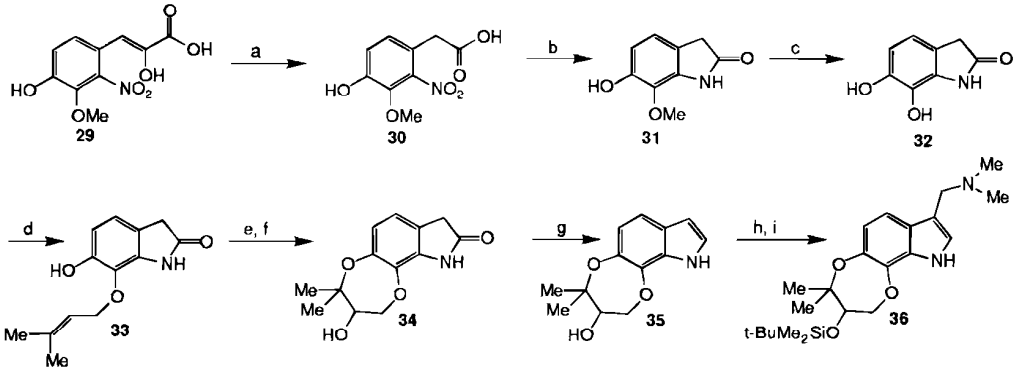
(22) (a) Nicolaou, K. C. *Tetrahedron* **1981**, *37*, 4097. (b) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784. (c) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049−1132.

(23) (a) Clive, D. J. L.; Chiiattu, G.; Curtis, N. J.; Kiel, W. A.; Wong, C. K. *J. Chem. Soc., Chem. Commun.* **1977**, 725. See also: (b) Liotta, D.; Zima, G. *Tetrahedron Lett.* **1978**, *50*, 4977. (c) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D.; Balducci, R. *J. Org. Chem.* **1990**, *55*, 429.

(24) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

(25) (a) Cookson, R. C.; Liverton, N. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1589. (b) Kocienski, P.; Love, C.; Whitby, R.; Roberts, D. A. *Tetrahedron Lett.* **1988**, *29*, 2867. See also: (c) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335.

Scheme 3[a]



[a] Reagents and conditions: (a) 4.0 equiv of NaOH, 1.0 equiv of 30% H_2O_2, 81−93%; (b) H_2, Pd/C, AcOH, 92%; (c) 2.5 equiv of BBr_3, CH_2Cl_2, −78 °C, 99%; (d) 1.2 equiv of prenyl bromide, 1.1 equiv of K_2CO_3, DMF, 0 °C to room temperature, 52%; (e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; (f) 1.2 equiv of $SnCl_4$, THF, 64%; (g) 1.6 equiv of $NaBH_4$, 3.5 equiv of $BF_3{\cdot}OEt_2$, THF, 44−50%; (h) *t*-$BuMe_2SiCl$, im, DMF, 40 °C, 83%; (i) CH_2O, $HNMe_2$, AcOH, H_2O, 99%.

resulting from a 1,2 hydride shift.[26] A number of methods were explored to effect the dehydration of the secondary alcohol of dioxepin **28**; the best result was realized with methyltriphenoxyphosphonium iodide (MTPI) in HMPA to provide **26**.[27]

With a proven method accessible for the construction of the dioxepin ring system, attention was focused on constructing the requisite gramine derivative. Oxygenated indoles are notoriously unstable and undergo facile autoxidation,[28] photooxidation,[29] dimerization, and polymerization.[30] In light of this problematic reactivity, our plan called for formation of the dioxepin ring system prior to indole (gramine) formation. The approach employed involved the formation of a suitably substituted oxindole (essentially a protected indole), followed by the construction of the dioxepin and final elaboration into the gramine derivative.

The known pyruvic acid **29** (Scheme 3)[31] (prepared in five steps from vanillin) was oxidatively decarboxylated[32] to afford the phenylacetic acid **30**, which was reductively cyclized to give the required oxindole **31**[33] in nearly quantitative yield.

At this point, a method was needed to differentiate between the two phenolic substituents for the prenylation reaction. A number of attempted selective protecting group strategies were explored, but nothing satisfactory was found; it was thus decided to forgo any protecting group for the 6-hydroxy position. Oxindole **31** was cleanly demethylated upon treatment with (clear) boron tribromide. The resulting oxindole **32** was subjected to the prenylation conditions, and the desired alkylated product **33** was obtained in 52% yield.[34,35] Both of the methods discussed above for the formation of the seven-membered ring were examined. The phenylselenoetherification procedure failed on this substrate, and only products resulting from electrophilic aromatic substitution were formed.

The alternative epoxidation/Lewis acid-mediated cyclization again proved to be successful on this substrate. The epoxidation reaction (*m*-CPBA) had to be buffered with $NaHCO_3$, to prevent the formation of the six-membered-ring tertiary alcohol. In most cases, the reaction was worked up and taken on to the next step without purification (the labile epoxide tended to cyclize to the six-membered tertiary alcohol upon contact with silica gel). The incipient epoxide product was directly treated with $SnCl_4$ in THF to provide the desired seven-membered-ring alcohol **34** (64% overall yield from **33**).

N-Alkylated oxindoles have been reported to be reduced to indoles by the use of DIBAL or $LiAlH_4$;[36] however, in the case of unsubstituted oxindoles, this reduction either fails or requires

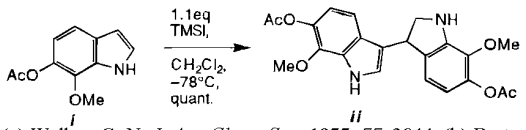
(26) For a related observation, see: Taylor, S. T.; Davisson, M. E.; Hissom, B. R., Jr.; Brown, S. J.; Pristach, H. A.; Schramm, S. B.; Harvey, S. M. *J. Org. Chem.* **1987**, *52*, 425.

(27) Hutchins, R. O.; Hutchins, M. G.; Milewski, C. A. *J. Org. Chem.* **1972**, *37*, 4191.

(28) Houlihan, W. J.; Remers, W. A.; Brown, R. K. *Indoles, Part one, The Chemistry of Heterocycles;* John Wiley & Sons, Inc.: New York, 1972.

(29) (a) Chan, A. C.; Hilliard, P. R., Jr. *Tetrahedron Lett.* **1989**, *30*, 6483. (b) d'Ischia, M.; Prota, G. *Tetrahedron* **1987**, *43*, 431.

(30) This difficulty was observed in a short synthesis of the known 6-acetoxy-7-methoxyindole (**i**). The unstable substance **i** was treated with TMSI, producing the dimer **ii** as the sole product.



i *ii*

See: (a) Walker, G. N. *J. Am. Chem. Soc.* **1955**, *77*, 3844. (b) Burton, H.; Duffield, J. A.; Prail, P. F. G. *J. Chem. Soc.* **1950**, 1062. (c) Beer, R. J. S.; Mcgrath, L.; Robertson, A.; Woodier, A. B. *J. Chem. Soc.* **1949**, 2061. (d) Beer, R. J S.; Clarke, K.; Khorana, H. G.; Robertson, A. *J. Chem. Soc.* **1948**, 2223. (e) Chan, A. C.; Hilliard, P. R., Jr. *Tetrahedron Lett.* **1989**, *30*, 6483. (f) d'Ischia, M.; Prota, G. *Tetrahedron* **1987**, *43*, 431. (g) Deibel, R. M. B.; Chedekel, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 5884. (h) Heacock, R. A. *Chem. Rev.* **1959**, *59*, 181.

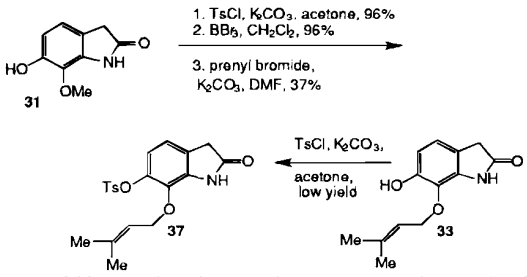
(31) (a) Beer, R. J. S.; Clarke, K.; Davenport, H. F.; Robertson, A. *J. Chem. Soc.* **1951**, 2029. (b) Bennington, F.; Morin, R. D.; Clark, L. C., Jr. *J. Org. Chem.* **1959**, *24*, 917.

(32) Kosuge, T.; Ishida, H.; Inabe, A.; Nukaya, H. *Chem. Pharm. Bull.* **1985**, *33*, 1414.

(33) This material has interesting chemical and physical characteristics. The solvent must be removed immediately after the hydrogenolysis to prevent the white product from turning to a black sludge. This oxindole **31** would also change from a white color to a metallic gray simply by drying on the vacuum pump. These decomposition properties are no doubt due to the autoxidation of the indole tautomer form.

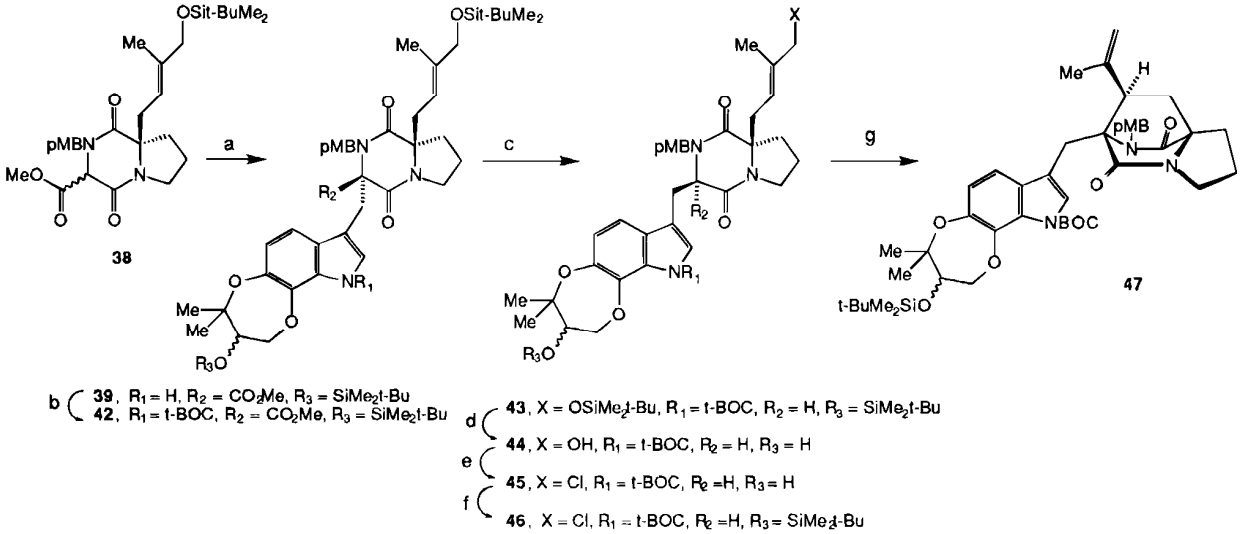
(34) The undesired regioisomer was obtained in less than 1% yield, and the bis-alkylated material was produced in only 8.3% yield. This selectivity is presumably a manifestation of the domination of inductive effects of the amide functionality directing the alkylation to the 7-position.

(35) The structure of compound **33** was confirmed by simply tosylating **33** and comparing the product (**37**) to the same substance prepared from **31**. The two independently synthesized products were identical in every way.



(36) (a) Kishi, Y.; Nakatsuka, S.; Fukuyama, T.; Havel, M. *J. Am. Chem. Soc.* **1973**, *95*, 6494. (b) Robinson, B. *Chem. Rev.* **1969**, *69*, 785.

Scheme 4[a]



[a] Reagents and conditions: (a) **36**, 0.5 equiv of PBu_3, MeCN, 51%; (b) DMAP, Et_3N, BOC_2O, CH_2Cl_2, 90%; (c) 5 equiv of LiCl, 1.5 equiv of H_2O, HMPA, 100 °C, 66%; (d) 3.0 equiv of *n*-Bu_4NF, THF, 79%; (e) 1.9 equiv of LiCl, 4.0 equiv of collidine, 4.0 equiv of MsCl, DMF, 86%; (f) *t*-$BuMe_2SiOTf$, 2,6-lutidine,CH_2Cl_2, 76%; (g) 10 equiv of NaH, benzene, 11%.

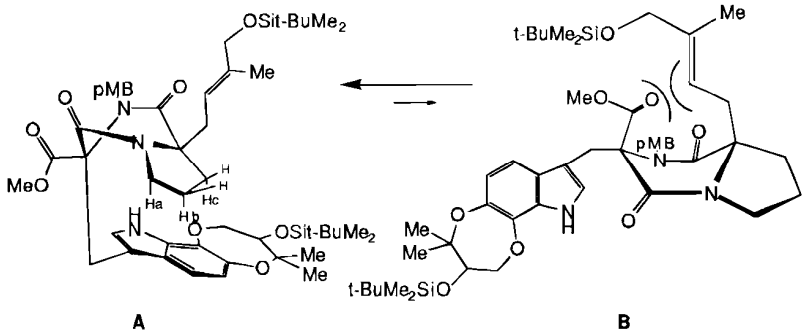


Figure 2.

more vigorous conditions. In 1972 it was reported[37] that substituted and unsubstituted oxindoles could be reduced to the corresponding indole in high yields with borane in THF at 0 °C. Oxindole **34** was subjected to these conditions (1.0 M BH_3/THF, Aldrich), but with no reaction. However, when oxindole **34** was treated with 1.6 equiv of $NaBH_4$ and 3.5 equiv of BF_3•-OEt_2 in THF for 1 day (0 °C to room temperature), the desired indole **35** was obtained in 43−50% yield. The indole **35** was treated with a warm solution of TBDMSCl and imidazole in DMF, to provide the required O-silylated indole, which was easily converted to the gramine **36** through the well-known Mannich procedure (Scheme 3).

Construction of the Bicyclo[2.2.2] Ring System. To probe the stability of the dioxepin−indole in subsequent transformations, a model study involving the previously synthesized racemic piperazinedione **38**[38] was investigated (Scheme 4). Indole **36** was condensed with the piperazinedione **38** following the Somei/Kametani conditions[18] to give the desired *syn* product **39** (a racemic mixture of two diastereomers) in 51% yield. The relative stereochemistry of this substance was evident by an examination of the ^1H NMR spectrum. There is a large upfield shift of the proline ring protons of **39** (δ Ha, Hb, Hc; 0.03−0.19 (m), 0.43−0.52 (m), 0.62−0.72 (m) ppm). It is well-known that N-alkylated piperazinediones prefer to adopt a boat-like conformation due to the planar geometry of the amides and A-1,3 steric interactions of *N*-alkyl residues. This forces the substituents on the amino acid α-carbons to adopt either pseudoaxial or pseudoequatorial dispositions. In conformer **B** (Figure 2) the carbomethoxy group is sterically congested by the bulky isopentenyl group, favoring the alternate boat conformer (**A**), which positions the indole ring under the piperazinedione, positioning the two pyrrolidine protons Ha and Hb directly over the shielding cone of the aromatic indole ring system; the corresponding *anti*-isomer cannot adopt this type of conformation. Furthermore, a consideration of the mechanism of the Somei/Kametani reaction[18] supports the expectation that the *syn*-isomer (**39**) should be the major product. The gramine derivative (**36**) reacts with tributylphosphine to form a bulky (tributylphosphino)indole intermediate that can only approach from the less congested face of the piperazinedione enolate, away from the isopentenyl moiety.

A similar phenomenon was observed when **39** was subjected to the decarbomethoxylation procedure (LiCl, H_2O, HMPA) directly. The two main products isolated were the *syn*-isomer **40** and the *anti*-isomer **41**, in a ratio of 3.3:1.0 (Figure 3). These stereochemical assignments were made by comparing the ^1H NMR spectral data of **40** and **41**. There was a pronounced upfield shift of three pyrrolidine ring protons in compound **41**, a shift that is not observed for diastereomer **40**.

Piperazinedione **39** was first converted to the BOC-protected indole **42**, which was subsequently subjected to a decarbomethoxylation reaction supplying the *syn*-diastereomer **43** as

(37) Sirowej, H.; Khan, S. A.; Plieninger, H. *Synthesis* **1972**, 84.

(38) Williams, R. M.; Glinka, T. *Tetrahedron Lett.* **1986**, *27*, 3581.

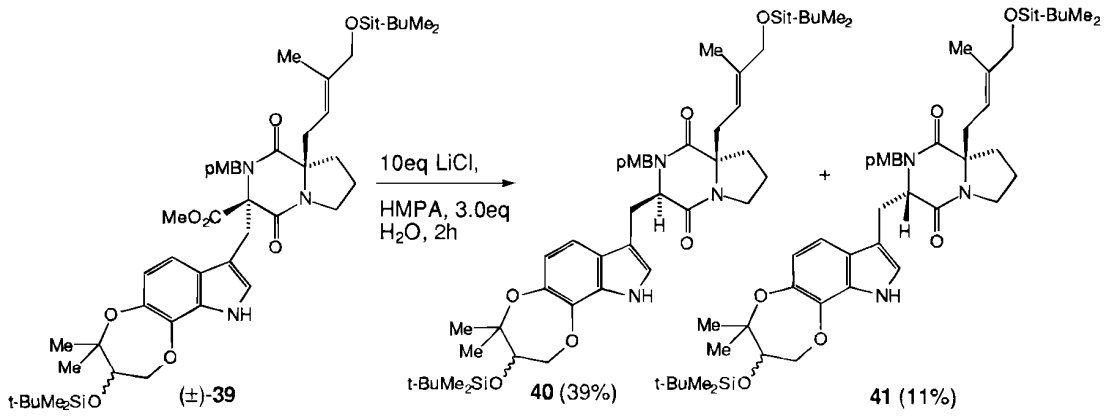
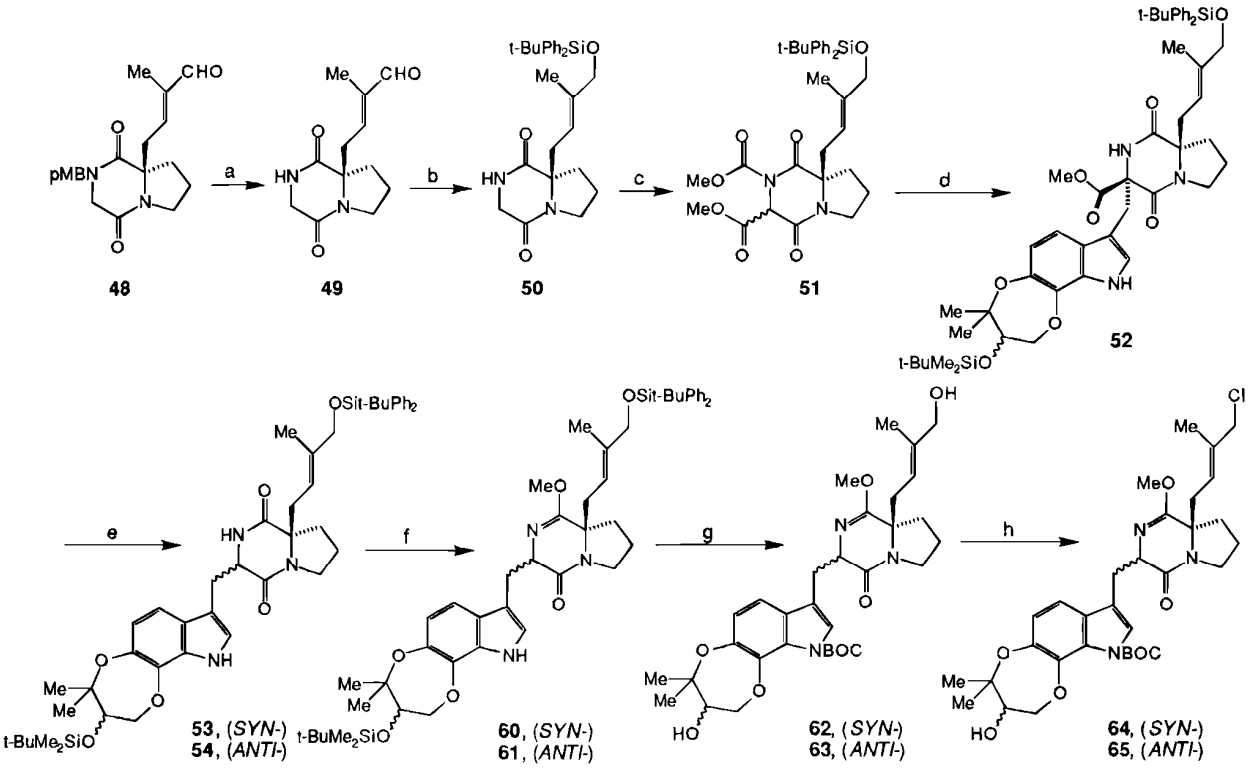


Figure 3.

Scheme 5[a]



[a] Reagents and conditions: (a) 3.8 equiv of CAN (0.33 M), 2:1 CH_3CN/H_2O, 2 h, 79%; (b) (i) 2 equiv of $NaBH_4$, EtOH; (ii) *t*-$BuPh_2SiCl$, im, DMF, 75%; (c) (i) 1.0 equiv of *n*-BuLi, 1.1 equiv of MeOCOCl, −78 °C; (ii) 2.2 equiv of $LiN(SiMe_3)_2$, 1.1 equiv of MeOCOCl, THF, −100 °C, 93%; (d) **36**, 0.5 equiv of PBu_3, CH_3CN, reflux, 73%; (e) LiCl, HMPA, 100 °C (*syn*/*anti* 3:1), 89%; (f) Me_3OBF_4, Na_2CO_3, CH_2Cl_2 (*syn*, 81%; *anti*, 62−71%); (g) (i) BOC_2O, DMAP, Et_3N, CH_2Cl_2; (ii) *n*-Bu_4NF, THF (*syn*, 90%; *anti*, 85%); (h) NCS, Me_2S (*syn*, 74−81%; *anti*, 86%).

the major product. Compound **43** (the minor, *anti*-diastereomer was not utilized) was desilylated to provide the diol **44**, which was converted to the allylic chloride **45**. Careful treatment of **45** with *t*-$BuMe_2SiOTf$, to prevent transesterification of the BOC groups,[39] gave the desired product **46** in 76% yield. Allylic chloride **46** was subjected to 10 equiv of NaH in refluxing benzene, but the reaction proved extremely sluggish. After 5 days, the desired product **47** was obtained in a poor 11% yield (19% based on recovered **46**; accompanied by extensive decomposition). The *syn*-isomer **47** was the only stereoisomer formed in this reaction; the corresponding *anti*-isomer was not detected. While this reaction demonstrated the potential viability of the stereoselective intramolecular S_N2' reaction, work on the racemic model system was halted, due to the low yield in this key transformation coupled with perceived difficulties associated with removing the *N*-*p*-methoxybenzyl group.

Total Synthesis of (+)-Paraherquamide B. Starting from the known piperazinedione **48** (prepared in eight steps from (S)-proline),[11] the enal **49** was obtained in 79% yield by treatment of **48** with a 0.33 M solution of ceric ammonium nitrate (Scheme 5).[40] The resulting product (**49**) was reduced with $NaBH_4$ and protected with *t*-$BuPh_2SiCl$ in a two-step process to give the silyl ether **50** in 75% yield. Compound **50** was then subjected to a two-step, one-pot acylation providing the required substrate **51** in 93% yield. The crude material was a mixture of epimers in a ratio of approximately 4:1 (*syn*:*anti*). Interestingly this mixture had a tendency to epimerize during column chroma-

(39) Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150.

(40) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001.

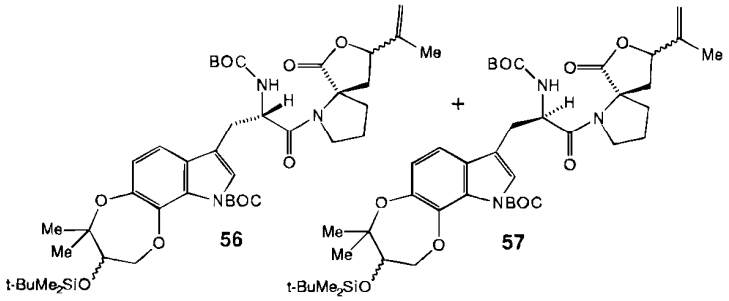
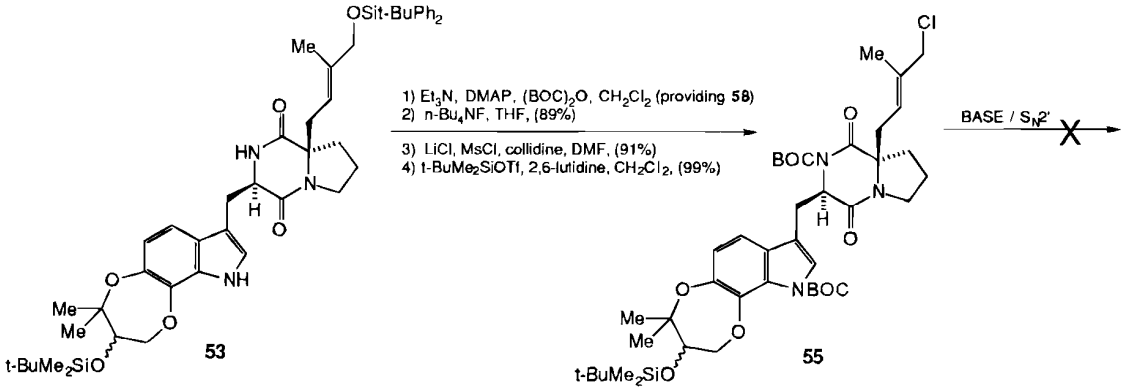


Figure 4.

Scheme 6



tography, resulting in an increase in the proportion of the *syn*-isomer. The two products were combined and condensed with the gramine **36** providing the indole **52** in 73% yield as a mixture of two diastereomers (epimeric at the secondary alcohol stereogenic center). Interestingly, the imidic carbamate group was also cleaved in the course of this reaction. Compound **52** was subjected to the decarbomethoxylation procedure, affording a 3:1 mixture of **53** (*syn*) and **54** (*anti*) in 89% combined yield.

The lactam **53** could be converted to the *N*-BOC-protected allylic chloride **55** in four steps and in good overall yield (Scheme 6), but numerous attempts to effect the S_N2' reaction on this substrate failed. These reactions were capricious and were accompanied by the occasional appearance of the spirolactones **56** and **57**, formed in low yield <5% (Figure 4). It seems likely that the failure of **55** to cyclize in the desired fashion can be attributed to nonbonding interactions between the *tert*-butoxycarbonyl group and the pendant dioxepin indole.[41,42]

These observations dictated that a suitable amide protecting group would have to be selected that was less electron withdrawing and less sterically demanding than both the *tert*-butoxycarbonyl and the *p*-methoxybenzyl groups. The loss of the lactam methoxycarbonyl group in the alkylation of **51** with the gramine **36** was presumably due to N → N acyl transfer to dimethylamine, a byproduct of the Somei/Kametani reaction. This appears to be a general reaction that was used to selectively deprotect the *N*-*tert*-butoxycarbonyl group of **58** without deblocking the *N*-*tert*-BOC-protected indole. Thus, refluxing a solution of **58** and Me_2NH in CH_3CN furnished compound **59** in 92% yield[43] (Scheme 7).

The strategy planned for the reduction of the tertiary amide called for the protection of the secondary lactam as a lactim ether,[44] and this group seemed suitable for use earlier in the synthesis and appeared compatible with the S_N2' cyclization. Thus, *syn*-isomer **53** was treated with 20 equiv (optimum) of Na_2CO_3 and 5 equiv of Me_3OBF_4 in dichloromethane for 4 h, to yield 81% of compound **60**. Even though the next two reactions could be carried out in a stepwise fashion, it proved most convenient to convert **60** directly to the protected diol **62** in a one-pot, two-step sequence. Diol **62** was then subjected to the chlorination procedure successfully used in the conversion of diol **44** to the allylic chloride **45**. Unfortunately, under these conditions, the reaction failed and the lactim ether was cleanly deblocked back to the lactam. This problem was finally solved by following the procedure of Corey,[45] which called for the addition of compound **62** to a mixture of *N*-chlorosuccinimide and dimethyl sulfide, which yielded the chloride **64** in 81% yield.

Allylic chloride **64** was reprotected with *t*-$BuPh_2SiOTf$ to provide **66** in 77−82% yield. The stage was now set to effect the S_N2' reaction. Compound **66** was refluxed in benzene with 20 equiv of sodium hydride, resulting in a very clean and high-yielding cyclization reaction furnishing the desired product **68** in 93% yield (Scheme 8).

(41) The formation of the two spiro compounds **56** and **57** is presumably due to the increased electrophilicity of the N-acylated amide. Apparently, trace moisture in the reaction mixture caused the production of hydroxide, which then hydrolyzed the reactive amide bond. The resulting carboxylic acid cyclized in an S_N2' fashion, furnishing the spiro lactones.

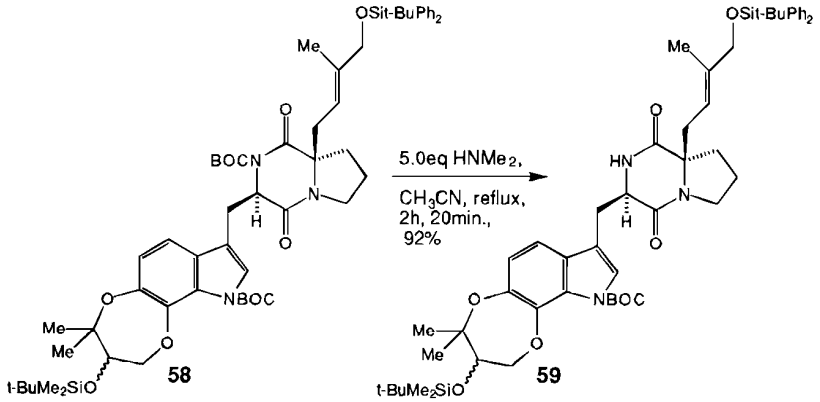
(42) (a) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228. (b) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

(43) This result is noteworthy, especially in light of a report that *tert*-butoxycarbonyl-protected amides are cleaved to the *tert*-butoxycarbonyl-protected amines with DEAEA (2-(*N*,*N*-diethylamino)ethylamine) in CH_3CN at room temperature; see: Grehn, L.; Gummarsonn, K.; Ragnarsson, U. *Acta Chem. Scand. B* **1987**, *41*, 18. However, the substrates examined in that report were all open-chain amides. Interestingly it is known that BOC-protected lactams can be cleaved by base but it is the amide bond that is broken as was observed on substrate **55**. Recently it has been reported that $Mg(OMe)_2$ will also cleave lactam carbamates including BOC-protected lactams; see: Wei, Z.-Y.; Knaus, E. E.; *Tetrahedron Lett.* **1994**, *35*, 847.

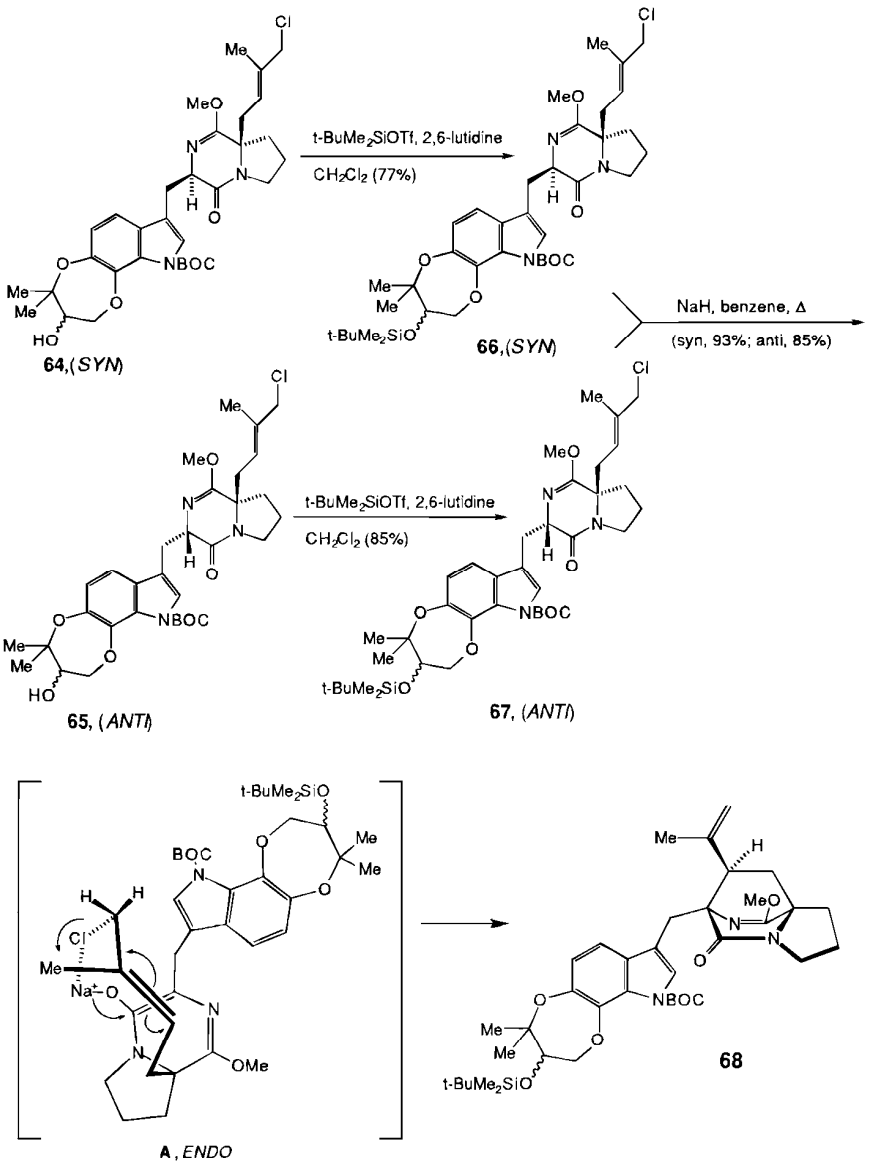
(44) Williams, R. M.; Brunner, E. J.; Sabol, M. R. *Synthesis* **1988**, 963.

(45) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 4339.

Scheme 7



Scheme 8



This last series of reactions was also carried out in parallel on the *anti*-isomer **54**. Following the same sequence (five steps) we obtained the fully protected chloride **67** in good yield. The chloride **67** was then refluxed in benzene with the required amount of sodium hydride to yield the same product (**68**, 85% yield) as that obtained from **66**. The yields of **68** from both routes were very high, and the undesired *anti*-diastereomer was not detected. The high degree of facial selectivity observed in the cyclizations to **68** and **47** is quite interesting and warrants some comments. It is generally accepted that S_N2' reactions

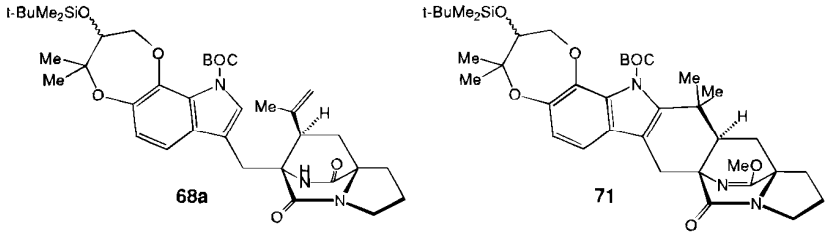


Figure 5.

favor a *syn* orientation[46] (i.e., the incoming nucleophile attacks the π-electrons from the same face as the departing leaving group, polarizing the π-system in the proper orientation for a "backside" displacement on the C−Cl bond). Alternatively, a frontier molecular orbital analysis has indicated[46a] that the stabilization imparted by a $HOMO_{Nuc}-LUMO_{allylic}$ interaction is greater for the *syn* overlap. While the greatest level of diastereoselectivity was observed with a nonpolar aprotic solvent (benzene), a fairly significant change in the relative amounts of the *syn*- and *anti*-diastereomers can be realized by simply changing the solvent to a more polar solvent such as DMF.[11] In the present system, additional stabilization for the *endo* transition state may be due to the formation of a tight contact ion pair between the chlorine atom and sodium atom of the enolate species (see **A**, Scheme 8) in the transition state for the formation of the C−C bond.[47] The poor ligating solvent benzene is not capable of effectively solvating the enolate cation nor the developing chloride anion in the transition state. It is reasonable that this type of association favors the rotamer that positions the allylic chloride moiety over the enolate, resulting in the desired *syn* stereochemistry.

With the bicyclo[2.2.2] ring system constructed in a reliable and high-yielding sequence, attention was turned to the final C−C bond-forming reaction on the indole. Due to the strongly acidic conditions that were used previously for a related cyclization reaction in the brevianamide synthesis, it was assumed that the silyl ether, the *tert*-butoxycarbonyl protecting group, and the lactim ether would be removed during this cyclization reaction. Subjecting compound **68** to the standard conditions (dilute, aqueous HCl in dioxane at 10 °C)[11,19,48] resulted in extensive decomposition, and none of the desired cyclized product was ever detected. The reaction conditions were extensively varied using different acids and temperatures, but the only recognizable products were those stemming from the loss of protecting groups. The problem might be attributed to the enhanced basicity of the indole at the 2-position (indole numbering) caused by the electron-donating oxygen atoms in the aromatic ring. If protonation at the 2-position is kinetically competitive with olefin protonation, cyclization would be precluded.

A search of the literature revealed a 1982 Trost and Fortunak paper[49] wherein $PdCl_2$ and $AgBF_4$ were utilized to effect the Heck-type cyclialkylations of various isoquinuclidine model compounds. Compound **68** was exposed to these conditions, affording the heptacycle **69** in 63−82% yields. During the course of the reaction, the lactim ether moiety was cleaved, restoring the free, secondary amide.[50] The main byproduct of this reaction was the uncyclized free lactam **68a** (Figure 5), which curiously did not cyclize to **69** when subjected to the same conditions. It was also observed that the lactim ether protected heptacycle **71** could not be deblocked to the free lactam **69** with $PdCl_2$ and $AgBF_4$ alone, implying that the cleavage of the lactim ether is due to the tetrafluoroboric acid produced in the cyclization, and that the cyclization occurs *prior* to lactim ether cleavage.

Trost and Fortunak speculated[49] that the cyclization mechanism was either a Heck-type arylation or the electrophilic aromatic substitution of a palladium-complexed olefin, and there was evidence to support both mechanistic possibilities. It is possible that the palladium chloride and the silver tetrafluoroborate react to form a powerful Lewis acid, since an incubation period involving these two reagents is needed prior to the introduction of the substrate. It was reported[49] that there is no reaction with other mixed-metal systems involving palladium chloride (e.g., boron trifluoride, aluminum chloride, stannous chloride, stannic chloride, titanium trichloride). The enhanced basicity (nucleophilicity) at the 2-position of indole **68** renders this substance perfectly disposed to undergo a Heck-type arylation reaction.

There are several reports of methods that will selectively reduce a tertiary amide in the presence of a secondary amide.[51] The secondary lactam of **69** was protected as the lactim ether **71** and treated with diborane; however, the spectral characteristics of the major products isolated were consistent with reduction of both the tertiary amide and the lactim ether. In 1991 Martin *et al.*[52] successfully used alane to reduce a tertiary amide in the presence of an oxindole (secondary amide) relying on the known rate difference for reduction between these two groups.[53] However, initial experiments with this reagent gave poor results, with the secondary amide undergoing reduction along with the tertiary amide. Compound **69** (and **71**) is sufficiently twisted such that the *gem*-dimethyl groups effectively block the β-face of the tertiary amide (Figure 6),

(46) (a) Magid, R. M.; Fruchey, O. S.; Johnson, W. L.; Allen, T. G. *J. Org. Chem.* **1979**, *44*, 359. (b) Magid, R. A. *Tetrahedron* **1980**, *36*, 1901.

(47) The idea that the stereochemical outcome of an intramolecular enolate alkylation is determined by chelation in the transition state was recently demonstrated by Denmark and Henke, who observed a marked preference for a "closed" transition state (coordination of the cationic counterion to an enolate and the developing alcohol) resulting in a *syn* product. For example, the highest *syn:anti* ratio (89:11) was obtained in toluene and the lowest *syn:anti* ratio (2:98) was obtained with a crown ether. These observations parallel the facial selectivities described herein and in ref 11 on the intramolecular S_N2' reaction; see: (a) Denmark, S. A.; Henke, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 2177. (b) Denmark, S. A.; Henke, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 8022.

(48) (a) Hutchison, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786. (b) Guller, R.; Borschberg, H.-J. *Tetrahedron Lett* **1994**, *35*, 865.

(49) Trost, B. M.; Fortunak, J. M. D. *Organometallics* **1982**, *1*, 7.

(50) (a) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. (b) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896. (c) Cava, M. P.; Kevinson, M. I. *Tetrahedron* **1985**, *41*, 5061 and literature cited therein.

(51) In a recently reported synthesis of gelsemine, a tertiary lactam was reduced in the presence of a secondary lactam with DIBAH. However, this reagent failed on substrates **69**; see: Dutton, J. K.; Steel, R. W.; Tasker, A. S.; Popsavin, V.; Johnson, A. P. *J. Chem. Soc., Chem. Commun.* **1994**, 765.

(52) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161.

(53) (a) Yoon, N. M.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 2927. (b) Marlett, E. M.; Park, W. S.; *J. Org. Chem.* **1990**, *55*, 2968. (c) Jorgenson, M. J. *Tetrahedron Lett.* **1962**, 559. (d) Another very recent synthesis of gelsemine reported the reduction of the same gelsemine precursor (as in ref 51) with AlH_3. Newcombe, N. J.; Fang, Y.; Vijn, R. J.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 767.

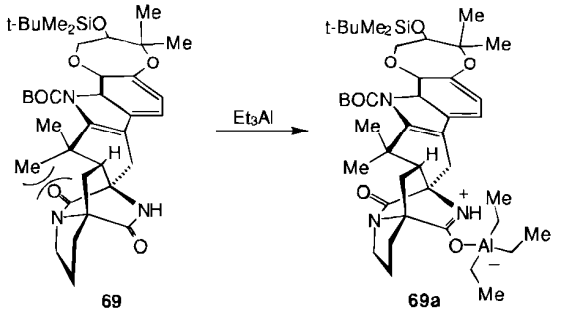


Figure 6.

leaving the α-face relatively unencumbered. However, a modification of the alane procedure[52] proved satisfactory for this transformation. The piperazinedione **69** was pretreated with $AlEt_3$, with the expectation that this Lewis acid would form a complex with the more exposed secondary lactam (**69a**, Figure 6) and leave the tertiary lactam accessible for reduction.

Following 10 min of precomplexation with $AlEt_3$, 5 equiv of AlH_3-Me_2NEt complex was added, followed by quenching with $NaCNBH_3$, acetic acid, and methanol to provide the desired amine **70** in 63% yield. Compound **70** was smoothly alkylated with methyl iodide, affording the N-methylated product **72** in 95−98% yield. Compound **72** was subsequently deblocked with 80 equiv of TFA in CH_2Cl_2 to yield the penultimate heptacycle **73** in 97% (Scheme 9).

The stage was now set for the final transformations involving the oxidative pinacol-type rearrangement and dehydration. Due to the difficulties encountered in the attempted cationic cyclization on the indole (cf. **68** → **69**), there was concern about the reactivity of the indole ring toward the electrophilic reagents that would be utilized in the oxidative pinacol-type reaction. There was the possibility that the electron-donating oxygen atoms on the indole ring would hinder the acid-catalyzed rearrangement of, for example, an intermediate chloroindolenine,[54] similarly to the way that strong acid hindered the cationic cyclization.[55] When compound **73** was treated with *tert*-butyl hypochlorite and triethylamine, there was an almost an instantaneous reaction resulting in the total disappearance of starting material and the appearance of two new components (≈1:2 ratio as evidenced by ^1H NMR analysis) that were presumed to be the expected diastereomeric chloroindolenines. When this mixture was subjected to the standard rearrangement procedure employing a refluxing solution of acetic acid, water, and methanol, these substances slowly decomposed (many bands in the PTLC).[56]

Since the tertiary amine of **73** might react with the chlorinating reagent and was thus considered to be a possible culprit in these oxidations, an attempt to effect the pinacol-type rearrangement before the amide reduction step was investigated. Thus, piperazinedione **69** was readily deblocked with TFA to provide the amide **76** in 95% yield (Scheme 10). This substance was treated with *t*-BuOCl and Et_3N in the same manner as before, producing two products **77**/**78** (≈1:4 ratio). Using a milder $MeOH/H_2O/AcOH$ system (stirring at room temperature), an oxindole compound **79** was formed in 29% yield. Although this result was encouraging, this substance appeared to possess the incorrect relative stereochemistry at the spiro-ring juncture. This assignment was supported by comparing the ^1H NMR spectra of **79** and an authentic sample of (−)-paraherquamide B (**1**). The *gem*-dimethyl signals of **79** were shifted upfield, indicating that one methyl group is in the shielding cone of the oxindole carbonyl.

After a careful reexamination of the decomposition products obtained from the attempted pinacol-type rearrangement of **73**, it was determined that there were mainly two decomposition pathways, and that they were in direct competition with the desired process. These two pathways involve the intermediacy of an oxonium-stabilized tertiary carbocation (at C-3 of the indole) that decomposes to quinone-type products. Additionally, products were isolated whose spectral characteristics were consistent with an elimination process followed by nucleophilic reaction with the solvent at the tryptophan benzylic carbon.

In the classical pinacol rearrangement there is a distinct carbonium ion intermediate, but recent studies have shown that this may in fact be more of a concerted process[57] and, furthermore, that the nature of the solvent can have an impact on which of the two processes, concerted or stepwise, will predominate. There have been conflicting reports in the literature on whether this type of rearrangement is, at all times, stereospecific.[58,59] A detailed study[59c] involving the isolation and separation of the two diastereomeric chloroindolenines derived from yohimbine demonstrated that this reaction can be entirely stereospecific. Alternatively, by increasing the solvating power of the reaction medium, each of these chloroindolenines formed two rearranged products, indicating that the reaction went (at least in part) by way of a carbocationic intermediate. This is consistent with the observed production of **79** from **77** and **78**. A less polar solvent system should minimize the side reactions involving carbocation intermediates and, at the same time, should increase the stereospecific nature of the pinacol-type rearrangement. Thus, treatment of **73** with *t*-BuOCl and Et_3N in CH_2Cl_2 provided the two chloroindolenines **74** and **75** (≈2.25:1 ratio, respectively). The solvent was removed, and the crude reaction mixture was refluxed with a solution of 95% THF, 4% H_2O, and 1% TFA, giving a 62% yield of oxindole products (43% of the desired **80** and 19% the epi product **81**).[60] The C-3-epi-isomer (**81**) was easily distinguishable from the desired isomer (**80**) by the upfield shift of the *gem*-dimethyl signals in the ^1H NMR spectrum. The relative amounts of products (**80** and **81**) indicate that the cyclization was stereospecific under these conditions. It was thus deduced that an increase in the ratio of the desired oxindole **80** to the undesired

(54) (a) Gaskell, A. J.; Radunz, H. -E.; Winterfeldt, E. *Tetrahedron Lett.* **1970**, 5361. (b) Winterfeldt, E.; Gaskell, A. J.; Korth, T.; Radnuz, H.-E.; Walkowiak, M. *Chem. Ber.* **1969**, *102*, 3558. (c) Hollinshead, S. P.; Grubisha, D. S.; Bennett, D. W.; Cook, J. M. *Heterocycles* **1989**, *29*, 529.

(55) Concern about this possible difficulty was somewhat ameliorated by the knowledge of an alternative procedure that employed OsO_4−pyridine. See: (a) Takayama, H.; Kitajima, M.; Ogata, K.; Sakai, S. *J. Org. Chem.* **1992**, *57*, 4583. (b) Takayama, H.; Odaka, H.; Aimi, N.; Sakai, S. *Tetrahedron Lett.* **1990**, *38*, 5483. (c) Takayama, H.; Masubuchi, K.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron* **1989**, *45*, 1327. (d) Fu, X.; Cook, J. M. *J. Org. Chem.* **1993**, *58*, 661. See also: (e) Takayama, H.; Tominaga, Y.; Kitajima, M.; Aimi, N.; Sakai, S. *J. Org. Chem.* **1994**, *59*, 4381.

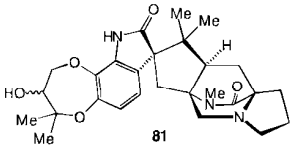
(56) Similar problems were observed during the total synthesis of isopteropodine and pteropodine; see: Martin, S. F.; Mortimore, M. *Tetrahedron Lett.* **1990**, *31*, 4557. In this system, the solution involved treating the chloroindolenines with silver perchlorate in methanolic perchloric acid. This method was attempted on substrate **73**, but unfortunately it failed to produce any desired product.

(57) Osamura, Y.; Nakamura, K. *J. Am. Chem. Soc.* **1993**, *115*, 9112.

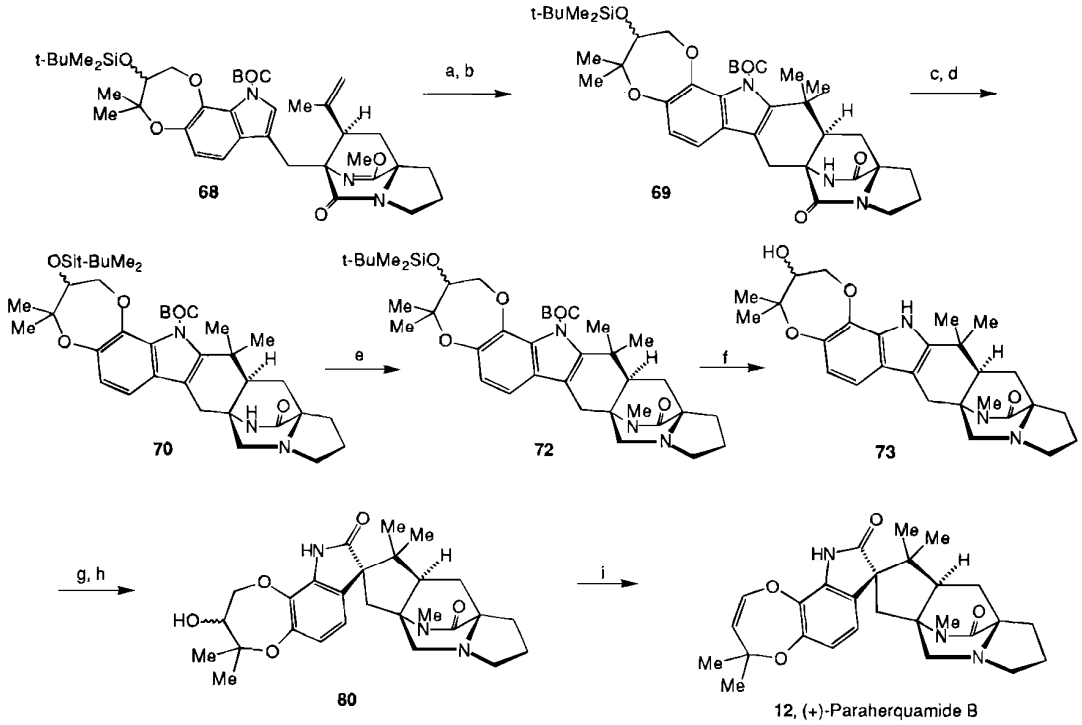
(58) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1.

(59) (a) Owellen, R. J.; Hartke, C. *J. Org. Chem.* **1976**, *41*, 102. (b) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3703. (c) Awang, D. V. C.; Vincent, A.; Kidack, D. *Can. J. Chem.* **1984**, *62*, 2667.

(60)

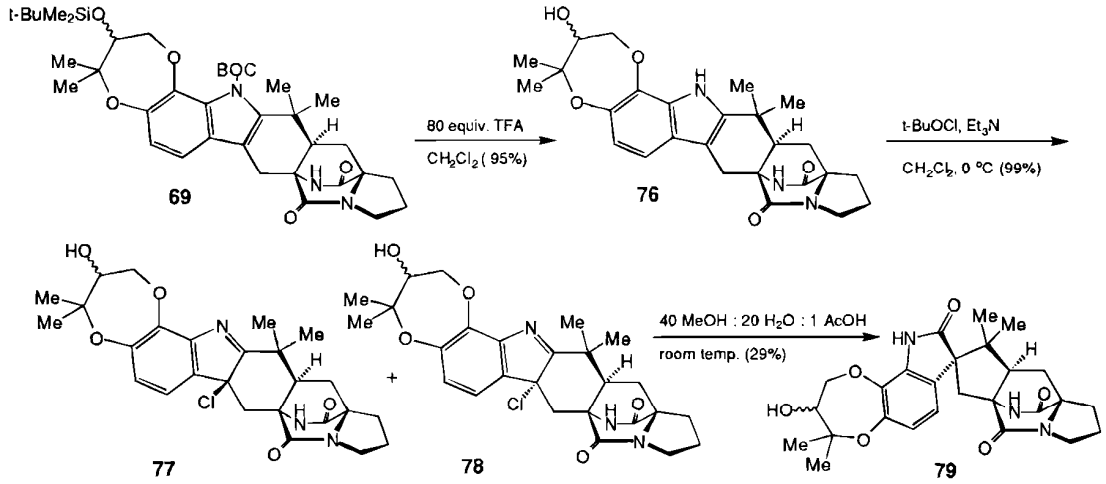


Scheme 9[a]

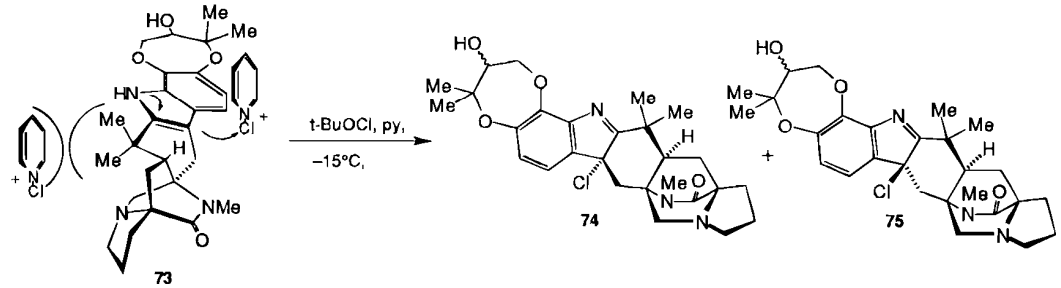


[a] Reagents and conditions: (a) $PdCl_2$, $AgBF_4$, MeCN; (b) $NaBH_4$ (63−82% from **68**); (c) 1.1 equiv of Et_3Al, 5.0 equiv of AlH_3−DMEA, THF, toluene; (d) 2.0 equiv of $NaCNBH_3$, AcOH, MeOH (65% from **69**); (e) 2.5 equiv of NaH, 2.0 equiv of MeI, DMF (98%); (f) 80 equiv of TFA, CH_2Cl_2 (96%); (g) *t*-BuOCl, pyridine, −15 °C; (h) 90% THF, 10% H_2O, pTsOH (76%); (i) MTPI, DMPU (79%).

Scheme 10



Scheme 11



isomer **81** could be achieved simply by finding a method that would increase the ratio of chloroindolenines (**74**:**75**). The α-face of **73** is considerably more hindered than the *β*-face, a supposition that was supported by the difficulties encountered in the reduction of **71** and **69**. Increasing the steric bulk of the chlorinating agent should favor attack on the *β*-face of **73**, thus

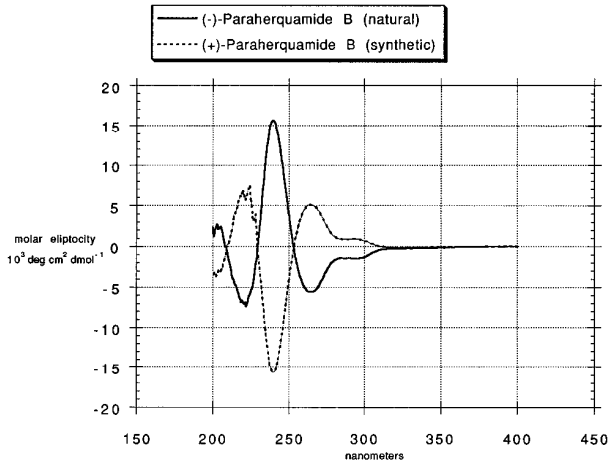


Figure 7.

providing a greater relative amount of chloroindolenine **74**. When **73** was treated with *t*-BuOCl in pyridine instead of triethylamine, the desired chloroindolenine **74** was produced in a much more stereoselective fashion. It can be speculated that *tert*-butyl hypochlorite forms a bulky complex with pyridine, delivering the chlorine more selectively to the least hindered α-face of **73** (only a small amount, ≈5%, of the undesired isomer **75** was formed under these conditions (Scheme 11)).

Employing a minor modification of the solvent system, the crude mixture of **74/75** was refluxed with a solution of 90% tetrahydrofuran, 10% H_2O containing 15 equiv of *p*-toluenesulfonic acid to give the desired oxindole **80** in 76% yield (from **73**), with only 4% of the undesired **81** being formed.

The stereospecific conversion of the chloroindolenines into the corresponding oxindoles requires that the water molecule attack the imine from the same face as the chlorine atom. *Anti* attack on the imine is not as likely because of certain stereoelectronic effects.[59c] The addition of water to the β-face of **74** situates the six-membered ring adjacent to the indole ring in a stable chair conformation that would also place the C−Cl bond and the migrating $(CH_3)_2CC$ group in an unfavorable *syn* alignment. Conversely, the addition of water to the α-face of compound **75** would result in an unfavorable boat conformation that would also place the C−Cl bond and the migrating $(CH_3)_2$-CC group in an unfavorable *syn* alignment. Thus, the major isomer **74** must either (1) suffer kinetically controlled attack by water on the same face of **74** as the chlorine atom, which aligns the migrating group and the C−Cl bond in a stereoelectronically favorable *anti* orientation, or (2) undergo reversible attack by water from either face, with only the correct carbinolamine, which aligns the migrating group and the C−Cl bond in a stereoelectronically favorable *anti* orientation, rearranging irreversibly to the oxindole.

The final dehydration reaction (MTPI, DMPU, 18 h) on the alcohol **80** produced (+)-paraherquamide B (**12**) in 79% yield (Scheme 9). This substance proved to be identical to the natural product by comparison of the ^1H and ^{13}C NMR spectra, mobility on TLC, IR spectra, mass spectra, and UV spectra. Comparison of the CD spectra of the natural (−)-paraherquamide B (**2**) and the synthetic (+)-paraherquamide B (**12**) (Figure 7) confirmed the expected enantiomeric relationship between these two products.

Conclusion

The first stereocontrolled, asymmetric total synthesis of (+)-paraherquamide B has been completed. The synthesis is convergent, starting from (S)-proline and vanillin with an overall yield of 1.4% from (S)-proline.

Key features of this synthesis include (1) a new method to effect reduction of unprotected oxindoles to indoles; (2) a complex application of the Somei/Kametani reaction that concomitantly effected a desired decarbomethoxylation; (3) a high-yielding and entirely stereocontrolled intramolecular S_N2' cyclization reaction; (4) a mild Pd(II)-mediated cyclization reaction that concomitantly deblocked a lactim ether protecting group; and (5) the chemoselective reduction of a highly hindered tertiary lactam in the presence of an unhindered secondary lactam, utilizing precoordination of the more reactive secondary lactam to triethylaluminum.

Experimental Section

General information. Melting points were determined in open-ended capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on either a Bruker WP-270SY 270 MHz or a Bruker AC300P 300 MHz NMR spectrometer. Chemical shifts are reported in ppm relative to $CHCl_3$ at δ 7.24 or TMS at δ 0.0. IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectrometer. Mass spectra were obtained on a V. G. Micromass Ltd. Model 16F spectrometer. The CD spectrum was obtained on a Jasco J710 spectropolarimeter. High-resolution mass spectra were obtained from the Midwest Center for Mass Spectrometry Department of Chemistry, University of Nebraska—Lincoln, Lincoln, NE. Elemental analyses were obtained from M-H-W Laboratories, Phoenix, AZ. Optical rotations were recorded on a Perkin-Elmer 24 polarimeter at a wavelength of 589 nm using a 1.0 dm cell of 1.0 mL total volume.

Column chromatography and flash column chromatography were performed with silica gel grade 60 (230−400 mesh). Radial chromatography was performed with a Harrison Research Chromatotron Model 7924 using E. Merck silica gel 60 PF-254 containing gypsum; 1, 2, 4, and 8 mm plates were used as needed. Preparatory thin layer chromatography (PTLC) was carried out with Merck Kieselgel 60 F_{254} precoated glass plates (either 0.25 or 0.50 mm); visualization was carried out with ultraviolet light and/or heating with a solution of 5−7% phosphomolybdic acid; staining with I_2; vanillin; or Dragendorf.

All solvents were commercial grade and were distilled and dried as follows: tetrahydrofuran (THF) from sodium benzophenone ketyl; diethyl ether from sodium benzophenone ketyl; carbon tetrachloride from calcium hydride; dioxane from sodium; benzene from sodium benzophenone ketyl; dichloromethane from calcium hydride; acetonitrile from P_2O_5. DMF was dried and stored over 3 Å molecular sieves, as were benzene and toluene. HMPA was dried and stored over 4 Å molecular sieves. Dimethyl sulfide, 2,6-lutidine, triethylamine, and pyridine were all distilled prior to use. Phenylselenium chloride was purified by sublimation. *N*-Chlorosuccinimide (NCS) was recrystallized from benzene. LiCl was dried and stored in the oven. All other reagents were commercial grade and used without further treatment. Abbreviations are used throughout: *N*,*N*-dimethylformamide (DMF); acetic acid (AcOH); di-*tert*-butyl dicarbonate ($(BOC)_2O$); methyltriphenoxyphosphonium iodide (MTPI); ethyl acetate (EtOAc); *m*-chloroperbenzoic acid (*m*-CPBA); (*N*,*N*-dimethylamino)pyridine (DMAP); hexamethylphosphoramide (HMPA); ceric ammonium nitrate (CAN); methanesulfonyl chloride (MsCl); *N*-chlorosuccinimide (NCS); trifluoroacetic acid (TFA); dimethylethylamine (DMEA); imidazole (im); 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU).

2-[(3-Methyl-2-butenyl)oxy]phenol (24). To a stirred, cold (0 °C), dark solution of catechol (2.07 g, 18.8 mmol, 5.0 equiv) in DMF (65 mL) in a reaction vessel that had been flushed with Ar was added anhydrous K_2CO_3 (0.520 g, 3.76 mmol, 1.0 equiv). After 5 min, prenyl bromide (0.441 mL, 3.76 mmol, 1.0 equiv) was added dropwise. The reaction mixture was kept at 0 °C for ∼6 h and stirred at room temperature for an additional 18 h. The mixture was then poured into a separatory funnel, diluted with H_2O (100 mL), and extracted five times with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by radial chromatography (eluted with 1% ethyl acetate/hexanes) to give 479 mg (71%) of **24** as a colorless oil. An analytical sample was obtained by PTLC on silica gel (eluted with hexanes).

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.74 (3H, s), 1.80 (3H, s), 4.57 (2H, d, J = 6.8 Hz), 5.49 (1H, m), 5.70 (1H, s, D_2O exch), 6.82−6.92 (4H, m). IR (NaCl, neat): 3533, 2932, 1612, 1502, 1467, 1385, 1259, 1221, 1106, 997, 743 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 178 (11), 161 (11), 110 (78), 69 (67), 32 (100). Microanalysis calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92 Found: C, 73.88; H, 8.00.

(±)-3,4-Dihydro-2,2-dimethyl-3-(phenylseleno)-2*H*-benzodioxepin (25). A solution of phenylselenium chloride (117.8 mg, 0.615 mmol, 1.05 equiv) in EtOAc (4.1 mL, 0.15 M) was slowly added (~1 mmol/h) to a stirred solution of **24** (104.4 mg, 0.58 mmol, 1.0 equiv) in EtOAc (3.90 mL, 0.15 M) at −75 °C under Ar. This mixture was allowed to warm to room temperature and was stirred for a total of 17 h. The solution was poured into a separatory funnel and washed twice with H_2O and once with brine. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by PTLC (eluted with 1:3 hexanes/benzene) to afford 62.1 mg (32%) of **25**. An analytical sample was obtained by PTLC (eluted with hexanes, and then distilled under reduced pressure).

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.28 (3H, s), 1.76 (3H, s), 3.62 (1H, dd, J = 3.4, 10.3 Hz), 4.17 (1H, dd, J = 10.3, 12.6 Hz), 4.40 (1H, dd, J = 3.5, 12.6 Hz), 6.94−6.98 (4H, m), 7.30−7.34 (3H, m), 7.59−7.62 (2H, m). IR (NaCl, neat): 2986, 1491, 1256, 1088, 1000 cm^{-1}. HRMS (EI): *m/e* 334.0473 ($C_{17}H_{18}O_2Se$ requires 334.0472).

2,2-Dimethyl-2*H*-1,5-benzodioxepin (26). To a stirred solution of **25** (61.7 mg, 0.185 mmol, 1.0 equiv) in THF (3 mL) was added H_2O_2 (0.21 mL, 0.5 mmol, 10 equiv) at 0 °C. The resulting solution was stirred for 0.5 h and then brought to reflux temperature for 0.5 h. The mixture was poured into a separatory funnel, diluted with water, and extracted with ether. The ethereal solution was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by PTLC (eluted with 1:3 hexanes/EtOAc) to afford 16.0 mg (49%) of **26** as a pale yellow oil (see data below).

Compound **26** was also obtained from **28** as follows: To a solution of **28** (76.2 mg, 0.39 mmol, 1.0 equiv) in HMPA (2 mL) under N_2 at room temperature was added MTPI (291.5 mg, 0.64 mmol, 1.6 equiv) all at once. After being stirred for 1 day, the mixture was poured into a separatory funnel containing 1 M NaOH and was extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation gave a crude yield of 163.5 mg. The crude product was purified by radial chromatography (eluted with 1:10 EtOAc/hexanes, then 1:5 EtOAc/hexanes) to afford 46 mg (66%) of **26**.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.42 (6H, s), 4.81 (1H, d, J = 7.8 Hz), 6.30 (1H, d, J = 7.8 Hz), 6.95−7.06 (4 H, m). IR (neat): 2978, 1654, 1587, 1495, 1311, 1242, 750 cm^{-1}. HRMS (EI): *m/e* 176.0835 ($C_{11}H_{12}O_2$ requires 176.0837).

(±)-2-[(3,3-Dimethyloxiranyl)methoxy]phenol (27). To a solution of **24** (1.31 g, 7.35 mmol, 1.0 equiv) in CH_2Cl_2 (40.0 mL) under N_2 at 0 °C was added $NaHCO_3$ (803 mg, 9.56 mmol, 1.3 equiv) followed by *m*-CPBA (1.27 g, 7.35 mmol, 1.0 equiv). After 1.5 h additional $NaHCO_3$ (812 mg, 9.66 mmol, 1.21 equiv) and *m*-CPBA (1.26 g, 7.35 mmol, 0.99 equiv) were added. This mixture was kept stirring at 0 °C for 2 h, when more $NaHCO_3$ (778 mg, 9.27 mmol, 1.3 equiv) and *m*-CPBA (1.12 g, 6.49 mmol, 0.88 mmol) were added. After 2 h, the cold mixture was filtered to remove the solids. The filtrate was washed three times with 10% $Na_2S_2O_3$ and three times with brine, dried over $MgSO_4$, and evaporated to dryness to afford 1.41 g (99%) of **27**. An analytical sample was recrystallized from toluene to give a glassy solid, mp 36−37 °C.

^{1}H NMR (270 MHz) ($CDCl_3$): δ TMS 1.37 (3H, s), 1.41 (3H, s), 3.18 (1H, dd, J = 4.2, 6.3 Hz), 4.07 (1H, dd, J = 6.4, 11.0 Hz), 4.28 (1H, dd, J = 4.2, 11.0 Hz), 5.78 (1H, s, D_2O exch), 6.81−6.97 (4H, m). IR (NaCl, neat): 3413, 2966, 1590, 1502, 1267, 744 cm^{-1}. Microanal. Calcd for $C_{11}H_{14}O_4$: C, 68.02; H, 7.26. Found: C, 67.91; H, 7.39.

(±)-3,4-Dihydro-2,2-dimethyl-2*H*-1,5-benzodioxepin-3-ol (28). A flame-dried flask, flushed with Ar, was charged with dry THF (85.4 mL). Tin tetrachloride (0.85 mL, 7.3 mmol, 1.0 equiv) was then added dropwise in 5 min. After 10 min a solution of **27** (1.41 g, 7.26 mmol, 1.0 equiv) in dry TIIF (13.8 mL) was added slowly (dropwise) to the mixture. The reaction mixture was stirred at room temperature for 20 min, poured into saturated $NaHCO_3$, washed with brine, dried over $MgSO_4$, and evaporated to dryness. The crude product was purified by radial chromatography (eluted with 1:7 EtOAc/hexanes) to afford 842 mg (60% or 59% for two steps) of **28** as an oil. An analytical sample was obtained by PTLC (eluted with 5:1 EtOAc/hexanes, and then distilled under reduced pressure).

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.20 (3H, s), 1.53 (3H, s), 2.96 (1H, d, J = 11.3 Hz, D_2O exch), 3.58 (1H, ddd, J = 1.1, 4.0, 11.3 Hz), 4.08 (1H, dd, J = 1.1, 12.6 Hz), 4.20 (1H, dd, J = 4.0, 12.6 Hz), 6.98−7.02 (4H, m). IR (NaCl, neat): 3448, 2978, 1596, 1490, 1261 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 194 (41), 176 (19), 136 (57), 121 (100), 59 (63). HRMS (EI) *m/e* 194.0943 ($C_{11}H_{14}O_3$ requires 194.0943).

4-Hydroxy-3-methoxy-2-nitrophenylacetic Acid (30). To a flask containing **29** (101 g, 397 mmol, 1.0 equiv) at 0 °C was added a solution of NaOH (63.5 g, 1.59 mol, 4.0 equiv) in H_2O (1.4 L). After 10 min, hydrogen peroxide (49.5 mL, 437 mmol, 1.1 equiv, 30% solution in water) was added dropwise. The deep purple solution slowly turned brown during the addition. The mixture was allowed to reach room temperature and stirred for 24 h. The reaction mixture was then acidified with concentrated HCl until pH ≈ 3, during which CO_2 was released and a fine yellow crystalline product precipitated. The mixture was filtered, washed with cold H_2O, and dried to yield 72.6 g (81%) of **30**. An analytical sample was recrystallized from H_2O to give bright yellow needles, mp 161−162 °C (when the reaction was carried out with 11.9 g of the phenylacetic acid, the yield was 93%).

^{1}H NMR (300 MHz) (acetone-d_6): δ TMS 2.83 (2H, br s, D_2O exch), 3.62 (2H,s), 3.91 (3H, s), 7.10 (2H, s). IR (KBr): 3488, 2958, 2641, 1668, 1533, 1399, 1344, 1296, 1225, 1051, 825 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 228 (M^+, 0.7), 227 (5.8), 166 (10.0), 106 (13.6), 44 (100). Microanal. Calcd for $C_9H_9NO_6$: C, 47.58; H, 3.99; N, 6.16. Found: C, 47.56; H, 4.06; N, 6.25.

1,3-Dihydro-6-hydroxy-7-methoxy-2*H*-indol-2-one (31). A mixture of **30** (23.0 g, 101 mmol, 1.0 equiv) in glacial acetic acid (100 mL) and Pd/C (10%, 1.5 g) was hydrogenated at 40 psi of H_2 in an oil bath (80 °C) for 5 h. The mixture was immediately filtered through a Celite plug and washed with a small amount of warm AcOH. The flask was kept under suction (cold) until a large quantity of white product had precipitated. This was filtered to collect the product, when an additional quantity of product precipitated under suction. This was collected, and the two crops of white flakes were combined and dried under reduced pressure to yield 17.2 g (95%) of **31**. An analytical sample was recrystallized from H_2O to give white crystals, mp 210−211 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 3.50 (2H, d, J = 1.0 Hz), 3.87 (3H, s), 5.49 (1H, s, D_2O exch), 6.60 (1H, d, J = 8.1 Hz), 6.86 (1H, d, J = 8.0 Hz), 7.94 (1H, s, D_2O exch). IR (KBr): 3287, 3014, 2953, 1686, 1633, 1504, 1466, 1315, 1163, 637 cm^{-1}. Microanal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.51; H, 5.05; N, 7.60.

1,3-Dihydro-7-methoxy-6-[(tolylsulfonyl)oxy]-2*H*-indol-2-one. To a stirred mixture of **31** (321.6 mg, 1.795 mmol, 1.0 equiv) in acetone (7 mL) at 0 °C under Ar were added K_2CO_3 (740.5 mg, 5.358 mmol, 2.98 equiv) and *p*-toluenesulfonyl chloride (376.4 mg, 1.974 mmol, 1.1 equiv). The mixture was stirred for 5 h at 0 °C and 1 h at room temperature. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed three times with 1 M NaOH and once with brine, dried over $MgSO_4$, and concentrated to dryness. The product, 572.3 mg (96%), was obtained as a rust-colored, amorphous solid.

^{1}H NMR (270 MHz) ($CDCl_3$): δ 2.47 (3H, s), 3.52 (2H, s), 3.81 (3H, s), 6.70 (1H, d, J = 8.2 Hz), 6.86 (1H, d, J = 8.1 Hz), 7.34 (2H, d, J = 8.1 Hz), 7.79 (2H, d, J = 8.3 Hz), 7.85 (1H, s, D_2O exch). IR (KBr): 3172 (br), 1709, 1616, 1496, 1458, 1371, 1338, 1175, 1093, 1050, 1000, 848, 815, 728, 662, 548, cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 333 (5.0), 269 (1.4), 178 (40), 91 (77), 28 (100).

1,3-Dihydro-7-hydroxy-6-[(tolylsulfonyl)oxy]-2*H*-indol-2-one. Boron tribromide (1.1 mL, 1.1 mmol, 2.0 equiv, 1 M/CH_2Cl_2) was added to a stirred mixture of 1,3-dihydro-7-methoxy-6-[(tolylsulfonyl)oxy]-2*H*-indol-2-one obtained above (181.5 mg, 0.54 mmol, 1.0 equiv) in CH_2Cl_2 (4.3 mL) under Ar, at −78 °C. The mixture was stirred for 8 h and stored at −20 °C for 12 h. The mixture was poured into ice/

water, stirred for 0.5 h, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness to give 164.7 mg (95%) of a red solid.

^{1}H NMR (270 MHz) (acetone-d_6): δ TMS 2.45 (3H, s), 3.43 (2H, d, J = 0.8 Hz), 6.61 (1H, d, J = 8.1 Hz), 6.71 (1H, d, J = 8.1 Hz), 7.46 (2H, d, J = 8.6 Hz), 7.79 (2H, d, J = 8.3 Hz), 8.50 (1H, s, D_2O exch), 9.28 (1H, s, D_2O exch). IR (NaCl, neat): 3259 (br), 2921, 1698, 1365, 1175, 1142, 728 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 319 (3.4), 278 (6.0), 246 (6.7), 163 (49), 139 (73), 91 (100).

1,3-Dihydro-7-[(3-methyl-2-butenyl)oxy]-6-[(tolylsulfonyl)oxy]-2*H*-indol-2-one (37). To a stirred solution of 1,3-dihydro-7-hydroxy-6-[(tolylsulfonyl)oxy]-2*H*-indol-2-one obtained above (159.4 mg, 0.49 mmol, 1.0 equiv) in DMF (1.5 mL) at 0 °C was added K_2CO_3 (103.5 mg, 0.75 mmol, 1.5 equiv) followed by prenyl bromide (0.09 mL, 0.75 mmol, 1.5 equiv). After 4 h the mixture was poured into water, extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated to dryness. The product was purified by radial chromatography (eluted with 3:2 hexanes/EtOAc) to afford 71.9 mg (37%) of **37** as a red solid.

^{1}H NMR (270 MHz) ($CDCl_3$): δ TMS 1.58 (3H, s), 1.70 (3H, s), 2.45 (3H, s), 3.52 (2H, s), 4.47 (2H, d, J = 7.3 Hz), 5.35 (1H, t, J = 7.3 Hz), 6.74 (1H, d, J = 8.2 Hz), 6.87 (1H, d, J = 8.1 Hz), 7.32 (2H, d, J = 8.0 Hz), 7.79 (2H, d, J = 8.3 Hz), 8.61 (1H, s, D_2O exch). IR (NaCl, neat): 3194 (br), 1714, 1627, 1464, 1376, 1196, 1175, 837, 728 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 387 (16), 319 (16), 164 (37), 91 (91), 67 (100).

1,3-Dihydro-6,7-dihydroxy-2*H*-indol-2-one (32). Boron tribromide (800 mL, 800 mmol, 2.5 equiv, 1M/CH_2Cl_2) was added dropwise to a stirred mixture of **31** (57.3 g, 320 mmol, 1.0 equiv)) in CH_2Cl_2 (640 mL) under N_2 at −78 °C. The reaction mixture was stirred at −78 °C for 8 h and was then poured into a large (4 L) beaker containing 1.5 L of ice/water, stirred for 10 min, and filtered to remove undissolved product. The remaining liquid was extracted with EtOAc, washed with brine, and dried over $MgSO_4$. The organic layer was evaporated to yield the pure product **32**, which was combined with the filter cake, total yield 52.3 g (99%). An analytical sample was recrystallized from H_2O (three times) to give a faint pink crystalline solid, mp 245 °C dec.

^{1}H NMR (300 MHz) (DMSO-d_6): δ TMS 3.32 (2H, s), 6.36 (1H, d, J = 7.9 Hz), 6.48 (1H, d, J = 2.9 Hz), 8.80 (2H, br s, D_2O exch), 10.0 (1H, br s, D_2O exch). IR (KBr): 3366−3123 (br), 1672, 1649, 1618, 1359, 1265, 1178, 786 cm^{-1}. Microanal. Calcd for $C_8H_7NO_3$: C, 58.18; N, 4.27; N, 8.48. Found: C, 58.34; H, 4.44; N, 8.25.

1,3-Dihydro-6-hydroxy-7-[(3-methyl-2-butenyl)oxy]-2*H*-indol-2-one (33). To a stirred solution of 6,7-dihydroxyoxindole (**32**) (19.0 g, 115 mmol, 1.0 equiv) in DMF (230 mL) at 0 °C under Ar was added K_2CO_3 (15.9 g, 115 mmol, 1.0 equiv). After 8 min prenyl bromide (14.8 mL, 127 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 6.5 h, poured into a separatory funnel, diluted with H_2O, and extracted with ether. The ethereal solution was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The product was purified by column chromatography (eluted with 3:1 hexanes/EtOAc, then 1:1 hexanes/EtOAc) to yield 14.5 g (54%) of **33**. An analytical sample was recrystallized from toluene to give a red-white solid, mp 111 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.65 (3H, s), 1.80 (3H, s), 3.50 (2H, s), 4.47 (1H, d, J = 7.4 Hz), 5.50−5.55 (1H, m), 5.57 (1H, s, D_2O exch), 6.59 (1H, d, J = 8.1 Hz), 6.84 (1H, d, J = 8.0 Hz), 7.77 (1H, s, D_2O exch). IR (KBr): 3367, 3192, 2971, 1694, 1664, 1635, 1461, 1356, 1286, 1199, 1047 cm^{-1}. Microanal. Calcd for $C_{13}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.16; H, 6.52; N, 6.07.

(±)-1,3-Dihydro-7-[(3,3-dimethyloxiranyl)methoxy]-6-hydroxy-2*H*-indol-2-one. To a stirred solution of **33** (14.5 g, 62.1 mmol, 1.0 equiv) in CH_2Cl_2 (620 mL) were added $NaHCO_3$ (5.7 g, 68.3 mmol, 1.1 equiv) and *m*-CPBA (10.7 g, 62.1 mmol, 1.0 equiv). The mixture was stirred for 1 h, and an additional amount of each reagent was added, $NaHCO_3$ (5.7 g, 68.3 mmol, 1.1 equiv) and *m*-CPBA (10.7 g, 62.1 mmol, 1.0 equiv). The mixture was stirred for an additional 1 h, and a third portion each of $NaHCO_3$ (5.7 g, 68.3 mmol, 1.1 equiv) and *m*-CPBA (10.7 g, 62.1 mmol, 1.0 equiv) was added. The resulting mixture was stirred for 3 h, while the temperature was maintained at 0 °C. The reaction mixture was filtered into a flask containing 10% $Na_2S_2O_3$ and 10% $NaHCO_3$. The organic layer was isolated, diluted with CH_2Cl_2, and washed with 10% $Na_2S_2O_3$ and saturated $NaHCO_3$ and finally with brine. The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and dried in vacuo to yield 17 g of the product, which was used directly for the next step. An analytical sample was recrystallized from toluene to give a white solid, mp 122−123 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.38 (3H, s), 1.42 (3H, s), 3.25 (1H, dd, J = 2.9, 8.5 Hz), 3.47−3.49 (2H, m), 3.80 (1H, dd, J = 8.5, 12.0 Hz), 4.54 (1H, dd, J = 2.9, 12.0 Hz), 6.25 (1H, s, D_2O exch), 6.58 (1H, d, J = 8.1 Hz), 6.84 (1H, d, J = 8.1 Hz), 8.44 (1H, s, D_2O exch). IR (KBr): 3495, 3146, 2982, 1717, 1694, 1635, 1501, 1466, 1321, 1187, 1047, 861 cm^{-1}. Microanal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.70; H, 6.15; N, 5.66.

(±)-3,4,8,10-Tetrahydro-3-hydroxy-4,4-dimethyl-2*H*,9*H*-[1,4]dioxepino[2,3-*g*]indol-9-one (34). $SnCl_4$ (9.6 mL, 81.8 mmol, 1.2 equiv) was slowly added dropwise to a flame-dried flask, which had been flushed with Ar and charged with dry THF (960 mL). After 10 min a solution of (±)-1,3-dihydro-7-[(3,3-dimethyloxiranyl)methoxy]-6-hydroxy-2*H*-indol-2-one obtained above (17 g, 62 mmol, 1.0 equiv) in THF (73 mL) was added dropwise to the reaction vessel and stirred for 2 h. Approximately one-half of the solvent was removed under reduced pressure and the remaining solution poured into a separatory funnel containing saturated $NaHCO_3$ and H_2O (~50:50), which was then exhaustively extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give a dark crude product. The product was purified by column chromatography (eluted with 1:2 hexanes/EtOAc) to yield 10 g (64% for two steps) of **34**. An analytical sample was recrystallized from toluene to give a yellow crystalline solid, mp 194 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.24 (3H, s), 1.54 (3H, s), 2.94 (1H, d, J = 11.2 Hz, D_2O exch), 3.51 (2H, s), 3.63 (1H, ddd, J = 1.0, 4.0, 11.2 Hz), 4.12 (1H, dd, J = 1.0, 12.4 Hz), 4.24 (1H, dd, J = 4.0, 12.5 Hz), 6.64 (1H, d, J = 8.0 Hz), 6.83 (1H, d, J = 7.9 Hz), 7.64 (1H, s, D_2O exch). IR (KBr): 3460, 3320, 3169, 2982, 1711, 1682, 1461, 1327, 1216, 1047 cm^{-1}. Microanal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.08; N, 5.61. Found: C, 62.28; H, 6.21; N, 5.56.

(±)-3-Hydroxy-4,4-dimethyl-3,4,dihydro-2*H*,10*H*-[1,4]dioxepino-[2,3-*g*]indole (35). To a stirred solution of **34** (11.2 g, 44.8 mmol, 1.0 equiv) in THF (225 mL) under Ar at 0 °C was added BF_3·OEt_2 (19.3 mL, 157 mmol, 3.5 equiv). After 10 min, $NaBH_4$ (2.71 g, 71.8 mmol, 1.6 equiv) was added at once, and the mixture was stirred for 8 h at 0 °C and then at room temperature for 40 h. The reaction was completed by the slow addition of water (1 L) and was stirred for 0.5 h. HCl (concentrated) was added until pH = 1, and the mixture was stirred for an additional 0.5 h. The mixture was treated with 1 M NaOH until pH = 14 and stirred for 0.5 h. The mixture was poured into a separatory funnel and extracted with EtOAc/ether. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to leave 10 g of a crude solid. The product was purified by column chromatography (eluted with 2:1 hexanes/EtOAc) to yield 4.5 g (43%) of **35**. An analytical sample was recrystallized from benzene to afford a white crystalline solid, mp 202−205 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.22 (3H, s), 1.56 (3H, s), 3.03 (1H, d, J = 11.4 Hz, D_2O exch), 3.63 (1H, ddd, J = 4.0, 0.9, 11.3 Hz), 4.19 (1H, dd, J = 0.9, 12.3 Hz), 4.31 (1H, dd, J = 4.0, 12.3 Hz), 6.49 (1H, dd, J = 2.2, 3.1 Hz), 6.78 (1H, d, J = 8.4 Hz), 7.16−7.19 (2H, m), 8.29 (1H, s, D_2O exch). IR (KBr): 3340, 2984, 1580, 1504, 1444, 1338, 1224, 1133, 1057, 814, 753 cm^{-1}. Microanal. Calcd for $C_{13}II_{15}NO_3$: C, 66.94; II, 6.48; N, 6.00. Found: C, 67.16; II, 6.63; N, 5.79.

(±)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4,4-dimethyl-3,4-dihydro-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole. To a stirred solution of **35** (11.6 g, 49.7 mmol, 1.0 equiv) in DMF (124 mL) at room temperature under N_2 was added *tert*-butyldimethylsilyl chloride (15.0 g, 99.4 mmol, 2.0 equiv) immediately followed by imidazole (23.7 g, 348 mmol, 7.0 equiv). The solution was slowly heated to 40 °C, stirred overnight, poured into a separatory funnel, and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed and the crude solid purified by column chromatography (eluted with 5:1 hexanes/EtOAc) to yield 14.2 g (82%) of

the product. An analytical sample was recrystallized from cyclohexane to give a white solid, mp 118−119 °C.

^{1}H NMR (300 Hz) ($CDCl_3$): δ TMS 0.14 (6H, s), 0.89 (9H, s), 1.12 (3H, s), 1.48 (3H, s), 3.88 (1H, dd, J = 9.2, 11.5 Hz), 3.98 (1H, dd, J = 3.2, 9.2 Hz), 4,22 (1H, dd, J = 3.2, 11.5 Hz), 6.48 (1H, dd, J = 2.2, 3.1 Hz), 6.76 (1H, d, J = 8.4 Hz), 7.14 (2H, ddd, J = 2.4, 3.4, 3.5 Hz), 8.21 (1H, s, D_2O exch). IR (neat): 3412, 2936, 1500, 1438, 1234, 1093, 833 cm^{-1}. Microanal. Calcd for $C_{19}H_{29}NO_3Si$: C, 65.66; H, 8.41; N, 4.03. Found: C, 65.59; H, 8.20; N, 3.90.

(±)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4,4-dimethyl-8-[(*N*,*N*-dimethylamino)methyl]-3,4-dihydro-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]-indole (36). To a flask charged with acetic acid (136 mL) under Ar were added formaldehyde (3.4 mL, 45 mmol, 1.1 equiv, 37%/H_2O) and dimethylamine (20.5 mL, 163 mmol, 4.0 equiv, 40% solution in H_2O) followed by (±)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4-dimethyl-3,4,dihydro-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole obtained above (14.2 g, 40.9 mmol, 1.0 equiv) over a 10 min period. The reaction mixture was stirred for 1 day when 10% K_2CO_3 was added until pH ≈ 8; then 2 M NaOH was added. The mixture was extracted with ether/EtOAc, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, leaving 17.3 g (quantitative) of the pure product **36**. An analytical sample was recrystallized from toluene to give a white flaky solid, mp 152 °C.

^{1}H NMR (300 Hz) ($CDCl_3$): δ TMS 0.15 (6H, s), 0.90 (9H, s), 1.13 (3H, s), 1.48 (3H, s), 2.28 (6H, s), 3.58 (2H, s), 3.58 (2H, s), 3.88 (1H, dd, J = 9.2, 11.4 Hz), 3.98 (1H, dd, J = 3.2, 9.1 Hz), 4.21 (1H, dd, J = 3.2, 11.5 Hz), 6.76 (1H, d, J = 8.4 Hz), 8.44 (1H, s, D_2O exch). IR (NaCl, neat): 2932, 1502, 1458, 1360, 1251, 1218, 1093, 837, 777 cm^{-1}. Microanal. Calcd for $C_{22}H_{36}N_2O_3Si$: C, 65.31; H, 8.97; N, 6.92. Found: C, 65.09; H, 8.77; N, 6.73.

(±)-6(*R*)-(2*E*)-Methyl 3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl]methyl]-8a-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazine-3-carboxylate (39). To a stirred solution of **38** (23.0 mg, 0.043 mmol, 1.0 equiv) in CH_3CN (0.3 mL) and PBu_3 (5.4 μL, 0.022 mmol, 0.5 equiv) was added a solution of **36** (19.3 mg, 0.048 mmol, 1.1 equiv) in CH_3CN (0.3 mL). The mixture was refluxed for 5.5 h and stirred at room temperature overnight. The reaction mixture was then diluted with ether, washed with water, dilute HCl, and brine, and dried over $MgSO_4$. The solvent was removed and the crude oily solid purified by PTLC on silica gel (eluted with 1:4 EtOAc/hexanes) to yield 19.8 mg (51%) of **39**. An analytical sample was recrystallized from cyclohexane to give a white crystalline solid, mp 168−168.5 °C.

^{1}H NMR (300 MHz) ($CDCl_3$) (a racemic mixture of two diastereomers): δ TMS 0.00 (6H, s), 0.01 (6H, s), 0.13 (6H, s), 0.14 (6H, s), 0.034−0.19 (2H, m), 0.43−0.52 (2H, m), 0.62−0.72 (2H, m), 0.84 (9H, s), 0.85 (9H, s), 0.86 (9H, s), 0.88 (9H, s), 1.05 (3H, s), 1.1 (3H, s), 1.45 (3H, s), 1.49 (3H, s), 1.537 (3H, s), 1.544 (3H, s), 1.33−1.67 (2H, m), 2.14−2.25 (2H, m), 2.52−2.60 (2H, m), 2.87−3.03 (2H, m), 3.27 (6H, s), 3.36−3.52 (2H, m), 3.66 (1H, $^1/_2$ ABq, J = 15.0 Hz), 3.66 (1H, $^1/_2$ ABq, J = 15.0 Hz), 3.75 (6H, s), 3.77−3.96 (12H, m), 4.14−4.20 (2H, m), 5.25−5.31 (2H, m); 5.48 (2H, $^1/_2$ ABq, J = 14.6 Hz), 6.70−6.89 (8H, m), 7.15−7.22 (6H, m), 8.29 (1H, s, D_2O exch), 8.32 (1H, s, D_2O exch). IR (NaCl, neat): 3303, 2954, 2856, 1752, 1660, 1512, 1447, 1251, 1098, 1049, 837, 777 cm^{-1}. Microanal. Calcd for $C_{48}H_{71}N_3O_9Si_2$: C, 64.76; H, 8.04; N, 4.72. Found: C, 64.95; H, 8.09; N, 4.53.

[(±)-[3α,8a*β*(*E*)]]-8-[[2-[(4-Methoxyphenyl)methyl]-8a-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-g]indole (40). [(±)-[3*β*,8aα(*E*)]]-8-[[2-[(4-Methoxyphenyl)methyl]-8a-[4-[[(1,1-dimethylethyl) dimethylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]-methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole (41). A dry flask containing **39** (24.4 mg, 0.027 mmol, 1.0 equiv) and lithium chloride (11.6 mg, 0.27 mmol, 10 equiv) under N_2 was charged with HMPA (0.21 mL) and water (1.5 × 10^{-3} mL, 0.082 mmol, 3.0 equiv). This mixture was heated to 100−105 °C for 2 h. The resulting solution was diluted with 1:1 EtOAc/hexanes and washed with water (5×) and brine. The organic layer was dried over $MgSO_4$ and concentrated to dryness. The product was purified by PTLC on silica gel (eluted with 1:3 EtOAc/hexanes) to yield 8.9 mg (39%) of **40** (oil) and 2.7 mg (12%) of **41** (oil). Total yield: 51%.

^{1}H NMR (300 MHz) ($CDCl_3$) (a racemic mixture of two diastereomers) (**40**): δ 0.036 (12H, s), 0.12 (6H, s), 0.13 (6H, s), 0.84 (9H, s), 0.87 (9H, s), 0.88 (9H, s), 0.882 (9H, s), 1.10 (3H, s), 1.11 (3H, s), 1.458 (9H, s), 1.463 (3H, s), 1.72−2.04 (10H, m), 2.12−2.23 (2H, m), 3.24−3.51 (8H, m), 3.72 (3H, s), 3.73 (3H, s), 3.79−3.82 (6H, m), 3.83 (2H, s), 3.86 (2H, s), 4.15−4.20 (4H, m), 5.15 (1H, $^1/_2$ ABq, J = 14.2 Hz), 5.20 (1H, $^1/_2$ ABq, J = 14.2 Hz), 5.28 (1H, m), 5.45 (1H, m), 6.67−6.71 (4H, m), 6.76 (2H, d, J = 8.5 Hz), 6.81−6.90 (6H, m), 7.16 (2H, d, J = 8.5 Hz), 8.12 (2H, s, D_2O exch). IR (*syn*) (NaCl, neat): 2920, 1655, 1508, 1449, 1250, 1220, 1091, 838 cm^{-1}.

^{1}H NMR (300 MHz) ($CDCl_3$) (a racemic mixture of two diastereomers) (**41**): δ −0.18 (12H, s), 0.12 (6H, s), 0.13 (6H, s), 0.26−0.41 (2H, m), 0.47−0.58 (2H, m), 0.62−0.72 (2H, m), 0.84 (18H, s), 0.87 (9H, s), 0.89 (9H, s), 1.06 (3H, s), 1.10 (3H, s), 1.44 (6H, s), 1.47 (3H, s), 1.48 (3H, s), 1.63−1.67 (2H, m), 2.10−2.17 (2H, m), 2.44−2.52 (2H, m), 2.89−3.05 (2H, m), 3.20−3.28 (2H, m), 3.40−3.52 (4H, m), 3.71−3.97 (16H, m), 4.08 (2H, br s), 4.14−4.21 (2H, m), 5.05 (2H, br s), 5.56 (1H, $^1/_2$ ABq, J = 14.2 Hz), 5.57 (1H, $^1/_2$ ABq, J = 14.5 Hz), 6.71 (1H, d, J = 8.6 Hz), 6.73 (1H, d, J = 8.6 Hz), 6.83−6.88 (6H, m), 7.14 (1H, d, J = 8.6 Hz), 7.18 (1H, d, J = 8.6 Hz), 7.22−7.23 (4H, m), 8.34 (2H, s, D_2O exch). IR (*anti*) (neat): 2932, 1649, 1508, 1455, 1250, 1220, 1103, 838 cm^{-1}. HRMS (EI) (*anti*): 831.46765 ($C_{46}H_{69}N_3O_7Si_2$ requires 831.4674).

[(±)-[3α,8aα(*E*)]]-1,1-Dimethylethyl 8-[[3-(Methoxycarbonyl)-2-[(4-methoxyphenyl)methyl]-8a-[4-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (42). To a stirred solution of **39** (260.0 mg, 0.292 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) at 0 °C under Ar were added DMAP (35.7 mg, 0.292 mmol, 1.0 equiv) and Et_3N (0.041 mL, 0.29 mmol, 1.0 equiv). After 5 min $(BOC)_2O$ (191.2 mg, 0.876 mmol, 3.0 equiv) was added in one portion. The resulting solution was stirred for 20 h, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude solid was purified by radial chromatography (eluted with 1:5 EtOAc/hexanes) to yield 260.4 mg (90%) of **42** as a white crystalline solid, mp 74−75 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ −0.01 (6H, s), 0.00 (6H, s), 0.113 (6H, s), 0.12 (6H, s), 0.58−0.68 (2H, m), 0.80−0.92 (38H, m), 1.06 (6H, s), 1.45−1.63 (2H, m), 1.47 (6H, s), 1.53 (6H, s), 1.60 (18H, s), 1.59−1.81 (2H, m), 2.22−2.34 (2H, m), 2.60 (2H, dd, J = 8.1, 15.0 Hz), 2.91−3.08 (2H, m), 3.26 (6H, s), 3.26−3.42 (2H, m), 3.56 (1H, $^1/_2$ ABq, J = 14.8 Hz), 3.59 (1H, $^1/_2$ ABq, J = 14.8 Hz), 3.71−3.80 (4H, m), 3.74 (6H, s), 3.83 (2H, s), 3.84 (2H, s), 3.90−3.97 (4H, m), 4.13−4.17 (2H, m), 3.32 (2H, m), 5.34 (1H, $^1/_2$ ABq, J = 14.8 Hz), 5.42 (1H, $^1/_2$ ABq, J = 14.8 Hz), 6.75−6.79 (4H, m), 6.88 (1H, d, J = 8.4 Hz), 6.89 (1H, d, J = 8.4 Hz), 7.03 (2H, s), 7.12−7.20 (6H, m). IR (NaCl, neat): 2943, 1752, 1660, 1507, 1496, 1464, 1463, 1404, 1365, 1251, 1153, 1109, 1082, 837, 772 cm^{-1}. HRMS (EI): 989.5249 ($C_{53}H_{79}N_3O_{11}Si_2$ requires 989.5253).

[(±)-[3*β*,8a*β*(*E*)]]-1,1-Dimethylethyl 8-[[8a-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)-methyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (*syn*-43). [(±)-[3α,8a*β*(*E*)]]-1,1-Dimethylethyl 8-[[8a-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]-octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]-dioxepino[2,3-*g*]indole-10-carboxylate (anti-43). A flask containing **42** (126.6 mg, 0.128 mmol, 1.0 equiv) and LiCl (27.1 mg, 0.64 mmol, 5.0 equiv) under N_2 was charged with HMPA (0.78 mL) and H_2O (3.4 × 10^{-3} mL, 1.9 × 10^{-4} mmol, 1.5 equiv). The solution was heated (100−105 °C) for 1.25 h and then poured into water and extracted with ether. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated, leaving a crude oily solid. The product

was purified by radial chromatography (eluted with 1:5 EtOAc/hexanes) to yield 79.2 mg (66%) of *syn*-**43** (an analytical sample was obtained by PTLC, eluted with 1:5 EtOAc/hexanes, to give an oil) and 3.1 mg (2.6%) of the *anti*-isomer (oil).

^{1}H NMR (300 MHz) ($CDCl_3$) (*syn*-**43**): δ 0.026 (6H, s), 0.32 (6H, s), 0.127 (6H, s), 0.14 (6H, s), 0.867 (9H, s), 0.873 (9H, s), 0.878 (9H, s), 0.883 (9H, s), 1.10 (6H, s), 1.48 (3H, s), 1.49 (3H, s), 1.55 (3H, s), 1.57 (3H, s), 1.610 (9H, s), 1.613 (9H, s), 1.83−1.96 (6H, s), 2.22−2.35 (4H, m), 2.46 (2H, dd, J = 6.0, 15.0 Hz), 3.11−3.21 (2H, m), 3.31−3.85 (2H, m), 3.37 (1H, ^{1}/2ABq, J = 14.5 Hz), 3.48 (1H, ^{1}/$_2$ ABq, J = 14.6 Hz), 3.71 (3H, s), 3.72 (3H, s), 3.76−3.98 (8H, m), 3.99 (2H, m), 4.02 (2H, s), 4.15−4.21 (4H, m), 5.17 (1H, ^{1}/$_2$ ABq, J = 14.5 Hz), 5.20 (1H, ^{1}/$_2$ ABq, J = 14.6 Hz), 5.35 (1H, m), 5.48 (1H, m), 6.62−6.70 (6H, m), 6.79 (2H, m), 6.91 (2H, d, J = 8.3 Hz), 7.14 (1H, d, J = 8.4 Hz), 7.16 (1H, d, J = 8.3 Hz), 7.22 (1H, s), 7.23 (1H, s). IR (NaCl, neat) (*syn*): 2932, 1755, 1661, 1455, 1367, 1250, 1156, 1114,1091, 838 cm^{-1}. HRMS (EI) (*syn*): 931.51955 ($C_{51}H_{77}N_3O_9Si_2$ requires 931.5198). Microanal. Calcd for $C_{51}H_{77}N_3O_9Si_2$: C, 65.70; H, 8.32; N, 4.51. Found: C, 65.37; H, 8.37; N, 4.54.

^{1}H NMR (300 MHz) ($CDCl_3$) (*anti*): δ −0.02 (6H, s), −0.01 (6H, s), 0.03−0.22 (2H, m), 0.12 (6H, s), 0.13 (6H, s), 0.146−0.62 (4H, m), 0.84 (9H, s), 0.85 (9H, s), 0.87 (18H, s), 1.05 (3H, s), 1.07 (3H, s), 1.43 (3H, s), 1.47 (3H, s), 1.49 (3H, s), 1.52 (3H, s), 1.55 (9H, s), 1.60 (9H, s), 1.80−1.91 (2H, m), 2.19−2.22 (2H, m), 2.50−2.61 (2H, m), 3.09−3.23 (2H, m), 3.29−3.52 (4H, m), 3.63−3.96 (18H, m), 4.13−4.20 (4H, m), 5.04−5.10 (1H, m), 5.28−5.32 (1H, m), 5.48 (1H, ^{1}/$_2$ ABq, J = 14.3 Hz), 5.52 (1H, ^{1}/$_2$ ABq, J = 14.3 Hz), 6.71−6.90 (6H, m), 7.04−7.22 (8H, m). IR (NaCl, neat) (*anti*: 3295 (br), 1753, 1657, 1510, 1447, 1249, 1152, 1090, 1034, 836, 773 cm^{-1}.

1,1-Dimethylethyl 8-[[8a-[4-Hydroxy-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-hydroxy-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (44). To a stirred solution of **43** (36.3 mg, 0.04 mmol, 1.0 equiv) under N_2 in THF (1.0 mL) was added *n*-Bu_4NF (0.12 mL, 0.12 mmol, 3.0 eq, 1.0M/THF). The solution was heated (~40 °C) for 3 h. At this time the solution was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. The residue was purified by PTLC on silica gel (eluted with EtOAc) to yield 24.9 mg (79%) of **44**.

^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.19 (3H, s), 1.22 (3H, s), 1.52 (3H, s), 1.53 (3H, s), 1.56 (3H, s), 1.57 (3H, s), 1.59 (9H, s), 1.60 (9H, s), 1.72−2.21 (12H, m), 2.71 (2H, br s, D_2O exch), 3.18−3.49 (4H, m), 3.51 (2H, ^{1}/$_2$ ABq, J = 14.5 Hz), 3.56 (1H, s, D_2O exch), 3.61 (1H, s, D_2O exch), 3.72 (3H, s), 3.74 (3H, s), 3.75−3.94 (6H, s), 4.18−4.30 (4H, s), 4.26−4.27 (4H, m), 4.44 (2H, m), 5.25 (2H, ^{1}/$_2$ ABq, J = 14.5 Hz), 5.25 (2H, ^{1}/$_2$ ABq, J = 14.4 Hz), 6.70 (2H, d, J = 8.7 Hz), 6.77 (2H, d, J = 8.6 Hz), 6.83 (2H, d, J = 8.6 Hz), 6.927 (1H, d, J = 8.4 Hz), 6.932 (1H, d, J = 8.3 Hz), 7.03 (2H, d, J = 8.6 Hz), 7.12 (1H, d, J = 8.3 Hz), 7.15 (1H, d, J = 8.4 Hz), 7.21 (1H, s), 7.23 (1H, s). IR (NaCl, neat): 3422, 2976, 1753, 1649, 1513, 1496, 1457, 1371, 1333, 1251, 1153, 1033, 733 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 703 (M^+, 8), 604 (37), 603 (100). HRMS (EI): 703.3461 ($C_{39}H_{49}N_3O_9$ requires 703.3472).

1,1-Dimethylethyl 8-[[8a-[4-Chloro-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-hydroxy-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (45). To **44** (24.9 mg, 0.035 mmol, 1.0 equiv) in DMF (0.35 mL) at 0 °C under Ar were added dry LiCl (2.9 mg, 0.07 mmol, 1.9 equiv) and collidine (7 μL, 0.05 mmol, 1.5 equiv). After stirring for 10 min, methanesulfonyl chloride (4 μL, 0.05 mmol, 1.5 equiv) was added dropwise. The ice bath was removed and the mixture stirred at room temperature for 24 h. At this time additional collidine (2.5 equiv) and methanesulfonyl chloride (2.5 equiv) were added, and the mixture was stirred for 2 h. It was then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness. The product was purified by PTLC on silica gel (eluted with 2:1 EtOAc/hexanes) to yield 21.9 mg (86%) of **45** as an oil.

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.22 (3H, s), 1.23 (3H, s), 1.57 (3H, s), 1.58 (3H, s), 1.62 (9H, s), 1.63 (9H, s), 1.66 (3H, s), 1.73 (3H, s), 1.83−1.93 (8H, m), 2.05−2.37 (4H, m), 3.06 (2H, dd, J = 3.8, 11.4 Hz), 3.35−3.42 (6H, m, 1H, D_2O exch), 3.46−3.69 (4H, m), 3.75 (3H, s), 3.77 (3H, s), 3.86−3.94 (2H, m), 3.96 (2H, s), 4.02 (2H, s), 4.21−4.29 (6H, m), 5.20−5.29 (3H, m), 5.53 (1H, m), 6.69−6.81 (6H, m), 6.94−6.99 (4H, m), 7.18−7.21 (4H, m). IR (NaCl, neat): 3433, 2976, 1752, 1654, 1513, 1496, 1453, 1371, 1251, 1153 cm^{-1}.

1,1-Dimethylethyl 8-[[8a-[4-Hydroxy-3-methyl-2-butenyl]-2-[(4-methoxyphenyl)methyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (46). To a solution of **45** (28.2 mg, 0.04 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL) at 0 °C under Ar was added *tert*-butyldimethylsilyl triflate (9.0 μL, 0.04 mmol, 1.2 equiv) followed immediately by 2,6-lutidine (6.0 μL, 0.047 mmol, 1.4 equiv). The mixture was stirred for 2 h, then diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by radial chromatography (eluted with 1:1 EtOAc/hexanes) to yield 24.9 mg (76%) of **46** as an oil.

^{1}H NMR (300 MHz) ($CDCl_3$): δ 0.12 (6H, s), 0.13 (6H, s), 0.87 (9H, s), 0.88 (9H, s), 1.08 (3H, s), 1.10 (3H, s), 1.48 (6H, s), 1.61 (9H, s), 1.63 (9H, s), 1.69 (3H, s), 1.79 (3H, s), 1.82−2.03 (8H, m), 2.16−2.24 (4H, m), 3.19 (2H, dd, J = 7.2, 8.5 Hz), 3.25−3.39 (4H, m), 3.49 (1H, ^{1}/$_2$ ABq, J = 14.5 Hz), 3.65 (1H, ^{1}/$_2$ ABq, J = 14.5 Hz), 3.72 (3H, s), 3.76 (3H, s), 3.79−3.99 (8H, m), 4.15−4.22 (4H, m), 5.19−5.28 (4H, m), 5.49 (2H, m), 6.67−6.81 (6H, m), 6.92 (4H, dd, J = 1.9, 8.4 Hz), 7.13 (1H, d, J = 8.4 Hz), 7.14 (1H, d, J = 8.4 Hz), 7.20 (1H, s), 7.24 (1H, s). IR (NaCl, neat): 2932, 1752, 1654, 1512, 1491, 1447, 1365, 1251, 1153, 1088, 837 cm^{-1}.

[(±)-[3α,8aα,10(R*)]-1,1-Dimethylethyl 8-[[Tetrahydro-2-[(4-methoxyphenyl)methyl]-10-(1-methylethenyl)-1,4-dioxo-6*H*-3,8a-ethanopyrrolo[1,2-*a*]pyrazin-3(4*H*)-yl]methyl]-3-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (47). To **46** (24.0 mg, 0.028 mmol, 1.0 equiv) in a flask equipped with a magnetic stir bar were added NaH (12.3 mg, 0.3 mmol, 10.8 equiv) and benzene (3.5 mL). The flask was fitted with a condenser and gently refluxed for 59 h (additional benzene (1.5 mL) was added during this time). The solution was stirred at room temperature for 8 days, after which NaI (10.8 mg, 0.072 mmol, 2.5 equiv) was added. The mixture was then stirred at reflux temperature for an additional 2 days. The resulting mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by PTLC on silica gel (eluted with 1:1 hexanes/EtOAc) to afford 2.5 mg (11% or 19% based on recovered **46**) of **47** as an amorphous yellow solid.

^{1}H NMR (300 MHz) ($CDCl_3$): δ 0.12 (6H, s), 0.14 (6H, s), 0.882 (9H, s), 0.885 (9H, s), 1.10 (3H, s), 1.13 (3H, s), 1.48 (3H, s), 1.49 (3H, s), 1.55 (3H, s), 1.56 (3H, s), 1.59 (18H, s), 1.80 (2H, dd, J = 5.7, 13.3 Hz), 1.90 (2H, dd, J = 13.2 Hz), 2.03−2.08 (4H, m), 2.22 (2H, dd, J = 10.4, 13.4 Hz), 2.85−2.98 (4H, m), 3.08 (2H, ^{1}/$_2$ ABq, J = 17.1 Hz), 3.29 (2H, ^{1}/$_2$ ABq, J = 17.6 Hz), 3.56−3.62 (4H, m), 3.72 (3H, s), 3.73 (3H, s), 3.74−3.83 (2H, dd, J = 9.4, 12.5 Hz), 3.91−3.96 (2H, m), 4.18 (2H, dd, J = 3.6, 12.2 Hz), 4.28 (1H, ^{1}/$_2$ ABq, J = 15.9 Hz), 4.37 (1H, ^{1}/$_2$ ABq, J = 15.9 Hz), 4.54−4.74 (6H, m), 6.62−6.75 (8H, m), 6.89−6.94 (2H, m), 6.99−7.04 (2H, m), 7.25 (1H, s), 7.28 (1H, s). IR (NaCl, neat): 2932, 1687, 1365, 1251, 1158, 1088 cm^{-1}. HRMS (EI): 799.4252 ($C_{45}H_{61}N_3O_8Si$ requires 799.4228).

(*R*)-(*E*)-8a-[3-Methyl-4-oxo-2-buten-yl]hexahydropyrrolo[1,2-*a*]-pyrazine-1,4-dione (49). To a stirred solution of **48** (17.25 g, 48.45 mmol, 1.0 equiv) in a 2:1 solution of CH_3CN (343 mL) and H_2O (171 mL) was added, in one portion, CAN (93 g, 170 mmol, 3.8 equiv). After stirring for 2 h, the orange solution was poured into a large separatory funnel and exhaustively extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The product was purified by column chromatography (eluted with 95:4:1 CH_2Cl_2/MeOH/AcOH) to yield 9.0 g (79%) of **49** as a yellow oil. An analytical sample was obtained by PTLC (silica gel, eluted with 1:1 hexanes/EtOAc).

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 1.76 (3H, s), 1.99−2.10 (2H, br s), 2.17−2.26 (2H, m), 2.78 (1H, dd, J = 7.3, 14.5 Hz), 2.90 (1H,

dd, J = 8.0, 14.8 Hz), 3.54−3.63 (1H, m), 3.84 (1H, dt, J = 12.3, 8.4 Hz), 3.95 (1H, d $^1/_2$ ABq, J = 3.4, 17.6 Hz), 4.10 (1H, $^1/_2$ ABq, J = 17.6 Hz), 6.55 (1H, t, J = 7.2 Hz), 7.96 (1H, br s, D_2O exch), 9.45 (1H, s). IR (NaCl, neat): 3246, 1684, 1448, 1326, 1107 cm^{-1}. $[\alpha]^{25}_D$ = −1.51/1.92 × 10^{-2})° = −78.4° (CH_2Cl_2, c = 0.164). Microanal. Calcd: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.88; H, 6.66; N, 11.71. HRMS (EI): 236.1155 ($C_{12}H_{16}N_2O_3$ requires 236.11609).

(*R*)-(*E*)-8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]hexahydro-2*H*-pyrrolo[1,2-*a*]pyrazine-1,4-dione (50). To a stirred solution of **49** (9.0 g, 37 mmol, 1.0 equiv) in absolute ethanol (742 mL) at room temperature was added $NaBH_4$ (2.85 g, 75.5 mmol, 2.0 equiv). After 2 h the excess hydride was quenched with water (500 mL) and the pH adjusted to 3−4 by the slow addition of 1 M HCl. Fifteen minutes later, the water and ethanol were removed under reduced pressure and the crude residue was dried in vacuo overnight. The resulting mass (10.87 g) was triturated (1:4 CH_3OH/CH_2Cl_2) and filtered to remove the salts. The remaining solution was concentrated to yield 9.1 g of the crude allylic alcohol, which was immediately utilized for the next step without additional purification. The crude allylic alcohol (9.1 g, 38 mmol, 1.0 equiv) was dissolved in DMF (191 mL) under Ar, and to this mixture was added imidazole (11.9 g, 175.3 mmol, 4.6 equiv) followed by *tert*-butyldiphenylsilyl chloride (12.9 mL, 49.5 mmol, 1.3 equiv). After 2 days the reaction mixture was diluted with water (1 L) and extracted with a 1:1 solution of hexanes and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude solid was recrystallized (ethyl acetate, two crops) to give 10.5 g of the product. The remaining mother liquor was chromatographed (eluted with EtOAc) to give 3.0 g of the pure product. Total yield of **50**: 13.5 g (75% from the enone, two steps). An analytical sample was recrystallized from acetone to provide a white crystalline solid, mp 132 °C.

^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.03 (9H, s), 1.54 (3H, s), 1.92−2.19 (4H, m), 2.49 (1H, dd, J = 8.6, 14.1 Hz), 2.58 (1H, dd, J = 7.5, 14.1 Hz), 3.44−3.53 (1H, m), 3.73 (1H, d $^1/_2$ ABq, J = 4.1, 16.9 Hz), 3.78−3.85 (1H, m), 4.01 (2H, s), 4.06 (1H, $^1/_2$ ABq, J = 16.9 Hz), 5.56−5.62 (1H, m), 6.38 (1H, d, J = 3.7 Hz, D_2O exch), 7.32−7.43 (6H, m), 7.62 (4H, dd, J = 1.8, 7.6 Hz). IR (NaCl, neat): 3232 (br), 2930, 2857, 1664, 1446, 1435, 1113, 822, 733, 702 cm^{-1}. $[\alpha]^{25}_D$ = −63.3° ($CDCl_3$, c = 0.0822). Microanal. Calcd for $C_{28}H_{36}N_2O_3Si$: C,70.55; H, 7.61; N, 5.88. Found C, 70.60; H, 7.56; N, 5.91.

[(R)-[3α*β*,8a*β*(*E*)]]-Methyl 8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-2-(methoxycarbonyl)-1,4-dioxopyrrolo[1,2-*a*]pyrazine-3-carboxylate (51). To a stirred solution of **50** (8.12 g, 17.0 mmol, 1.0 equiv) in THF (208 mL) at −78 °C, was added a solution of *n*-BuLi (10.65 mL, 17.03 mmol, 1.0 equiv, 1.6 M/hexanes) dropwise. After 25 min methyl chloroformate (1.45 mL, 18.7 mmol, 1.1 equiv) was added dropwise to the reaction mixture and stirred for 25 min. The solution was then transferred via cannula to a cold (−100 °C) flask charged with $LiN[Si(CH_3)_3]_2$ (37.47 mL, 37.47 mmol, 2.2 equiv, 1.0 M/THF) and methyl chloroformate (1.45 mL, 18.7 mmol, 1.1 equiv). The resulting solution was stirred for 45 min, diluted with EtOAc, and washed with saturated aqueous NH_4Cl and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluted with 2:1 hexanes/EtOAc) to yield 9.4 g (93%) of **51** (as a mixture of two diastereomers, *anti*/*syn*). An analytical sample (oil) was obtained by PTLC (eluted with 2:1 hexanes/EtOAc).

^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.04 (9H, s), 1.40 (3H, s), 1.86−2.03 (2H, m), 2.12−2.31 (2H, m), 2.55 (1H, d, J = 7.4 Hz), 3.43−3.52 (2H, m), 3.74−3.82 (1H, m), 3.83 (3H, s), 3.88 (3H, s), 4.03 (2H, br s), 5.48−5.53 (2H, m), 7.34−7.41 (6H, m), 7.57−7.66 (4H, m). IR (NaCl, neat): 2960, 1790, 1740, 1681, 1430, 1366, 1272, 1223, 1109, 735, 705 cm^{-1}. Microanal. Calcd for $C_{32}H_{40}N_2O_7Si$: C, 68.06; H, 7.14; N, 4.96. Found: C, 67.87; H, 7.27; N, 4.77.

[3*β*,8a*β*(*E*)]-Methyl 3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl]methyl]-8a-[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazine-3-carboxylate (52). To a flask containing **51** (5.89 g, 14.56 mmol, 1.0 equiv) and **36** (8.64 g, 14.56 mmol, 1.1 equiv) were added CII_3CN (291 mL) and tributylphosphine (1.82 mL, 7.28 mmol, 0.5 equiv). The resulting mixture was gently refluxed for 3.5 h and then stirred at room temperature overnight. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (eluted with 1:2 EtOAc/hexanes) to yield 9.56 g (73%) of **52**. An analytical sample was purified by PTLC on silica gel (eluted with 1:2 EtOAc/hexanes) to give a white crystalline solid, mp 106−108 °C.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.10 (6H, s), 0.115 (3H, s), 0.12 (3H, s), 0.87 (9H, s), 0.88 (9H, s), 1.02 (18H, s), 1.096 (3H, s), 1.10 (3H, s), 1.45 (3H, s), 1.46 (3H, s), 1.54 (6H, s), 1.60−1.88 (6H, m), 2.02−2.11 (2H, m): 2.92 (2H, dd, J = 7.1, 14.4 Hz), 2.44 (2H, dd, J = 8.1, 14.5 Hz), 3.32−3.44 (4H, m), 3.60 (3H, s), 3.62 (3H, s), 3.72−3.93 (8H, m), 3.98 (4H, br s), 4.18 (2H, dd, J = 2.9, 8.4 Hz), 5.43 (2H, m), 6.38 (1H, s, D_2O exch), 6.41 (1H, s, D_2O exch), 6.74 (1H, d, J = 8.5 Hz), 6.75 (1H, d, J = 8.5 Hz), 6.89 (1H, d, J = 2.3 Hz), 6.92 (1H, d, J = 2.3 Hz), 7.08 (2H, d, J = 8.5 Hz), 7.33−7.41 (12H, m), 7.61−7.63 (8H, m), 8.43 (1H, d, J = 2.9 Hz, D_2O exch), 8.64 (1H, d, J = 1.9 Hz, D_2O exch.). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 4.8, 4.2, 9.5, 17.9, 19.2, 19.3, 19.5, 20.3, 25.7, 26.8, 28.0, 28.3, 29.7, 33.7, 35.6, 46.1, 46.2, 53.3, 66.9, 68.0, 71.6, 76.3, 80.7, 80.8, 108.2, 112.9, 117.1, 117.9, 118.0, 123.5, 123.6, 125.5, 127.6, 129.1, 129.2, 129.6, 133.6, 135.5, 138.8, 141.6, 141.8, 161.4, 169.7, 170.5, 170.6. IR (NaCl, neat): 3281 (br), 2954, 2932, 2856, 1747, 1670, 1665, 1649, 1431, 1251, 1224, 1109, 1088, 733, 706 cm^{-1}. HRMS (EI): 893.4457 ($C_{50}H_{67}N_3O_8Si_2$ requires 893.4467). Microanal. Calcd for $C_{50}H_{67}N_3O_8Si_2$: C, 67.16; H, 7.55; N, 4.70. Found: C, 66.93; H, 7.36; N, 4.51.

[3*β*,8a*β*(*E*)]-8-[[8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole (53). [3α,8a*β*(*E*)] 8-[[8a-[4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-a]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole (54). A flask containing **52** (9.56 g, 10.7 mmol, 1.0 equiv) and LiCl (2.26 g, 53.45 mmol, 5.0 equiv) under Ar was charged with HMPA (82 mL) and water (0.29 mL, 16.0 mmol, 1.5 equiv). This mixture was gently heated (100−105 °C) for 9 h and then diluted with 1:1 hexanes/EtOAc. The resulting solution was washed with water. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by column chromatography (eluted with 1:2 EtOAc/hexanes) to yield 5.90 g (66%) of **53** (two diastereomers; an analytical sample was recrystallized from CCl_4, mp (*syn*) 167−168 °C) and 2.10 g (23%) of **54** (two diastereomers); an analytical sample was obtained by PTLC on silica gel (eluted with 1:2 EtOAc/hexanes, mp (*anti*) 95−99 °C, white crystalline solid). Total combined yield: 8.00 g (89%).

^{1}H NMR (300 MHz) ($CDCl_3$) (**53**, mixture of two diastereomers): δ TMS 0.12 (6H, s), 0.13 (6H, s), 0.90 (18H, s), 1.0 (18H, s), 1.126 (3H, s), 1.13 (3H, s), 1.48 (6H, s), 1.64 (6H, s), 1.94−2.06 (6H, m), 2.20−2.24 (2H, m), 2.36−2.46 (2H, m), 2.60−2.72 (2H, m), 2.98 (2H, dd, J = 11.6, 14.1 Hz), 3.44−3.57 (4H, m), 3.88 (2H, dd, J = 6.7, 9.2 Hz), 3.97 (2H, dd, J = 3.1, 9.1 Hz), 4.02−4.06 (2H, m), 4.10 (4H, s), 4.17−4.25 (4H, m), 5.58 (2H, m), 5.68 (2H, br s, D_2O exch), 6.75 (2H, d, J = 8.5 Hz), 6.86 (1H, d, J = 2.2 Hz), 6.88 (1H, J = 2.2 Hz), 7.14 (2H, d, J = 8.4 Hz), 7.26−7.44 (12H, m), 7.60−7.64 (8H, m), 8.04 (1H, s, D_2O exch), 8.06 (1H, s, D_2O exch).

The analytical samples of the *syn*-diastereomers were separable by PTLC.

^{1}H NMR (300 MHz) ($CDCl_3$) (**53a**, less polar): δ TMS 0.12 (3H, s), 0.13 (3H, s), 0.88 (9H, s), 1.03 (9H, s), 1.11 (3H, s), 1.46 (3H, s), 1.63 (3H, s), 1.92−2.04 (3H, m), 2.18−2.23 (1H, m), 2.39 (1H, dd, J = 7.2, 14.2 Hz), 2.64 (1H, dd, J = 8.7, 14.2 Hz), 2.99 (1H, dd, J = 11.4, 14.2 Hz), 3.42−3.46 (1H, m), 3.51 (1H, dd, J = 2.7, 14.2 Hz), 3.85 (1H, dd, J = 9.2, 11.3 Hz), 3.94 (1H, dd, J = 3.0, 9 Hz), 3.99−4.06 (1H, m), 4.08 (2H, s), 4.11−4.15 (1H, m), 4.19 (1H, dd, J = 3.0, 11.3 Hz), 5.58 (1H, t, J = 7.8 Hz), 5.76 (1H, d, J = 2.7 Hz, D_2O exch), 6.73 (1H, d, J = 8.4 Hz), 6.85 (1H, d, J = 2.1 Hz), 7.11 (1H, d, J = 8.5 Hz), 7.26−7.42 (6H, m), 7.57−7.63 (4H, m), 8.15 (1H, s, D_2O exch).

^{1}II NMR (300 MIIz) ($CDCl_3$) (**53b**, more polar): δ TMS 0.12 (3II, s), 0.14 (3H, s), 0.88 (9H, s), 1.03 (9H, s), 1.11 (3H, s), 1.46 (3H, s), 1.62 (3H, s), 1.91−2.04 (3H, m), 2.18−2.22 (1H, m), 2.36 (1H, dd, J

= 7.3, 14.2 Hz), 2.60 (1H, dd, J = 8.6, 14.3 Hz), 2.97 (1H, dd, J = 11.3, 14.2 Hz), 3.41−3.44 (1H, m), 3.50 (1H, dd, J = 3.1, 14.2 Hz), 3.86 (1H, dd, J = 9.3, 11.3 Hz), 3.95 (1H, dd, J = 3.0, 9.1 Hz), 3.99−4.03 (1H, m), 4.08 (2H, s), 4.14−4.16 (1H, m), 4.20 (1H, dd, J = 2.9, 11.6 Hz), 5.56 (1H, t, J =7.5 Hz), 5.72 (1H, d, J = 2.6 Hz, D_2O exch), 6.73 (1H, d, J = 8.4 Hz), 6.84 (1H, d, J = 2.1 Hz), 7.11 (1H, d, J = 8.4 Hz), 7.26−7.42 (6H, m), 7.57−7.62 (4H, m), 8.07 (1H, s, D_2O exch). IR (NaCl, neat) (*syn*): 3274 (br), 2929, 2858, 1666, 1651, 1453, 1428, 1250, 1224, 1112, 1052, 858, 838, 777 cm^{-1}. Microanal. Calcd for $C_{49}H_{65}N_3O_6Si_2$ (*syn*): C, 68.94; H, 7.84; N, 5.02. Found: C, 69.06; H, 7.76; N, 5.03.

^{1}H NMR (300 MHz) ($CDCl_3$) (**54**, mixture of two diastereomers): δ TMS 0.14 (6H, s), 0.16 (6H, s), 0.90 (18H, s), 1.04 (9H, s), 1.045 (9H, s), 1.09 (3H, s), 1.13 (3H, s), 1.47 (6H, s), 1.53 (3H, m), 1.54 (3H, m), 1.97−2.17 (8H, m), 2.47−2.62 (4H, m), 2.78−2.88 (2H, m), 3.54−3.65 (4H, m), 3.82−3.99 (6H, m), 4.02 (4H, s), 4.21 (2H, dd, J = 3.1, 11.0 Hz), 4.35−4.39 (2H, m), 5.52−5.54 (2H, m), 5.69 (2H, br s, D_2O exch), 6.60 (2H, d, J = 8.4 Hz), 6.63 (2H, d, J = 8.4 Hz), 6.89 (2H, d, J = 2.1 Hz), 6.98 (2H, d, J = 8.4 Hz), 7.36−7.42 (10H, m), 7.62−7.69 (8H, m), 8.08 (2H, br s, D_2O exch). IR (NaCl, neat) (*anti*): 3289 (br), 2929, 2855, 1666, 1444, 1428, 1254, 1222, 1111, 857, 836, 704 cm^{-1}. Mass spectrum (EI) (*anti*): *m/e* (relative intensity) 833 (M^+, 0.1), 512 (6.4), 361 (26), 360 (100), 199 (47). Microanal. Calcd for $C_{48}H_{65}N_3O_6Si_2$ (*anti*): C, 68.94; H, 7.84; N, 5.02. Found: C, 68.76; H, 7.60; N, 4.82.

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[2-[(1,1-Dimethylethoxy)carbonyl]-8a-[4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (58). To a stirred solution of **53** (310 mg, 0.37 mmol, 1.0 equiv) at 0 °C under Ar in CH_2Cl_2 (7.4 mL) were added Et_3N (0.1 mL, 0.74 mmol, 2.0 equiv) and DMAP (90.7 mg, 0.74 mmol, 2.0 equiv). After 5 min, $(BOC)_2O$ (486.2 mg, 2.2 mmol, 6.0 equiv) was added in one portion. The resulting solution was stirred for 8.5 h, poured into water, and extracted with EtOAc. The organic layer was washed with 10% $CuSO_4$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 1:2 EtOAc/hexanes) to yield 375 mg (97%) of **58** as an amorphous solid.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.12 (6H, s), 0.13 (6H, s), 0.879 (9H, s), 0.880 (9H, s), 1.01 (18H, s), 1.05 (3H, s), 1.07 (3H, s), 1.14 (9H, s), 1.18 (9H, s), 1.55 (6H, s), 1.47 (6H, s), 1.57 (18H, s), 1.88−2.16 (6H, m), 2.17−2.26 (2H, m), 2.28−2.36 (2H, m), 2.50 (2H, dd, J = 8.1, 14.5 Hz), 3.22 (2H, m), 3.32−3.45 (4H, m), 3.71−3.81 (2H, m), 3.84−3.96 (4H, m), 4.00 (4H, br s), 4.13−4.18 (2H, m), 5.02−5.07 (2H, m), 5.42 (1H, t, J = 7.3 Hz), 5.53 (1H, t, J = 7.5 Hz), 6.91 (2H, d, J = 8.3 Hz), 7.16 (1H, d, J = 8.0 Hz), 7.19 (1H, d, J = 8.2 Hz),7.22 (1H, s), 7.24 (1H, s), 7.30−7.40 (12H, m), 7.57−7.61 (8H, m). IR (NaCl, neat): 2932, 1752, 1730, 1660, 1371, 1251, 1153, 1109, 1088, 706 cm^{-1}. HRMS (EI): 1035.5481 ($C_{58}H_{81}N_3O_{10}Si_2$ requires 1035.5461).

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[2-[(1,1-Dimethylethoxy)carbonyl]-8a-[4-hydroxy-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo-[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-4,4-dimethyl-3-hydroxy-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate. To a stirred solution of **53** (511 mg, 0.61 mmol, 1.0 equiv) at 0 °C under Ar in CH_2Cl_2 (12.2 mL) were added DMAP (149.4 mg, 1.2 mmol, 2.0 equiv) and Et_3N (0.17 mL, 1.2 mmol, 2.0 equiv). After 5 min, $(BOC)_2O$ (801.0 mg, 3.67 mmol, 6.0 equiv) was added in one portion. The resulting solution was stirred for 2.7 h, and reaction was found to be complete by TLC analysis; during this period, the reaction temperature slowly reached 15 °C. The reaction flask was then charged with THF (12 mL) and the CH_2Cl_2 removed by evaporation (until the volume of the flask was approximately 12 mL). The solution was stirred at room temperature and *n*-Bu_4NF (1.96 mL, 1.96 mmol, 3.2 eq, 1.0 M/THF) added quickly. After 22 h, additional *n*-Bu_4NF (1.0 mL, 1.0 mmol, 1.6 equiv, 1.0 M/THF) was added to the reaction flask and stirred for 24 h. The reaction was complete by TLC and was poured into water and extracted with EtOAc. The organic layer was washed with 10% $CuSO_4$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with EtOAc) to yield 369 mg (89%) of the diol (obtained as a pale yellow, amorphous solid).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.21 (3H, s), 1.24 (3H, s), 1.29 ((9H, s), 1.35 (9H, s), 1.47 (6H, s), 1.52 (6H, s), 1.56 (18H, s), 1.63−2.21 (14H, m), 3.21−3.38 (8H, m), 3.54 (1H, br s, D_2O exch), 3.58 (1H, br s, D_2O exch), 3.81−3.87 (6H, m, 2H D_2O exch), 4.22 (4H, d, J = 8.0 Hz), 4.62 (1H, t, J = 8.4 Hz), 4.96−5.01 (2H, m), 5.07 (1H, t, J = 7.2 Hz), 6.90 (1H, d, J = 8.4 Hz), 6.91 (1H, d, J = 8.4 Hz), 7.13 (1H, d, J = 8.4 Hz), 7.18 (1H, d, J = 8.4 Hz), 7.22 (1H, s), 7.23 (1H, s). IR (NaCl, neat): 3436, 2978, 1755, 1649, 1367, 1249, 1149, 732 cm^{-1}.

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[2-[(1,1-Dimethylethoxy)carbonyl]-8a-[4-chloro-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo-[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-4,4-dimethyl-3-hydroxy-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate. To a stirred solution of the diol obtained above (50.0 mg, 0.0725 mmol, 1.0 equiv) in DMF (0.73 mL) at 0 °C under Ar were added collidine (0.014 mL, 0.11 mmol, 1.5 equiv) and LiCl (5.27 mg, 0.12 mmol, 1.7 equiv). After 15 min, MsCl (8.4 μL, 0.11 mmol, 1.5 equiv) was added and the reaction mixture allowed to reach room temperature in the course of 16 h. At this time an additional amount (1.0 equiv) of each reagent was added in the same manner as above. After 8.5 h there was little change by TLC, so a large excess of MsCl (0.06 mL, 0.775 mmol, 10.7 equiv) was added at 0 °C and stirred for ∼12 h until only the desired product was apparent by TLC. The solution was diluted with 1:1 hexanes/EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated, under reduced pressure. The residue was purified by radial chromatography, 1:1 EtOAc/hexanes, to yield 45.5 mg (91%) of the product allylic chloride (obtained as a foamy glass).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.18 (3H, s), 1.20 (3H, s), 1.24 (9H, s), 1.30 (9H, s), 1.51 (3H, s), 1.54 (3H, s), 1.58 (18H, s), 1.64 (3H, s), 1.66 (3H, s), 1.74−2.18 (10H, m), 2.27 (2H, dd, J = 8.1, 15.0 Hz), 3.02 (2H, br s, D_2O exch), 3.19 (2H, dd, J = 7.2, 14.8 Hz), 3.27−3.44 (4H, m), 3.56 (2H, br s), 3.81−3.89 (2H, m), 3.91 (2H, s), 3.94 (2H, s), 4.18−4.30 (4H, m), 4.99−5.06 (2H, m), 5.21 (1H, t, J = 8.3 Hz), 5.38−5.43 (1H, m), 6.93 (2H, d, J = 8.3 Hz), 7.17 (1H, d, J = 8.3 Hz), 7.20 (1H, d, J = 8.3 Hz), 7.21 (1H, s), 7.24 (1H, s). IR (NaCl, neat): 3384, 2920, 1750, 1736, 1657, 1367, 1250, 1149 cm^{-1}.

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[2-[(1,1-Dimethylethoxy)carbonyl]-8a-[4-chloro-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo-[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (55). To a stirred solution of the allylic chloride obtained above (96.2 mg, 0.37 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) under Ar were added 2,6-lutidine (0.016 mL, 0.14 mmol, 0.38 equiv) and *tert*-butyldimethylsilyl triflate (0.03 mL, 0.14 mmol, 0.38 equiv). After 1 h an additional amount (0.5 equiv) of the two reagents was added. The mixture was stirred for 1 h, and another portion (0.5 equiv) of each reagent was added. The solution was stirred for 75 min and was then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 1:2 EtOAc/hexanes) to yield 106.5 mg (99%) of **55** as a white crystalline solid, mp 70−73 °C.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.10 (3H, s), 0.11 (6H, s), 0.12 (3H, s), 0.877 (18H, s), 1.04 (3H, s), 1.06 (3H, s), 1.22 (9H, s), 1.29 (9H, s), 1.44 (3H, s), 1.46 (3H, s), 1.58 (18H, s), 1.62 (3H, s), 1.65 (3H, s), 1.76−2.13 (10H, m), 2.22 (2H, dd, J = 8.4, 14.8 Hz), 3.19 (2H, dd, J = 7.1, 14.7 Hz), 3.26−3.42 (4H, m), 3.68−3.78 (2H, m), 3.81−3.87 (4H, m), 3.90 (2H, s), 3.94 (2H, s), 4.10−4.17 (2H, m), 5.00−5.05 (2H, m), 5.22 (1H, t, J = 7.6 Hz), 5.41 (1H, t, J = 7.6 Hz), 6.91 (2H, d, J = 8.3 Hz), 7.14 (1H, d, J = 8.3 Hz), 7.16 (1H, d, J = 8.3 Hz), 7.21 (1H, s), 7.24 (1H, s). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ −5.0, −4.1, −4.0, 14.3, 17.8, 18.3, 19.7, 19.8, 25.6 27.3, 27.4, 27.9, 28.5, 29.6, 30.1, 34.5, 34.7, 36.1, 45.2, 45.32, 51.3, 51.4, 60.5, 68.1, 68.2, 70.9, 70.9, 75.7, 80.2, 83.1, 84.2, 84.2, 113.6, 113.8, 114.1, 114.2, 120.0, 120.1, 122.6, 122.7, 126.9, 127.1, 127.8, 127.9, 129.0, 135.6, 135.8, 140.43, 146.3, 146.4, 148.3, 148.4, 150.3, 150.5, 164.4, 164.5, 168.6, 168.7. IR (NaCl, neat): 2936, 1754, 1729, 1663, 1496, 1456, 1370,

1248, 1152, 1086, 838 cm^{-1}. HRMS (EI): 815.3973 ($C_{42}H_{62}N_3O_9SiCl$ requires 815.3944).

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[8a-[4-[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]octahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (59). To a flask fitted with a reflux condenser was added **58** (799 mg, 0.771 mmol, 1.0 equiv) followed by CH_3CN (15.4 mL) and dimethylamine (0.53 mL, 3.85 mmol, 5.0 equiv, 40% solution in water). The resulting solution was refluxed for 2 h and 20 min. The solvent was removed under reduced pressure and the residue purified by radial chromatography (eluted with 1:2 EtOAc/hexanes) to yield 657 mg (92%) of **59**. An analytical sample was obtained by PTLC, on silica gel (eluted with 1:2 EtOAc/hexanes) (foamy oil).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.14 (6H, s), 0.23 (6H, s), 0.88 (18H, s), 1.01 (18H, s), 1.10 (6H, s), 1.48 (6H, d), 1.59 (18H, s), 1.62 (6H, s), 1.98−2.05 (6H, m), 2.07−2.19 (2H, m), 2.37−2.47 (2H, m), 2.64−2.75 (2H, m), 2.94 (2H, dd, J = 11.6, 14.1 Hz), 3.41−3.47 (4H, m), 3.82 (2H, dd, J = 9.6, 12.2 Hz), 3.93−4.03 (4H, m), 4.07 (4H, br s), 4.10−4.15 (2H, m), 4.20 (2H, dd, J = 2.7, 12.4 Hz), 5.56−5.61 (2H, m), 5.78 (1H, d, J = 3.0 Hz, D_2O exch), 5.81 (1H, d, J = 2.8 Hz, D_2O exch), 6.877 (1H, d, J = 8.4 Hz), 6.884 (1H, d, J = 8.4 Hz), 7.09 (2H, d, J = 8.4 Hz), 7.20−7.40 (14H, m), 7.56 − 7.61 (8H, m). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ −5.0, −4.1, 13.7, 14.0, 17.8, 18.6, 18.8, 19.1, 19.6, 22.5, 25.7, 26.7, 28.0, 28.4, 28.4, 31.4, 31.6, 31.7, 34.9, 35.8, 44.81, 57.5, 67.5, 68.2, 71.0, 75.8, 76.6, 77.0, 77.4, 80.3, 83.3, 83.1, 113.3, 114.6, 116.6, 120.1, 126.3, 126.3, 127.5 127.6, 128.1, 128.2, 128.4, 128.4, 128.6, 133.1, 133.2, 135.4, 139.2, 140.5, 140.6, 146.4, 146.5, 148.4, 164.4, 169.6, 169.7. IR (NaCl, neat): 3246, 2960 2861, 1750, 1676, 1662, 1430, 1366, 1252, 1159, 1109, 1090 cm^{-1}. HRMS (EI): 935.48955 ($C_{53}H_{73}N_3O_8Si_2$ requires 935.4936). Microanal. Calcd for $C_{53}H_{73}N_3O_8Si_2$: C, 67.57; H, 7.96; N, 4.54. Found: C, 67.62; H, 7.94; N, 4.32.

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-[4-[(1,1-dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (60). To a stirred solution of **53** (3.87 g, 4.63 mmol, 1.0 equiv) in CH_2Cl_2 (46 mL) under Ar at 0 °C was added Na_2CO_3 (9.8 g, 92.6 mmol, 20.0 equiv). After 10 min, Me_3OBF_4 (3.42 g, 23.15 mmol, 5.0 equiv) was added in one portion. The mixture was stirred for 4.0 h at room temperature, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography (eluted with 1:2 hexanes/EtOAc; then 1:1 hexanes/EtOAc) to yield 3.20 g (81%) of **60**. An analytical sample was obtained by PTLC on silica gel (eluted with EtOAc) (isolated as a white solid, mp 74−76 °C).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.120 (12H, s), 0.875 (18H, s), 1.02 (18H, s), 1.06 (3H, s), 1.07 (3H, s), 1.45 (12H, s), 1.65−2.08 (14H, m), 3.07−3.15 (2H, m), 3.26 (2H, dd, J = 6.2, 12.6 Hz), 3.32−3.40 (2H, m), 3.61 (6H, s), 3.70−3.86 (2H, m), 3.91−3.95 (4H, m), 3.99 (2H, s), 4.15 (2H, dd, J = 3.6, 11.7 Hz), 4.36−4.40 (2H, m), 5.37−5.44 (2H, br m), 6.69 (2H, d, J = 8.4 Hz), 7.01 (2H, d, J = 1.7 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.26−7.41 (12H, m), 7.58−7.62 (8H, m), 8.06 (2H, s, D_2O exch). IR (NaCl, neat): 3292, 2932, 1687, 1643, 1447, 1251, 1218, 1109, 837 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 849 (M^+, 8.9), 361 (26), 360 (95), 167 (100). Microanal. Calcd for $C_{49}H_{67}N_3O_6Si_2$: C, 69.02; H, 7.94; N, 4.94. Found: C, 69.02; H, 7.88; N, 4.79.

[3α,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-[4-[(1,1-dimethylethyl)diphenylsilyl]oxy]-3-methyl-2-butenyl]-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (61). To a stirred solution of **54** (8.47 g,10.13 mmol, 1.0 equiv) in CH_2Cl_2 (101 mL) at 0 °C under Ar was added Na_2CO_3 (21.26 g, 202.6 mmol, 20.0 equiv). After 15 min Me_3OBF_4 (7.49 g, 50.64 mmol, 5.0 equiv) was added in one portion. The mixture was stirred for 5 min, the ice bath was removed, and the reaction mixture was stirred for 4.5 h. The mixture was then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by column chromatography (eluted with 1:2 EtOAc/hexanes) to yield 5.30 g (62%) of **61**. [The yield of **61** was 365 mg (71%) from 508 mg of **54**.] An analytical sample was obtained by PTLC on silica gel (eluted with 1:2 EtOAc/hexanes and obtained as a white crystalline solid, mp 54−58 °C).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.13 (3H, s), 0.14 (9H, s), 0.89 (18H, s), 1.03 (9H, s), 1.04 (9H, s), 1.087 (3H, s), 1.093 (3H, s), 1.28−1.43 (4H, m), 1.48 (6H, s), 1.50 (6H, s), 1.79−1.89 (4H, m), 2.24−2.38 (4H, m), 3.22−3.42 (6H, m), 3.60 (3H, s), 3.62 (3H, s), 3.68−3.76 (2H, m), 3.79−3.87 (2H, m), 3.94 (2H, d, J = 3.4 Hz), 3.97 (4H, br s), 4.15−4.20 (2H, m), 4.26−4.32 (2H, m), 5.41 (2H, t, J = 7.8 Hz), 6.701 (1H, d, J = 8.5 Hz), 6.703 (1H, d, J = 8.4 Hz), 6.96 (1H, d, J = 2.6 Hz), 6.97 (1H, d, J = 2.6 Hz), 7.28 (2H, d, J = 8.5 Hz), 7.32−7.44 (12H, m), 7.60−7.64 (8H, m), 7.97 (2H, br s, D_2O exch). IR (NaCl, neat): 3304, 2930, 1695, 1645, 1447, 1249, 1221, 836 cm^{-1}. HRMS (EI): 849.4550 ($C_{49}H_{67}N_3O_6Si_2$ requires 849.4568). Microanal. Calcd for $C_{49}H_{67}N_3O_6Si_2$: C, 69.22; H, 7.94; N, 4.94. Found: C, 59.06; H, 8.04; N, 4.89.

[3*β*,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-(4-hydroxy-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (62). To stirred solution of **60** (5.45 g, 6.41 mmol, 1.0 equiv) in CH_2Cl_2 (32 mL) under Ar at 0 °C were added Et_3N (0.89 mL, 6.41 mmol, 1.0 equiv) and DMAP (783.1 mg, 6.41 mmol, 1.0 equiv). After 10 min $(BOC)_2O$ (4.20 g, 19.2 mmol, 3.0 equiv) was added in one portion. The reaction mixture was stirred for 6 h and diluted with THF (45 mL). The remaining CH_2Cl_2 was removed by evaporation under reduced pressure (until the volume in the flask was 45 mL). The flask was charged with *n*-Bu_4NF (19.2 mL, 19.2 mmol, 3.0 equiv, 1.0 M/THF), and the mixture was stirred at room temperature for approximately 12 h. The solution was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by column chromatography (eluted with 1:2 EtOAc/hexanes; then 2:1 EtOAc/hexanes) to yield 3.45 g (90%) of **62**. [The yield of **62** was 243 mg (97%) from 355 mg of **60**.] An analytical sample was obtained by PTLC on silica gel (eluted with 2:1 EtOAc/hexanes) to afford a white solid, mp 72−85 °C.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.18 (6H, s), 1.52 (3H, s), 1.53 (3H, s), 1.56 (3H, s), 1.57 (21H, s), 1.61−2.07 (10H, m), 2.14 (2H, dd, J = 8.6, 14.5 Hz), 2.85 (2H, br s, D_2O exch), 2.92−3.01 (2H, m), 3.18−3.35 (6H, m), 3.56 (2H, br s, D_2O exch), 3.62 (3H, s), 3.64 (3H, s), 3.88 (4H, br s), 3.91−4.00 (2H, m), 4.25 (4H, br s), 4.30−4.39 (2H, m), 4.98−5.01 (2H, m), 6.87 (1H, d, J = 8.3 Hz), 6.88 (1H, d, J = 8.3 Hz), 7.16 (1H, d, J = 8.3 Hz), 7.17 (1H, d, J = 8.3 Hz), 7.34 (1H, s), 7.35 (1H, s). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 13.4, 19.5, 19.7, 23.5, 23.6, 25.1, 25.3, 27.9, 30.3, 30.5, 34.4, 34.8, 35.1, 35.3, 43.4, 43.6, 52.6, 52.7, 62.0, 62.4, 65.3, 65.4, 67.7, 67.8, 70.6, 75.4, 82.6, 82.6, 114.5, 114.7, 116.8, 116.9, 118.2, 118.3 119.0, 119.1, 126.3, 128.0, 128.1, 129.9 130.0, 138.6, 138.7, 140.7, 146.2, 148.5, 161.32, 161.5, 168.5, 168.7 IR (NaCl, neat): 3390 (br), 2976, 1752, 1692, 1632, 1491, 1453, 1371, 1251, 1158, 733 cm^{-1}. Microanal. Calcd for $C_{32}H_{43}N_3O_8$: C, 64.30; H, 7.25; N, 7.03. Found: C, 64.12; H, 7.41; N, 6.88. HRMS (EI): m/e 597.3065 ($C_{32}H_{43}N_3O_8$ requires 597.3050).

[3α,8a*β*(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-(4-hydroxy-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (63). To a stirred solution of **61** (5.30 g, 5.65 mmol, 1.0 equiv) under Ar in CH_2Cl_2 (1.5 mL) at 0 °C were added Et_3N (0.79 mL, 5.65 mmol, 1.0 equiv) and DMAP (689.7 mg, 5.65 mmol, 1.0 equiv). After 5 min $(BOC)_2O$ (3.70 g, 16.94 mmol, 3.0 equiv) was added in one portion. The reaction mixture was stirred for 4.5 h and diluted with THF (40 mL). The remaining CH_2Cl_2 was removed under reduced pressure (until the reaction volume was 40 mL). The flask was charged with *n*-Bu_4NF (17.0 mL, 17.0 mmol, 3.0 equiv, 1.0 M/THF), and the mixture was stirred at room temperature for ~12 h. The solution was diluted with water and extracted with EtOAc.

The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness. The residue was purified by column chromatography (eluted with EtOAc) to yield 3.16 g (85%) of **63** as a white, amorphous solid, mp 72−80 °C [The yield of **63** was 179 mg (98%) with 260 mg of **61**].

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.16 (3H, s), 1.18 (3H, s), 1.51 (3H, s), 1.52 (3H, s), 1.55 (6H, s), 1.57 (18H, s), 1.60−2.14 (10H, m, 2H D_2O exch), 2.22−2.37 (4H, m), 3.06−3.18 (3H, m, 1H D_2O exch), 3.26−3.36 (5H, m, 1H D_2O exch), 3.55 (3H, s), 3.56 (2H, br s), 3.60 (3H, s), 3.63−3.72 (2H, m), 3.89 (4H, m), 4.18−4.23 (2H, m), 4.25 (4H, br s), 5.21−5.27 (2H, m), 6.857 (1H, d, J = 8.3 Hz), 6.861 (1H, d, J = 8.3 Hz), 7.22 (2H, d, J = 8.3 Hz), 7.24 (2H, s). IR (NaCl, neat): 3401 (br), 2976, 1747, 1692, 1632, 1496, 1436, 1371, 1251, 1158, 733 cm^{-1}. HRMS (EI): 597.3050 ($C_{32}H_{43}N_3O_8$ requires 597.3050).

[3β,8aβ(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-(4-chloro-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (64). Dimethyl sulfide (0.67 mL, 9.13 mmol, 8.0 equiv) was added dropwise to a stirred solution of NCS (1.22 g, 9.13 mmol, 8.0 equiv) in CH_2Cl_2 (51 mL) at 0 °C under Ar. The resulting mixture was stirred for 10 min and then cooled to −23 °C. After 10 min, **62** (682.4 mg, 1.14 mmol, 1.0 equiv) was added to the flask in one portion and stirring continued for 6 h. At this time the reaction flask was placed in a freezer (−35 °C) for 16 h, followed by an additional 10 h of stirring at −23 °C. The mixture was then diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 1:2 hexanes/EtOAc) to yield 565.8 mg (81%) of **64** as a white amorphous solid. [The yield of **64** was 2.12 g (37% or 74% based on recovered **62**) with 5.60 g of **62**.] An analytical sample was obtained by PTLC on silica gel (eluted with 2:1 EtOAc/hexanes).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.17 (6H, s), 1.52 (6H, s), 1.57 (18H, s), 1.65 (6H, s), 1.73−2.20 (10H, m), 2.84 (2H, dd, J = 9.0, 14.4 Hz), 3.06 (1H, br s, D_2O exch), 3.10 (1H, br s, D_2O exch), 3.26−3.36 (4H, m), 3.55−3.58 (4H, m), 3.62 (3H, s), 3.63 (3H, s), 3.91 (4H, s), 3.95−4.05 (2H, m), 4.24−4.25 (4H, m), 4.30−4.36 (2H, m), 5.28 (2H, m), 6.88 (2H, d, J = 8.3 Hz), 7.14 (1H, d, J = 8.3 Hz), 7.15 (1H, d, J = 8.3 Hz), 7.376 (1H, s), 7.384 (1H, s). IR (NaCl, neat): 3403, 2979, 1750, 1716, 1642, 1348, 1154 cm^{-1}. HRMS (EI): 615.2709 ($C_{32}H_{42}N_3O_7Cl$ requires 615.2711). Microanal. Calcd for $C_{32}H_{42}N_3O_7Cl$: C, 62.38; H, 6.87; N, 6.82. Found: C, 62.53; H, 6.86; N, 6.67.

[3α,8aβ(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-(4-chloro-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]-indole-10-carboxylate (65). To a stirred solution of NCS (5.67 g, 42.4 mmol, 8.0 equiv) at 0 °C under Ar in CH_2Cl_2 (206 mL) was added dimethyl sulfide (3.12 mL, 42.4 mmol, 8.0 equiv) dropwise. After 0.5 h the mixture was cooled (−23 °C) and stirred for an additional 0.5 h. At this time the lactim ether−diol **63** (3.17 g, 5.30 mmol, 1.0 equiv) was added [approximately 3 g was added as a solid; the remaining amount was added as a solution in CH_2Cl_2 (30 mL) via cannula]. The white mixture was stirred for 12 h, diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluted with 2:1 hexanes/EtOAc; then 1:1 hexanes/EtOAc) to afford 2.80 g (86%) of **65** as a glass.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.17 (3H, s), 1.18 (3H, s), 1.52 (3H, s), 1.54 (3H, s), 1.57 (18H, s), 1.65 (6H, s), 1.71−1.92 (8H, m), 2.24−2.39 (4H, m), 3.03−3.19 (4H, m, 2H D_2O exch), 3.28−3.37 (4H, m), 3.56 (3H, s), 3.60 (3H, s), 3.59−3.75 (4H, m), 3.89 (4H, s), 4.21−4.29 (6H, m), 5.35 (2H, t, J = 7.5 Hz), 6.86 (1H, d, J = 8.3 Hz), 6.87 (1H, d, J = 8.3 Hz), 7.23 (2H, d, J = 8.3 Hz), 7.22 (1H, s), 7.27 (1H, s). IR (NaCl, neat): 3412 (br), 2976, 1752, 1698, 1638, 1365, 1251, 1158 cm^{-1}. HRMS (EI): 615.2714 ($C_{32}H_{42}N_3O_7Cl$ requires 615.2711).

[3β,8aβ(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-(4-chloro-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (66). To a stirred solution of **64** (3.55 g, 5.76 mmol, 1.0 equiv) in CH_2Cl_2 (23 mL) at 0 °C under Ar was added 2,6-lutidine (0.74 mL, 6.34 mmol, 1.1 equiv) followed by *tert*-butyldimethylsilyl triflate (1.08 mL, 6.34 mmol, 1.1 equiv). After 3 h an additional amount (1.1 equiv) of each reagent was added to the reaction flask; after stirring for 2 h, an additional amount (1.1 equiv) of each reagent was added. The mixture was stirred for 1 h, diluted with EtOAc, washed four times with water and once with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (eluted with 1:1 hexanes/EtOAc) to yield 3.23 g (77%) of **66** as an amorphous, white solid. An analytical sample was obtained by PTLC on silica gel (eluted with 1:1 hexanes/EtOAc).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.12 (6H, s), 0.13 (6H, s), 0.88 (18H, s), 1.06 (6H, s), 1.47 (6H, s), 1.59 (18H, s), 1.65 (6H, s), 1.78−1.98 (8H, s), 2.02−2.12 (2H, m), 2.86 (2H, dd, J = 9.0, 14.6 Hz), 3.31−3.34 (2H, m), 3.33 (2H, dd, J = 4.0, 13.6 Hz), 3.62 (3H, s), 3.64 (3H, s), 3.71−3.79 (2H, m), 3.73 (1H, dd, J = 4.2, 9.8 Hz), 3.77 (1H, dd, J = 4.4, 9.7 Hz), 3.92 (4H, s), 3.94−4.01 (4H, m), 4.15 (2H, dd, J = 3.8, 12.4 Hz), 4.32−4.37 (2H, m), 5.28−5.30 (2H, m), 6.87 (2H, d, J = 8.3 Hz), 7.12 (1H, d, J = 8.3 Hz), 7.13 (1H, d, J = 8.3 Hz), 7.38 (2H, s). IR (NaCl, neat): 2930, 1750, 1691, 1652, 1494, 1424, 1366, 1248, 1159, 1088 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 729 (M^+, 4.2), 731 (M + 2, 2.1), 629 (9.4), 361 (24.1), 360 (100), 167 (94.8), 57.2 (63). Microanal. Calcd for $C_{38}H_{56}N_3O_7SiCl$: C, 62.49; H, 7.73; N, 5.75. Found: C, 62.57; H, 7.71; N, 5.55.

[3α,8aβ(*E*)]-1,1-Dimethylethyl 8-[[3,4,6,7,8,8a-Hexahydro-8a-(4-chloro-3-methyl-2-butenyl)-1-methoxy-4-oxopyrrolo[1,2-*a*]pyrazin-3-yl]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (67). To a stirred solution of **65** (2.73 g, 4.43 mmol, 1.0 equiv) under Ar at 0 °C in CH_2Cl_2 (18 mL) was added 2,6-lutidine (0.57 mL, 4.87 mmol, 1.1 equiv) followed by *tert*-butyldimethylsilyl triflate (0.87 mL, 4.87 mmol, 1.1 equiv). After 1 h, 1.1 equiv of each reagent was added and stirred for 3 h. The solution was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (eluted with 1:2 EtOAc/hexanes) to yield 2.76 g (85%) of **67** as a white amorphous solid. An analytical sample was obtained by PTLC on silica gel (eluted with 1:2 EtOAc/hexanes).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.12 (6H, s), 0.13 (6H, s), 0.87 (18H, s), 1.05 (3H, s), 1.06 (3H, s), 1.47 (6H, s), 1.50−1.53 (2H, m), 1.58 (18H, s), 1.65 (6H, s), 1.72−1.91 (6H, m), 2.21−2.37 (4H, m), 3.06−3.19 (2H, m), 3.28−3.36 (4H, m), 3.56 (3H, s), 3.60 (3H, s), 3.63−3.87 (4H, m): 3.89 (4H, s), 3.93 (2H, dd, J = 3.9, 9.8 Hz), 4.13−4.18 (2H, m), 4.22−4.35 (2H, m), 5.30−5.40 (2H, m), 6.85 (1H, d, J = 8.3 Hz), 6.86 (1H, d, J = 8.3 Hz), 7.19−7.26 (4H, m). IR (NaCl, neat): 2949, 1751, 1693, 1652, 1493, 1424, 1369, 1250, 1156, 1086 cm^{-1}. Microanal. Calcd for $C_{38}H_{56}N_3O_7SiCl$: C, 62.49; H, 7.73; N, 5.75. Found: C, 62.29; H, 7.61; N, 5.76. HRMS (EI): 729.3555 ($C_{38}H_{56}N_3O_7SiCl$ requires 729.3576).

1,1-Dimethylethyl 8-[[7,8-Dihydro-1-methoxy-10-(1-methylethenyl)-4-oxo-6*H*-3,8a-ethanopyrrolo[1,2-*a*]pyrazin-3(4*H*)-yl]]methyl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylate (68). To a stirred solution of **66** (1.43 g, 1.96 mmol, 1.0 equiv) in benzene (300 mL) was added NaH (939 mg, 39.16 mmol, 20.0 equiv, freshly washed in pentane). This mixture was gently stirred at reflux temperature for 8.25 h, diluted with EtOAc, and washed with water and dilute HCl. The organic layer was isolated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 1:3 EtOAc/hexanes) to yield 1.26 g of **68** (93%). [The yield of **68** was 2.52 g (86%) from 3.10 g of **66**.]

To a stirred solution of **67** (1.60 g, 2.19 mmol, 1.0 equiv) in benzene (313 mL) was added NaH (1.05 g, 43.8 mmol, 20.0 equiv, freshly washed in pentane). This mixture was gently stirred at reflux temperature for 5.5 h and stirred at room temperature overnight. At this time, a small sample was removed, washed with water, and extracted with EtOAc. A crude proton NMR (in $CDCl_3$) indicated that the reaction was complete. The remaining mixture was diluted with EtOAc and washed with water. The organic layer was washed with

brine, dried over Na_2SO_4, and concentrated under reduced pressure. The two samples were combined and purified by radial chromatography (eluted with 1:3 EtOAc/hexanes) to yield 1.29 g of **68** (85%). An analytical sample was obtained by PTLC on silica gel (eluted with 1:3 EtOAc/hexanes); the product was obtained as a white solid, mp 105−108 °C.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.12 (6H, s), 0.13 (6H, s), 0.872 (9H, s), 0.875 (9H, s), 1.06 (3H, s), 1.07 (3H, s), 1.46 (6H, s), 1.58 (18H, s), 1.61 (3H, s), 1.64 (3H, s), 1.72−2.03 (8H, m), 2.25−2.42 (2H, m), 2.47 (2H, dd, J = 5.1, 9.7 Hz), 2.54 (2H, dd, J = 5.8, 9.7 Hz), 3.05 (1H, $^1/_2$ ABq, J = 15.0 Hz), 3.07 (1H, $^1/_2$ ABq, J = 15.0 Hz), 3.31−3.53 (6H, m), 3.57 (3H, s), 3.64 (3H, s), 3.73−3.89 (2H, m), 3.94 (2H, dd, J = 3.7, 9.7 Hz), 4.17 (2H, dd, J = 3.1, 11.6 Hz), 4.62 (1H, s), 4.75 (1H, s), 4.78 (1H, s), 4.85 (1H, s), 6.82 (2H, d, J = 8.4 Hz), 7.31 (1H, d, J = 8.4 Hz), 7.38 (1H, d, J = 8.4 Hz), 7.44 (1H, s), 7.52 (1H, s). IR (NaCl, neat): 2935, 1752, 1684, 1637, 1496, 1418, 1365, 1350, 1250, 1220, 1156, 1083 cm^{-1}. HRMS (EI): *m/e* 693.3834 ($C_{38}H_{55}N_3O_7Si$ requires 693.3809). Microanal. Calcd for $C_{38}H_{55}N_3O_7Si$: C, 65.77; H, 7.99; N, 6.05. Found: C, 65.85; H, 7.99; N, 5.91.

1,1-Dimethylethyl 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,4,8,-12,13,14,14a,15-octahydro-4,4,15,15-tetramethyl-9,17-dioxo-11*H*,16*H*-8a,13a-(iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*] carbazole-16-carboxylate (69). To a flask charged with $PdCl_2$ (827.9 mg, 4.67 mmol, 3.0 equiv) and $AgBF_4$ (605.3 mg, 3.11 mmol, 2.0 equiv) was added dry CH_3CN (50 mL). The mixture was stirred for 6.5 h, when a solution of **68** (1.08 g, 1.56 mmol, 1.0 equiv) in CH_3CN (5.0 mL) was syringed into the flask. The reaction mixture was stirred for 48 h, and EtOH (55 mL) was added, followed by small portions of $NaBH_4$ (590 mg, 15.6 mmol, 10.0 equiv) at 0 °C. The addition was complete in 0.5 h, and the mixture was stirred for an additional 0.5 h. The black mixture was filtered to remove palladium and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc, washed with dilute aqueous HCl (0.01 M) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 25:25:1 CH_2Cl_2/Et_2O/MeOH) to afford 676.3 mg (63%) of **69** as a white amorphous solid. An analytical sample was obtained by PTLC on silica gel (eluted with 25:25:1 CH_2Cl_2/Et_2O/MeOH).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.081 (6H, s), 0.11 (6H, s), 0.87 (9H, s), 0.88 (9H, s), 1.08 (3H, s), 1.17 (3H, s), 1.26 (3H, s), 1.27 (3H, s), 1.34 (3H, s), 1.35 (3H, s), 1.44 (3H, s), 1.46 (3H, s), 1.56 (9H, s), 1.58 (9H, s), 1.81−1.90 (2H, m), 1.96−2.06 (6H, m), 2.20 (2H, dd, J = 10.3, 13.5 Hz), 2.52−2.60 (4H, m), 2.78 (2H, dt, J = 6.5, 12.9 Hz), 3.36−3.49 (2H, m), 3.51−3.57 (2H, m), 3.63−3.84 (4H, m), 3.88−3.92 (2H, m), 4.04−4.16 (2H, m), 6.24 (1H, s, D_2O exch), 6.26 (1H, s, D_2O exch), 6.78 (1H, d, J = 8.3 Hz), 6.80 (1H, d, J = 8.5 Hz), 6.98 (1H, d, J = 8.2 Hz), 6.99 (1H, d, J = 8.4 Hz). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ −5.2, −5.1, −5.0, −4.5, −4.3, 17.6. 18.7, 19.3, 19.7, 19.9, 24.3,.25.5, 25.6, 26.9, 26.2, 27.2, 27.8, 27.9, 28.3, 28.5, 29.1, 31.1, 36.2, 43.8, 50.5, 50.6, 53.3, 54.8, 55.7, 59.4, 60.2, 60.2, 66.3, 67.6, 71.1, 72.7, 75.9, 78.0, 80.5, 84.1, 84.3, 108.3, 112.4, 112.5, 113.6, 117.9, 118.5, 124.6, 124.9, 128.7, 128.9, 129.4, 137.7, 138.3, 139.4, 139.6, 143.0, 143.2, 152.9, 153.0, 168.3, 174.1. IR (neat): 3214, 2928, 2856, 1745, 1556, 1496, 1443, 1368, 1252, 1233, 1154, 1141, 1091, 1052, 994, 859, 838, 777, 733. Microanal. Calcd for $C_{37}H_{53}N_3O_7$-Si: C, 65.36; H, 7.86; N, 6.18. Found: C, 65.18; H, 7.77; N, 6.18. MS (EI): *m/e* (relative intensity) 679 (M^+, 0.3), 580 (20.4), 579 (51), 73 (100). HRMS (EI): *m/e* 679.3661 ($C_{37}H_{53}N_3O_7Si$ requires 679.3653).

1,1-Dimethylethyl 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,4,8,-12,13,14,14a,15-octahydro-4,4,15,15-tetramethyl-17-methoxy-9-oxo-11*H*,16*H*-8a,13a-(iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole-16-carboxylate (71). To a stirred solution of **69** (26.1 mg, 0.38 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) under Ar at 0 °C was added Na_2CO_3 (81.0 mg, 0.76 mmol, 20.0 equiv). After 10 min Me_3OBF_4 (28.3 mg, 0.191 mmol, 5.0 equiv) was added in one portion. The mixture was stirred for 4 h at room temperature, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by PTLC on silica gel (eluted with 1:2 hexanes/EtOAc) to afford 19.6 mg (74%) of **71** as a white amorphous solid.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ TMS 0.10−0.15 (12H, m), 0.89 (9H, s), 0.90 (9H, s), 1.09 (6H, s), 1.26 (3H, s), 1.29 (3H, s), 1.33 (3H, s), 1.36 (3H, s), 1.46 (3H, s), 1.48 (3H, s), 1.58 (9H, s), 1.60 (9H, s), 1.76−2.51 (10H, m), 2.23−2.31 (2H, m), 2.60−2.70 (2H, m), 3.027 (1H, $^1/_2$ ABq, J = 16.4 Hz), 3.032 (1H, $^1/_2$ ABq, J = 16.4 Hz), 3.31−3.41 (2H, m), 3.46−3.54 (2H, m), 3.68 (2H, dd, J = 9.1, 12.1 Hz), 3.77 (6H, s), 3.87−3.94 (2H, m), 3.90 (2H, $^1/_2$ ABq, J = 16.3 Hz), 4.08 (2H, dd, J = 3.5, 11.9 Hz), 6.79 (1H, d, J = 8.3 Hz), 6.80 (1H, d, J = 8.3 Hz), 7.063 (1H, d, J = 8.3 Hz), 7.061 (1H, d, J = 8.3 Hz). IR (NaCl, neat): 2952, 2886, 1745, 1683, 1640, 1496, 1412, 1355, 1252, 1232, 1156, 1140, 1111, 1090, 1052, 992, 838, 770 cm^{-1}. HRMS (EI): *m/e* 693.3810 ($C_{38}H_{55}N_3O_7Si$ requires 693.3810).

3-(Hydroxy)-3,4,8,12,13,14,14a,15-octahydro-4,4,15,15-tetramethyl-9,17-dioxo-11*H*,16*H*-8a,13a-(iminomethano)-2*H*,9*H*-[1,4]dioxepino-[2,3-*a*]indolizino[6,7-*h*]carbazole (76). To a stirred solution of **69** (150 mg, 0.22 mmol, 1.0 equiv) in CH_2Cl_2 (4.4 mL) under N_2 at 0 °C was added TFA (1.4 mL, 17.8 mmol, 80 equiv) dropwise. The reaction mixture was allowed to reach room temperature overnight. The solution was concentrated and the residue taken up in EtOAc. The resulting solution was washed with 10% Na_2CO_3 and brine. The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was purified by radial chromatography (eluted with EtOAc) to yield 102 mg (95%) of **76**. An analytical sample was obtained by PTLC on silica gel (eluted with 1:1 EtOAc/hexanes) as a white amorphous solid.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.06 (3H, s), 1.08 (3H, s), 1.18 (3H, s), 1.20 (3H, s), 1.23 (3H, s), 1.29 (3H, s), 1.49 (3H, s), 1.55 (3H, s), 1.79−2.04 (8H, m), 2.17 (2H, td, J = 5.1, 11.9 Hz), 2.43 (1H, m), 2.43 (1H, $^1/_2$ ABq, J = 15.5 Hz), 2.51 (1H, dd, J = 4.8, 10.2 Hz), 2.59 (1H, $^1/_2$ ABq, J = 15.5 Hz), 2.78 (2H, dt, J = 6.5, 12.9 Hz), 3.21 (1H, br s, D_2O exch), 3.33−3.41 (3H, m), 3.41−3.56 (3H, m), 3.60 (1H, br s, D_2O exch), 3.70 (1H, $^1/_2$ ABq, J = 15.4 Hz), 3.78 (1H, $^1/_2$ ABq, J = 15.4 Hz), 4.12 (2H, dd, J = 8.4, 12.0 Hz), 4.25 (2H, td, J = 4.0, 12.2 Hz), 6.65 (2H, s, D_2O exch), 6.72 (1H, d, J = 8.3 Hz), 6.73 (1H, d, J = 8.3 Hz), 7.02 (1H, d, J = 7.9 Hz), 7.05 (1H, d, J = 8.1 Hz), 7.98 (1H, s, D_2O exch), 8.10 (1H, s, D_2O exch). IR (NaCl, neat): 3308, 1684, 1679, 1402, 1367, 1232, 1044, 733 cm^{-1}. HRMS (EI): *m/e* 465.2248 ($C_{26}H_{31}N_3O_5$ requires 465.2264).

14-Deoxy-29-demethyl-24,25-dihydro-25-hydroxy-12-oxo-17-nor-paraherquamide (79). To a stirred mixture of **76** (16.5 mg, 0.035 mmol, 1.0 equiv) in CH_2Cl_2 (0.7 mL) at 0 °C under N_2 was added Et_3N (4.6 μL, 0.04 mmol, 1.1 equiv) followed by *t*-BuOCl (5.4 μL, 0.04 mmol, 1.1 equiv). After 0.5 h, the resulting clear, yellow solution was concentrated to dryness (the flask being kept cold). The residue was immediately subjected to a solution of MeOH/H_2O/AcOH (40:20:1) and stirred under N_2 at room temperature for 0.5 h. The solution was diluted with saturated $NaHCO_3$, and the organic layer was washed three times with saturated $NaHCO_3$, washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by PTLC on silica gel (eluted with 20:1 CH_2Cl_2/MeOH) to yield 5.0 mg (29%) of **79** as an amorphous solid.

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.46 (3H, s), 0.48 (3H, s), 0.93 (6H, s), 1.22 (3H, s), 1.23 (3H, s), 1.45 (3H, s), 1.51 (3H, s), 1.65−2.09 (14H, m), 2.71−2.79 (2H, m), 2.87 (2H, td, J = 3.2, 9.3 Hz), 3.40−4.99 (2H, m), 3.56−3.66 (6H, m, 2H D_2O exch), 4.08−4.26 (4H, m), 6.56 (1H, d, J = 8.1 Hz), 6.61 (1H, d, J = 8.1 Hz), 6.80 (1H, d, J = 7.7 Hz), 6.82 (1H, d, J = 7.8 Hz), 6.96 (1H, s, D_2O exch), 7.09 (1H, s, D_2O exch), 8.03 (1H, s, D_2O exch), 8.11 (1H, s, D_2O exch). IR (NaCl, neat): 3411, 3237, 1698, 1632, 1496, 1404, 1333, 1213, 728 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 481 (M^+, 23.9), 412 (15.2), 249 (12.7), 220 (100), 149 (60.6). HRMS (EI): *m/e* 481.2194 ($C_{26}H_{31}N_3O_6$ requires 481.2213).

1,1-Dimethylethyl 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,4,8,-12,13,14,14a,15-octahydro-4,4,15,15-tetramethyl-17-oxo-11*H*,16*H*-8a,13a-(iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole-16-carboxylate (70). To a stirred solution of **69** (164 mg, 0.24 mmol, 1.0 equiv) in THF (4.9 mL) at −78 °C under Ar was added Et_3Al (0.14 mL, 0.26 mmol, 1.1 equiv, 1.9 M in toluene)

dropwise. After 10 min the solution was warmed to 0 °C and AlH_3·DMEA (6.0 mL, 1.20 mmol, 5.0 equiv, 0.2 M in toluene) was added dropwise. The ice bath was removed and the solution stirred for 1 h and 20 min at room temperature. At this time MeOH (4.7 mL) and AcOH (0.31 mL) were syringed into the flask, followed by $NaCNBH_3$ (179 mg, 2.85 mmol, 11.9 equiv). This mixture was stirred for 10 min, and the solvent was removed under reduced pressure and replaced with ethyl acetate. The resulting solution was washed with $NaHCO_3$ (saturated) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 1:1 hexanes/EtOAc) to yield 102 mg (65%) of **70** as a white amorphous solid. An analytical sample was obtained by PTLC on silica gel (eluted with 1:1 EtOAc/hexanes).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.085 (6H, s), 0.11 (6H, s), 0.87 (9H, s), 0.88 (9H, s), 1.12 (3H, s), 1.15 (3H, s), 1.23 (3H, s), 1.24 (3H, s), 1.36 (3H, s), 1.37 (3H, s), 1.45 (6H, s), 1.59 (9H, s), 1.61 (9H, s), 1.88−1.92 (6H, s), 1.97−2.10 (2H, m), 2.17−2.26 (2H, m), 2.54−2.63 (2H, m), 2.70 (2H, $^1/_2$ ABq, J = 15.5 Hz), 2.829 (1H, $^1/_2$ ABq, J =15.4 Hz), 2.835 (1H, $^1/_2$ ABq, J = 15.6 Hz), 3.06−3.09 (2H, m), 3.45−3.49 (4H, m), 3.67−3.85 (4H, m), 3.90 (2H, dd, J = 3.4, 8.7 Hz), 4.09−4.18 (4H, m), 6.03 (2H, s, D_2O exch), 6.78 (1H, d, J = 8.3 Hz), 6.79 (1H, d, J = 8.3 Hz), 6.89 (2H, d, J = 8.3 Hz). IR (NaCl, neat): 3227, 2928, 1746, 1683, 1597, 1371, 1254, 1233, 1154, 1138, 1090, 836 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 665 (M^+, 0.3), 565 (30.6), 521 (40.1), 164 (100). Microanal. Calcd for $C_{37}H_{55}N_3O_6Si$: C, 66.73; H, 8.32; N, 6.31. Found: C, 66.50; H, 8.18; N, 6.33. HRMS (EI): *m/e* 665.38365 ($C_{37}H_{55}N_3O_6Si$ requires 665.3860).

1,1-Dimethylethyl 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,4,8,-12,13,14,14a,15-octahydro-4,4,15,15,18-pentamethyl-17-oxo-11*H*,-16*H*-8a,13a-(iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-*a*]indolizino-[6,7-*h*]carbazole-16-carboxylate (72). To a stirred solution of **70** (147.5 mg, 0.22 mmol, 1.0 equiv) in DMF (2.2 mL) under Ar at 0 °C was added NaH (13.3 mg, 0.55 mmol, 2.5 equiv). After 5 min, MeI (27.6 μL, 0.44 mmol, 2.0 equiv) was syringed in dropwise. The mixture was stirred for 4 h, when a small amount of water and mercaptoethanol (21.6 μL) were added. After a few minutes, the mixture was diluted with water and extracted with 1:1 hexanes/EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with 1:2 hexanes/EtOAc) to yield 146.9 mg (98%) of **72** as a white amorphous solid. An analytical sample was obtained by PTLC on silica gel (eluted with 1:1 EtOAc/hexanes).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 0.089 (6H, s), 0.11 (6H, s), 0.87 (9H, s), 0.88 (9H, s), 1.13 (3H, s), 1.15 (3H, s), 1.25 (6H, s), 1.36 (3H, s), 1.37 (3H, s), 1.46 (6H, s), 1.59 (9H, s), 1.61 (9H, s), 1.86−2.06 (10H, m), 2.09−2.20 (6H, m), 2.61−2.70 (2H, m), 2.747 (1H, $^1/_2$ ABq, J = 15.4 Hz), 2.754 (1H, $^1/_2$ ABq, J = 15.4 Hz), 2.30−3.05 (2H, m), 3.05 (6H, s), 3.14 (2H, $^1/_2$ ABq, J = 15.4 Hz), 3.39 (2H, d, J = 10.5 Hz), 3.74−3.85 (2H, m), 3.89−3.93 (2H, m), 4.07−4.18 (2H, m), 6.797 (1H, d, J = 8.3 Hz), 6.804 (1H, d, J = 8.3 Hz), 6.93 (2H, d, J = 8.3 Hz). IR (NaCl, neat): 2921, 1747, 1665, 1496, 1371, 1251, 1235, 1158, 1142, 1108, 1093, 837, 755 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 679 (M^+, 2.1), 579 (4.2), 520 (4.2), 178 (100). Microanal. Calcd for $C_{38}H_{57}N_3O_6Si$: C, 67.12; H, 8.45; N, 6.18. Found: C, 67.33; H, 8.27; N, 6.44. HRMS (EI): *m/e* 679.4008 ($C_{38}H_{57}N_3O_6Si$ requires 679.4017).

3-Hydroxy-3,4,8,12,13,14,14a,15-octahydro-4,4,15,15,18-pentamethyl-17-oxo-11*H*,16*H*-8a,13a-(iminomethano)-2*H*,9*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole (73). To a stirred solution of **72** (294.7 mg, 0.43 mmol, 1.0 equiv) in CH_2Cl_2 (8.7 mL) at 0 °C under Ar was added TFA (2.77 mL, 34.7 mmol, 80.0 equiv) dropwise. The solution was stirred for 15 h, the temperature being maintained at 15 °C. At this time the solution was concentrated under reduced pressure, diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by radial chromatography (eluted with EtOAc) to yield 194.8 mg (96%) of **73** as a white amorphous solid. An analytical sample was obtained by PTLC on silica gel (eluted with 1:1 EtOAc/hexanes).

^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 1.21 (3H, s), 1.23 (3H, s), 1.29 (3H, s), 1.32 (3H, s), 1.42 (3H, s), 1.45 (3H, s), 1.54 (6H, s), 1.88−2.00 (10H, m), 2.07−2.22 (6H, m), 2.63−2.72 (2H, m), 2.79 (1H, $^1/_2$ ABq, J = 15.1 Hz), 2.80 (1H, $^1/_2$ ABq, J = 15.1 Hz), 3.01−3.07 (4H, m, 2H D_2O exch), 3.07 (6H, s), 3.17 (1H, $^1/_2$ ABq, J = 15.1 Hz), 3.19 (1H, $^1/_2$ ABq, J = 15.4 Hz), 3.37−3.43 (2H, m), 3.62 (2H, br s), 4.20 (2H, dd, J = 4.4, 12.3 Hz), 4.29 (1H, dd, J = 4.0, 12.3 Hz), 4.31 (1H, dd, J = 4.0, 12.3 Hz), 6.750 (1H, d, J = 8.4 Hz), 6.753 (1H, d, J = 8.3 Hz), 7.01 (2H, d, J = 8.4 Hz), 8.01 (2H, s, D_2O exch). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ 14.0, 20.8, 22.6, 23.9, 24.4, 24.5, 24.7, 25.1, 27.7, 27.9, 30.2, 30.3, 31.3, 34.4, 45.9, 54.3, 57.4, 60.0, 60.2, 64.0, 71.0, 75.5, 76.6, 77.0, 77.4, 79.5, 104.6, 112.2, 116.17, 116.22, 125.0, 129.2, 137.2, 140.4, 141.6, 171.0, 174.3. IR (NaCl, neat): 3324, 2954, 1654, 1507, 1474, 1365, 1235, 1071, 1049, 908, 733 cm^{-1}. Microanal. Calcd for $C_{27}H_{35}N_3O_4Si$: C, 69.65; H, 7.58; N, 9.02. Found: C, 69.54; H, 7.66; N, 8.89. Mass spectrum (EI): *m/e* (relative intensity) 465 (M^+, 9.7), 406 (14.5), 287 (11.8), 178 (100). HRMS (EI): *m/e* 465.2625 ($C_{27}H_{35}N_3O_4Si$ requires 465.2628).

14-Deoxy-24,25-dihydro-25-hydroxy-17-norparaherquamide (80). To a stirred solution of **73** (99 mg, 0.21 mmol, 1.0 equiv) in pyridine (4 mL) at −15 °C under Ar was added *t*-BuOCl (37 μL, 0.32 mmol, 1.5 equiv). After 2 h the solvent was removed under reduced pressure to give 106 mg (quantitative) of the crude chloroindolenines (**74**/**75** as a mixture of epimers). The majority of the crude chloroindolenines, **74**/**75** (71 mg, 0.14 mmol, 1.0 equiv), was dissolved in THF (10 mL) and water (1 mL), and *p*-toluenesulfonic acid monohydrate (135 mg, 0.41 mmol, 15 equiv) was added. The resulting yellow solution was stirred at reflux temperature for 20 min and diluted with EtOAc and aqueous K_2CO_3. The organic layer was isolated, washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by PTLC on silica gel (eluted with 20:1 CH_2Cl_2/MeOH) to yield (from the chloroindolenines) 52 mg (76%) of **80** and 2.7 mg (4%) of **81**.

^{1}H NMR (300 MHz) ($CDCl_3$) (**80** mixture of two diastereomers): δ TMS 0.80 (3H, s), 0.83 (3H, s), 1.08 (3H, s), 1.10 (3H, s), 1.22 (3H, s), 1.26 (3H, s), 1.50 (3H, s): 1.52 (3H, s), 1.40−1.60 (8H, m), 1.77−1.93 (8H, m), 2.05−2.21 (2H, m), 2.55−2.71 (4H, m), 3.02−3.10 (4H, m), 3.06 (6H, s), 3.63 (4H, br s, 2H D_2O exch), 4.05−4.24 (4H, m), 6.60 (1H, d, J = 8.1 Hz), 6.62 (1H, d, J = 8.2 Hz), 6.78 (1H, d, J = 8.1 Hz), 6.79 (1H, d, J = 8.2 Hz), 7.42 (1H, s, D_2O exch), 7.45 (1H, s, D_2O exch). IR (NaCl, neat): 3333, 2974, 2933, 1703, 1651, 1646, 1631, 1456, 1395, 1323, 1200, 1046, 903, 728 cm^{-1}. Mass spectrum (EI): *m/e* (relative intensity) 481 (M^+, 0.7), 422 (20.7), 421 (15), 135 (48), 133 (100). HRMS (CI): *m/e* 481 ($C_{27}H_{35}N_3O_5$ requires 481.2578), [M + H] 482.2645 ($C_{27}H_{36}N_3O_5$ requires 482.2655).

^{1}H NMR (500 MHz) ($CDCl_3$) (**81** mixture of two diastereomers): δ TMS 0.53 (3H, s), 0.56 (3H, s), 0.84 (3H, s), 0.86 (3H, s), 1.22 (3H, s), 1.25 (3H, s), 1.50 (3H, s), 1.52 (3H, s), 1.41−1.73 (8H, m), 1.83−1.90 (8H, m), 2.09−2.13 (2H, m), 2.28−2.41 (6H, m), 2.51−2.58 (2H, m), 3.00 (3H, s), 3.01 (3H, s), 3.63 (2H, br s), 3.78 (1H, D_2O exch), 3.81 (1H, s D_2O exch), 4.05−4.24 (4H, m), 6.60 (2H, d, J = 8.0 Hz), 6.62 (2H, d, J = 7.4 Hz), 7.42 (2H, s, D_2O exch). IR (NaCl, neat): 3271, 2924, 2854, 1714, 1644, 1496, 1464, 1393, 1375, 1211, 1142, 1066 cm^{-1}.

(+)-Paraherquamide B (12). To a stirred solution of **80** (22.5 mg, 0.047 mmol, 1.0 equiv) in DMPU (500 μL) under Ar at room temperature was added MTPI (90 mg, 0.20 mmol, 4.0 equiv). After 16 h KOH (10 mL, 1 M) was added, and the mixture was stirred for an additional 10 min. The pH was adjusted to 2 (addition of HCl) and the mixture extracted with EtOAc. The mixture was diluted with 1:1 hexanes/EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by PTLC on silica gel (eluted with 20:1 CH_2Cl_2/MeOH) to afford 17.1 mg (79%) of (+)-paraherquamide B (**12**) as a white, amorphous solid. This material proved to be identical to an authentic sample of natural (−)-paraherquamide B by ^{1}H NMR, ^{13}C NMR, TLC mobility, IR, mass spectrum, and UV (see text for CD spectrum, Figure 7).

^{1}H NMR (300 MHz) ($CDCl_3$): δ TMS 0.82 (3H, s), 1.09 (3H, s), 1.40 (3H, s), 1.41 (3H, s), 1.64 (1H, dd, J = 9.7, 12.4 Hz), 1.73−1.92 (4H, m), 1.82 (1H, $^1/_2$ ABq, J = 15.5 Hz), 2.16 (1H, dd, J = 8.6, 17.8 Hz), 2.54−2.59 (1H, m), 2.61 (1H, $^1/_2$ ABq, J = 11.1 Hz), 2.66 (1H, $^1/_2$ ABq, J = 15.5 Hz), 3.03−3.10 (2H, m), 3.05 (3H, s), 3.60 (1H, $^1/_2$

ABq, J = 11.1 Hz), 4.87 (1H, d, J = 7.7 Hz), 6.30 (1H, d, J = 7.7 Hz), 6.64 (1H, d, J = 8.2 Hz), 6.78 (1H, d, J = 8.2 Hz), 8.5 (1H, br s, D_2O exch). ^{13}C NMR (75.5 MHz) ($CDCl_3$): δ 20.7 (q), 23.8 (q), 26.2 (q), 28.2 (q), 28.8 (t), 29.8 (t), 29.9 (q), 37.2 (t), 46.1 (s), 52.8 (d), 53.8 (t), 59.5 (t), 63.0 (s), 65.2 (s), 67.4 (s), 79.7 (s), 115.0 (d), 117.2 (d), 120.3 (d), 125.3 (s), 132.5 (s), 135.3 (s), 139.0 (d), 146.0 (s), 172.9 (s), 183.1 (s). IR (NaCl, neat): 3190, 2974, 2933, 1703, 1697, 1651, 1631, 1503, 1456, 1328, 1195, 1046 728 cm^{-1}. UV: λ_{max} 226 nm (ϵ = 30 200). $[\alpha]^{25}_D = (+0.4/7.75 \times 10^{-3})^\circ = +51.6^\circ$ ($CHCl_3$, c = 0.008). Mass spectrum (EI): *m/e* (relative intensity) 463 (M^+, 0.5), 404 (15.6), 135 (41.5), 133 (100). HRMS (EI): *m/e* 463.2456 ($C_{27}H_{33}N_3O_4$ requires 463.2471).

Spiro Product 56. ^1H NMR (300 MHz) (acetone-d_6) (mixture of two diastereomers): δ TMS 0.21 (12H, s), 0.93 (18H, s), 1.13 (6H, s), 1.41 (18H, s), 1.48 (6H, s), 1.62 (18H, s), 1.82 (6H, s), 1.88−2.15 (6H, m), 2.54 (2H, t, J = 11.3 Hz), 2.81−2.83 (4H, m), 3.02−3.06 (4H, m), 3.36−3.42 (2H, m), 3.62−3.64 (2H, m), 3.88 (2H, dd, J = 9.3, 12.2 Hz), 3.99 (2H, dd, J = 3.5, 9.3 Hz), 4.21 (2H, dd, J = 3.5, 12.2 Hz), 4.61−4.83 (4H, m), 4.96 (2H, br s), 5.07 (2H, br s), 5.94 (2H, d, J = 8.5 Hz, D_2O exch), 6.92 (2H, d, J = 8.3 Hz), 7.25 (2H, d, J = 8.3 Hz), 7.41 (2H, s). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ −4.9 (q), −4.0 (q), 16.5 (q), 17.9 (s), 18.4 (q), 24.1 (t), 25.7 (q), 28.0 (q), 28.3 (q), 28.6 (q), 29.4 (t), 29.7 (d), 35.6 (t), 36.6 (t), 47.9 (t), 51.7 (d), 66.6 (s), 70.9 (t), 75.9 (d), 76.6 (s), 79.8 (d), 80.4 (s), 83.1 (s), 113.7 (d), 113.9 (t), 114.6 (s), 120.3 (d), 126.4 (d), 127.9 (s), 129.3 (s), 140.4 (s), 141.8 (s), 146.6 (s), 148.5 (s), 155.0 (s), 169.7 (s), 176.6 (s). IR (NaCl, neat): 2932, 1780, 1752, 1714, 1649, 1496, 1425, 1365, 1251, 1229, 1158, 1088 cm^{-1}.

Spiro Product 57. ^1H NMR (300 MHz) (acetone-d_6) (mixture of two diastereomers): δ TMS 0.21 (12H, s), 0.94 (18H, s), 1.14 (6H, s), 1.41 (18H, s), 1.47 (6H, s), 1.62 (18H, s), 1.80 (6H, s), 1.96−2.07 (6H, m), 2.58 (2H, t, J = 11.3 Hz), 2.84 (4H, br s), 2.98−3.13 (4H, m), 3.48−3.50 (2H, m), 3.51−3.52 (2H, m), 3.88 (2H, dd, J = 9.3, 12.1 Hz), 4.00 (2H, dd, J = 3.4, 9.1 Hz), 4.22 (2H, dd, J = 3.4, 12.2 Hz), 4.72 (2H, dd, J = 6.6, 15.0 Hz), 4.84 (2H, dd, J = 6.3, 10.7 Hz), 4.96 (2H, br s), 5.08 (2H, br s), 5.95 (2H, d, J = 8.6 Hz, D_2O exch), 6.91 (2H, d, J = 8.3 Hz), 7.23 (2H, d, J = 8.3 Hz), 7.38 (2H, s). ^{13}C NMR (75.5 MHz) ($CDCl_3$) (mixture of two diastereomers): δ −4.9 (q), −4.0 (q), 16.5 (q), 17.9 (s), 18.8 (q), 24.1 (t), 25.7 (q), 28.0 (q), 28.3 (q), 29.0 (t), 29.7 (d), 35.6 (t), 36.7 (t), 48.0 (t), 52.4 (d), 66.7 (s), 71.0 (t), 75.8 (d), 76.6 (s), 79.8 (d), 80.4 (s), 83.1 (s), 113.6 (d), 113.8 (t), 114.7 (s), 120.0 (d), 126.1 (d), 127.8 (s), 129.3 (s), 140.4 (s), 141.7 (s), 146.4 (s), 148.6 (s), 155.0 (s), 169.8 (s), 175.7 (s). IR (neat): 2926, 1783, 1754, 1715, 1652, 1494, 1457, 1367, 1250, 1160, 1087 cm^{-1}.

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EXHIBIT 18

JOC Article

Synthetic Studies on Et-743. Assembly of the Pentacyclic Core and a Formal Total Synthesis

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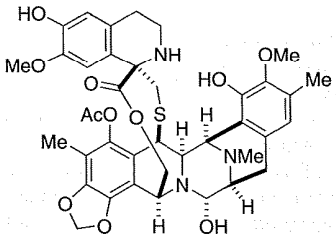
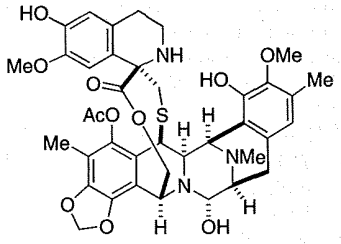


1, ecteinascidin 743

A formal total synthesis of the potent anticancer agent Et-743 is described. The tetrahydroisoquinoline core is stereoselectively constructed using a novel radical cyclization of a glyoxalimine. Further elaboration of this core rapidly accessed the pentacyclic core of Et-743, but a mixture of regiosisomers was obtained in the key Pictet−Spengler ring closure. A known advanced intermediate in the synthesis of Et-743 was intercepted, constituting a formal synthesis of the molecule.

Introduction

Members of the tetrahydroisoquinoline family of alkaloids display a wide range of biological properties such as antitumor and antimicrobial activities.[1] Of particular significance within this family is Ecteinascidin 743 (Et-743, **1**, Figure 1,) which has been demonstrated to possess extremely potent cytotoxic activity with in vitro IC_{50} values in the 0.1−1 ng/mL range in several cell lines (as a measure of RNA, DNA, and protein synthesis inhibition).[2] Et-743 is currently in phase II/III clinical trials for the treatment of ovarian, endometrial, and breast cancers and several sarcoma lines.[3]The scarcity of the natural product from marine sources renders Et-743 an important target for synthesis. Corey and co-workers reported the first total synthesis of Et-743 in 36 steps with an overall yield of 0.72%.[4a]



1, ecteinascidin 743

FIGURE 1. Ecteinascidin 743 (**1**).

A second-generation synthesis improved the overall yield to 2.04%, but still required 36 steps.[4b] Fukuyama and co-workers achieved a total synthesis of Et-743 in 50 steps and 0.56% overall yield.[5] More recently, Zhu and co-workers reported a 31 step synthesis in 1.7% overall yield.[6] Most recently, Danishefsky and co-workers reported a formal total synthesis[7]via a pentacyclic compound that intercepted a late-stage intermediate of Fukuyama's route.[5] Despite the advancements in the state-of-the-art in total synthetic approaches to Et-743, the clinical supply of this complex drug is semisynthetically derived from natural cyanosafracin B, obtained by fermentation as reported by PharmaMar.[8]

Our laboratory has been developing methodology for the assembly of tetrahydroisoquinoline natural products and has

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[‡] University of Colorado Cancer Center.

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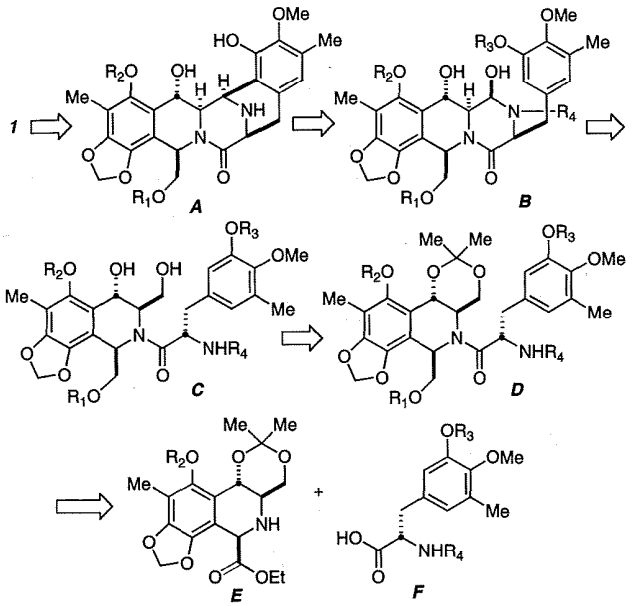
SCHEME 1. Synthetic Plan



reported syntheses of D,L-quinocarcinamide,[9] (−)-tetrazomine,[10] (−)-renieramycin G,[11] (−)-jorumycin,[11] and cribrostatin 4 (renieramycin H).[12] As a part of this program, we have targeted Et-743 by a convergent route that envisioned coupling of a suitably functionalized tyrosine derivative[13] with the complete tetrahydroisoquinoline core (Scheme 1.) We have successfully deployed this strategy, with the present objective of construction of pentacycle **A**, in the synthesis of (−)-renieramycin G and (−)-jorumycin.[11,12]

We have previously reported a concise and highly diastereoselective synthesis of the tetrahydroisoquinoline core of Et-743 (**E**).[14] This was achieved via an intramolecular 6-*endo* radical closure on a glyoxalimine, and the desired 1,3-*cis*-diastereomer was obtained exclusively. The synthesis of a tetrahydroisoquinoline such as **E** can be problematic because of the acid sensitivity of the benzylic hydroxyl, particularly because it is *ortho* to the phenolic hydroxyl of the aromatic ring and thus has a high propensity for *ortho*-quinonemethide formation. Herein, we report a formal total synthesis of Et-743 as part of our ongoing efforts to devise a practical and scalable synthesis of this potent antitumor antibiotic that would be amenable to the construction of analogues with anticipated potent cytotoxic activity.

Results and Discussion

The synthesis began with Borchardt's catechol **3**[15] that was regioselectively brominated to generate **4** (92% yield) (Scheme 2.) Conversion of catechol **4** to the methylenedioxy aldehyde **5** was accomplished using bromochloromethane in a sealed vessel (69% yield). Baeyer−Villiger oxidation using *m*-CPBA provided bromophenol **6** as an off-white solid following hydrolysis of the resulting formate intermediate (73% yield). Stereoselective aldol condensation of the titanium phenolate of **6** with (*R*)-Garner's aldehyde (**7**)[16] using a modification of Casiraghi's method[17] provided the *anti*-product **8** followed by allyl protection of the phenolic oxygen delivering **9** (65% yield, two steps). Subsequent hydrolysis of the oxazolidine and formation of the *trans*-acetonide (84% yield, two steps) provided **10** as an oil that cleanly underwent *N*-Boc deprotection using Ohfune's protocol[18] (76% yield) to afford free amine **11** as a stable crystalline solid. From **11**, the glyoxalimine intermediate **13** (see Scheme 3) was readily obtained by condensation with ethyl glyoxalate. Following isolation by filtration through Celite and concentration, the radical ring closure commenced with slow addition of Bu_3SnH and AIBN via syringe pump to a refluxing dilute solution of the glyoxalimine (**13**). Concentration and KF/silica chromatography[19] of the crude reaction mixture provided solid **12** as a single diastereomer (58% yield, two steps). The relative stereochemistry of **12** was secured ^{1}H NMR data and corroborated by X-ray crystallography. Examination of the crude ^{1}H NMR revealed the formation of a single diastereomer in the radical closure and exclusive 6-*endo* regioselectivity. In addition to **12** and tin impurities visible in the ^{1}H NMR spectrum, an aromatic proton arising from hydride quenching of the aryl radical revealed a ~6.6:1 ratio of **12** to reduced substrate. Slower addition rates (over 18 or 36 h) did not improve the isolated yield of **12**.

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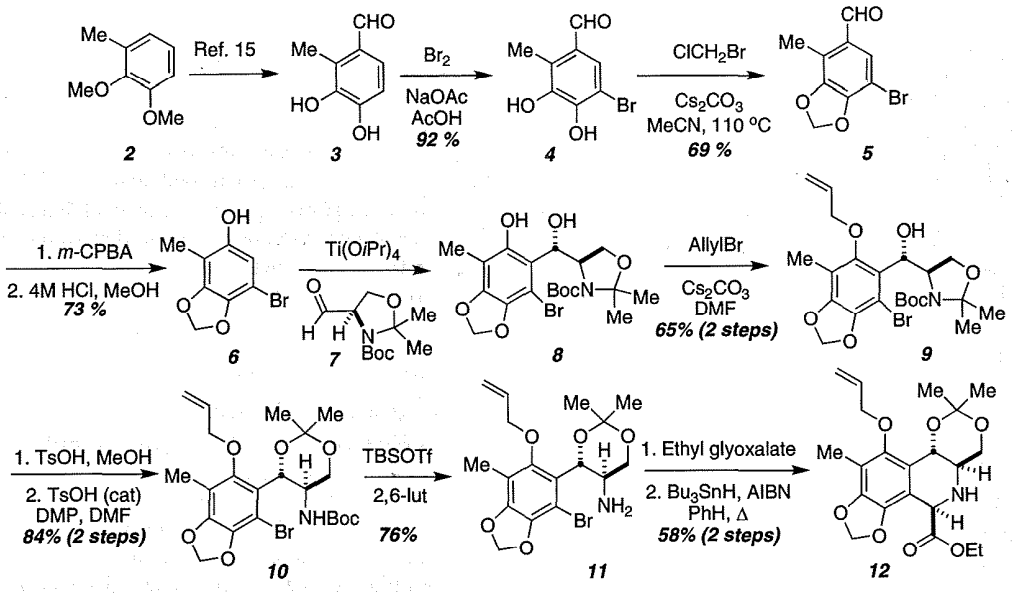
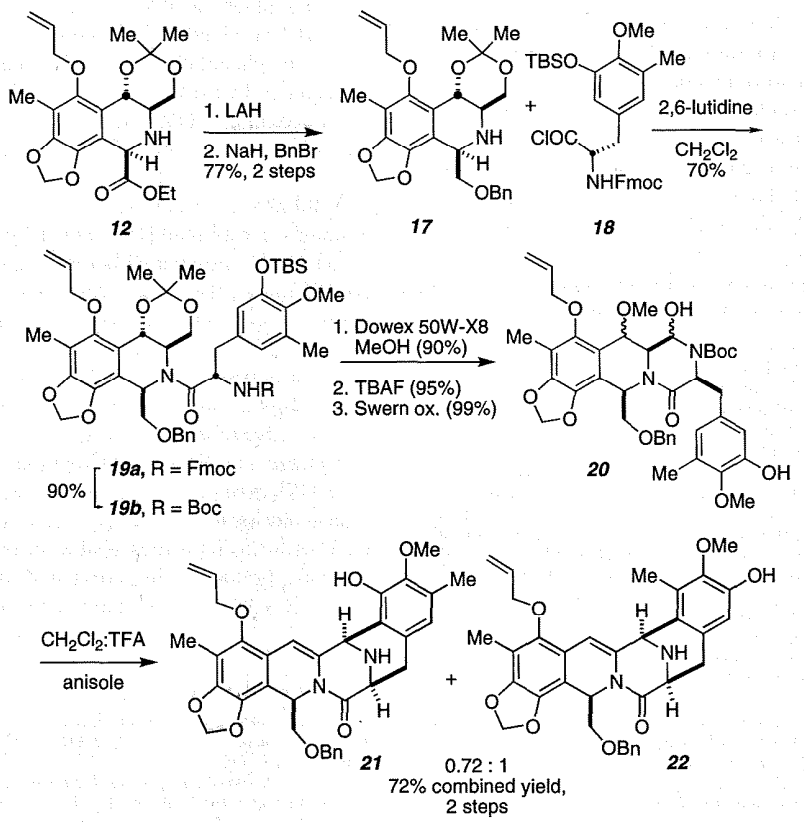
SCHEME 2. Tetrahydroisoquinoline Core of Et-743



SCHEME 3. Pentacycle Construction



The diastereoselectivity of this reaction stands apart from numerous Pictet–Spengler cyclizations on related substrates that provide tetrahydroisoquinolines exclusively as the 1,3-*trans*-diastereomers.[11,20,21] We qualitatively rationalize the *cis*-diastereoselectivity of this radical process using the Beckwith–Houk chairlike transition state model for intramolecular radical ring closures (Figure 2).[22] The lowest-energy chair conformation (**A**) adopted by the *trans*-acetonide of the substrate (**13**) results in both the glyoxalimine and aryl substituent being in an equatorial disposition. In this conformation, 1,3-diaxial steric effects and allylic strain interactions are minimized in the ring-forming transition state. To further examine the stereocontrol imparted by the acetonide ring, the *cis*-acetonide substrate **14** was prepared (using Casiraghi's method from the magnesium phenolate of **6**).[17] Substrate **14** resulted in a 1:1 mixture of 1,3-

(22) (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925–3941. (b) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959–974.

(23) Chen, X.; Zhu, J. *Angew. Chem., Int. Ed* **2007**, *46*, 3962–3965.

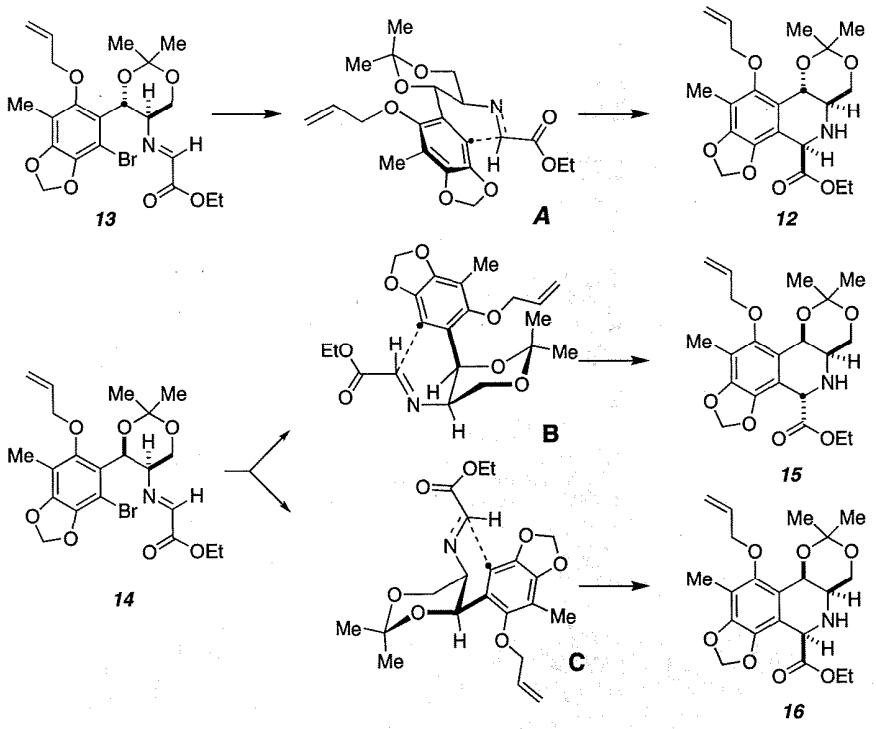


FIGURE 2. Transition state models to rationalize the observed 1,3 relative stereochemistry in the tetrahydroisoquinoline radical ring closure.

trans- and 1,3-*cis*-tetrahydroisoquinolines (**15** and **16**, both are known compounds),[20] which suggests the energy difference between transition state conformations **B** and **C** (axial aryl group versus axial glyoxalimine) is negligible.

As shown in Scheme 3, reduction of the tetrahydroisoquinoline ester (**12**)[14] with LAH, followed by immediate protection as the benzyl ether (**17**), proceeded cleanly in 77% yield over two steps. The substituted tyrosine amino acid component (**18**) has been previously reported by us, utilizing the oxazinone template technology developed in our laboratory that was benzylated with the advanced aromatic side chain.[13] Thus, acylation of the tetrahydroisoquinoline (**17**) was achieved via the *N*-Fmoc-protected amino acid chloride (**18**) to give amide **19a** without epimerization. The use of the *N*-Boc free acid with a variety of coupling agents (DCC, HOBt, HATU) all resulted in very sluggish reactions with poor isolated yields, as did the attempted use of the *N*-Boc acid fluoride.

Treatment of **19a** with diethylamine provided the free amine, which was not isolated in favor of immediate evaporation of excess base and solvent and subsequent Boc protection of the crude material. Isolation following chromatography provided compound **19b** in 90% yield. Removal of the acetonide from **19b** was accomplished using the extremely mild, albeit slow, method of stirring with Dowex 50W-X8 cationic resin in methanol. Complete deprotection took 8−12 h, but the yield was quantitative following simple filtration and concentration. Instead of providing the usual diol product, this substrate incorporated methanol at the benzylic position thus providing the methyl ether as a ~1:1 mixture of diastereomers. Not unexpectedly, the benzylic stereogenic center loses stereochemical integrity since the methanol is incorporated via the incipient *ortho*-quinonemethide species arising from the acidic deprotection conditions.

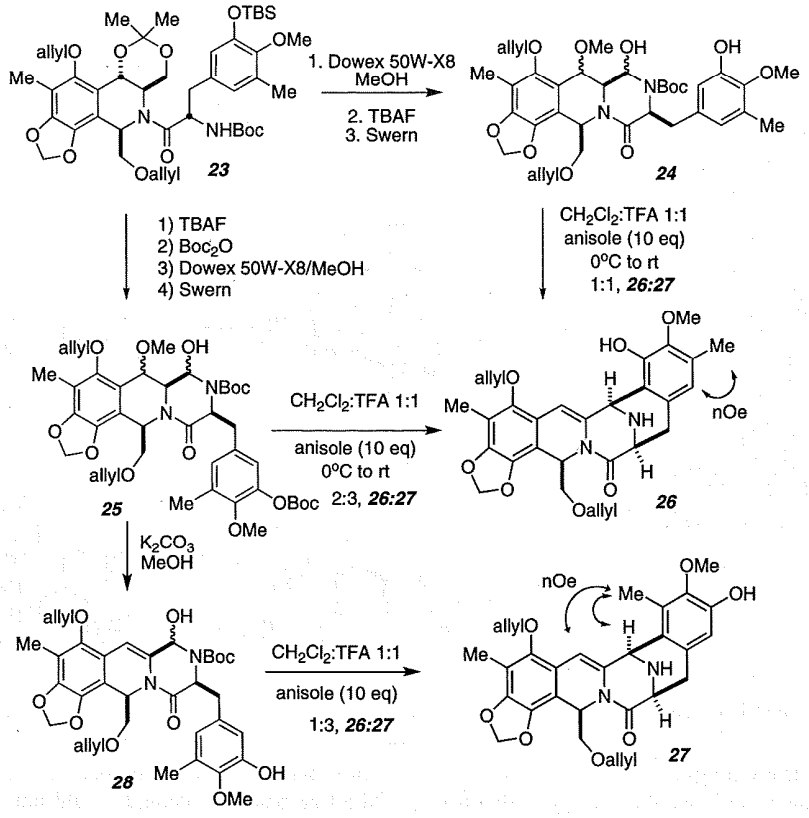
Alternatively, we found that the use of water/dichloromethane with cationic resin on **19b** could provide the corresponding free diol, but oxidation of the primary alcohol (in the presence of the free benzylic alcohol) could not, in our hands, be cleanly accomplished. The methyl ether was thus a fortuitous selective protection of the benzylic alcohol, ultimately simplifying the subsequent manipulations.

Facile deprotection of the *O*-TBS-protected phenol using TBAF was followed by oxidation of the primary alcohol using Swern conditions in high yield. This oxidation product (**20**) existed as an equilibrium mixture of the aldehyde and the corresponding hemiaminal species (illustrated) as observed by ^{1}H NMR, which was otherwise additionally complicated by amide and carbamate rotamers. The attempted oxidation using either Dess−Martin periodinane or TPAP/NMO both failed, leading to extensive decomposition. Following filtration of crude **20** through a plug of silica gel, this substance was immediately subjected to the Pictet−Spengler conditions.

The objective at this stage was to achieve the Pictet−Spengler reaction via *N*-Boc deprotection, iminium ion formation, and electrophilic aromatic substitution to provide the desired pentacyclic core of Et-743. This meant that the aromatic substitution must occur *ortho* to the free phenol, and the benzylic methyl ether must survive these conditions. Unfortunately, it had already been demonstrated above that the electron-rich aromatic ring of the tetrahydroisoquinoline component was highly sensitive to protic conditions, leading to *ortho*-quinonemethide formation.

Indeed, when substrate **20** was treated with trifluoroacetic acid in methylene chloride, it cleanly underwent the expected pentacycle formation furnishing **21** + **22** as a ~0.72:1 *ortho:para* mixture of regioisomers in 72% combined yield. As anticipated, the benzylic methoxy group was eliminated presumably via the incipient *ortho*-quinonemethide species that forms under these conditions. In a fruitless effort to circumvent the vexing olefin formation, pentacycle formation with TFA in dry methanol resulted in extensive decomposition of the substrate.

SCHEME 4. Pictet–Spengler Regioselectivity



As part of these synthetic investigations, the intermediate **23** was prepared (in parallel with the *O*-benzyl-protected synthesis) bearing an *O*-allyl-protected hydroxymethyl at C1 of the THIQ core. This substrate was used to examine the regioselectivity of the pentacycle-forming ring closure and was utilized to acquire detailed ^{1}H NMR data, while the *O*-benzyl material **21** was carried forward in the synthesis. One interesting observation was the behavior of compound **25** containing the *O*-Boc carbonate-protected phenolic oxygen. Treatment of **25** under the same reaction conditions provided the pentacycles **26** + **27** in a 2:3 ratio of *ortho*:*para* regioisomers. The *O*-Boc carbonate would presumably be deprotected quickly under these conditions to reveal the free phenol-containing reactive species, thus resulting in a comparable regioselectivity as observed with substrate **20** (beginning with a free phenol on the aryl nucleophile moiety). Notably, however, when substrate **25** was treated with K_2CO_3/MeOH, the *O*-Boc carbonate was selectively removed (**28**) with apparent olefin formation prior to the Pictet–Spengler reaction and pentacycle formation. Treatment of **28** with TFA in dichloromethane produced the pentacycles **26** + **27** in a 1:3 ratio of *ortho*:*para* regioisomers, supporting the hypothesis that some regioselectivity in the closure might arise from an intramolecular H bond with a heteroatom at the benzylic position.[11c]

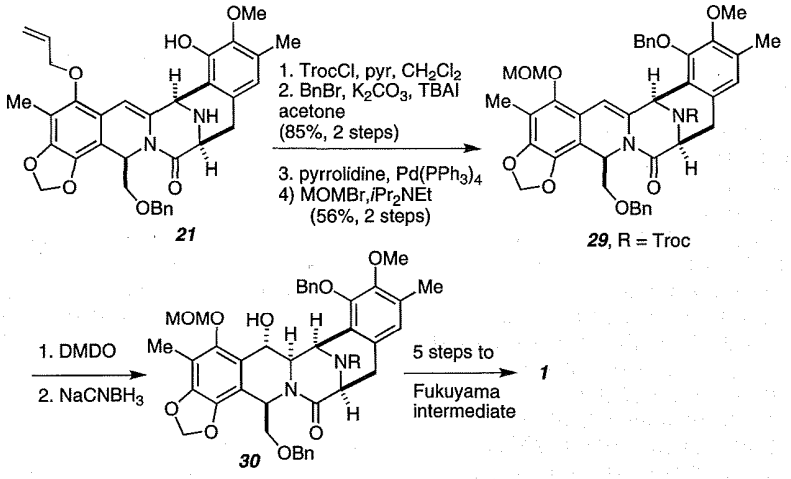
In their synthesis of renieramycin H, the Zhu group has interestingly reported control of Pictet–Spengler regioselectivity in a related system by variation of acid concentration (Scheme 4).[23] It was found in that case that lowering the concentration of methanesulfonic acid to 0.01% in CH_2Cl_2 could invert the *ortho:para* selectivity from 3.4:1 to 2:3. Furthermore, the use of acetonitrile as the solvent instead of dichloromethane favored the undesired isomer, giving *ortho:para* selectivity of 1:10. Our attempt to reproduce the Zhu conditions on substrate **24** using 0.01% methanesulfonic acid in CH_2Cl_2 did not affect the regioselectivity of this reaction. The substrate was consumed to provide some material that appeared to still contain the *N*-Boc protecting group, but the ^{1}H NMR of the crude product was prohibitively complex. Subsequent treatment of this reaction crude with a TFA/anisole/CH_2Cl_2 mixture provided the pentacycles **26** + **27** with ~1:1 regioselectivity. The same ratio is obtained if the TFA/anisole conditions are used directly on substrate **24**.

In order to redeem the synthetic utility of the olefinic products (**21** or **26**), our attention was captured by the recent formal synthesis of Et-743 reported by the Danishefsky group[7] in which the olefin (**29**, Scheme 5) underwent facile oxidation using DMDO and immediate hydride reduction delivering the benzylic alcohol **30**. With the availability of this methodology in the literature, our efforts were briefly redirected to convert our synthetic pentacycle **21** into compound **29** which would constitute a formal total synthesis of Et-743 by relay through the Danishefsky[7] and then Fukuyama[5] syntheses, respectively.

In the event, the desired pentacycle **21** (Scheme 3) was *N*-protected as the trichloroethyl carbamate (Troc), and the phenolic residue was protected as the corresponding *O*-benzyl ether in 85% yield for the two steps (Scheme 5). Removal of the *O*-allyl group under standard conditions followed by reprotection as the corresponding MOM ether provided compound **29** (56% yield for the two steps). Compound **29** perfectly matched Danishefsky's substrate by ^{1}H, ^{13}C NMR, and optical rotation, confirming the structure of compound **29**.

Since Danishefsky has previously converted[7] compound **29** into a late-stage intermediate in Fukuyama's total synthesis[5] (namely, compound **30**, Scheme 5), this two-stage relay of our

SCHEME 5. Formal Synthesis of Et-743 via 21 to 29 and Danishefsky to Fukuyama Relay



synthetic **21** thus constitutes a formal total synthesis of Et-743 and provides firm structural corroboration of our synthetic material and methods.

While the present formal synthesis reveals that our glyoxalimine radical cyclization technology[14] holds considerable potential for the efficient total synthesis of Et-743 and congeners, we are currently endeavoring to improve the regioselectivity of the key pentacycle formation (**20** to **21**) as well as refining the overall synthetic efficiency of our approach. These objectives are currently under study in our laboratory and will be reported in due course.

Experimental Section

For general methods and considerations, see Supporting Information.

Compound 19. The Fmoc-amino acid (410 mg, 0.727 mmol, 1.2 equiv) was dissolved in dry toluene and concentrated (×2), and then dried under high vacuum. This oil was dissolved in dry CH_2Cl_2 (4 mL) to which was added oxalyl chloride (1 mL) at room temperature, followed by dry DMF (20 μL). After stirring for 20 min, the solution was concentrated and reconcentrated from dry toluene (×2) and then dried under high vacuum. This acid chloride **18** was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C. THIQ(OBn) **17** (275 mg, 0.61 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and 2,6-lutidine (77 μL 0.67 mmol, 1.1 equiv). This solution was transferred into the acid chloride solution slowly dropwise, and the resulting mixture was warmed to rt and stirred 7 h (TLC showed consumption of the THIQ(OBn) starting material). The reaction was quenched with saturated NH_4Cl (aq) and then extracted to EtOAc (×3). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated to provide a crude orange oil. Purification by flash chromatography (hexanes:EtOAc 5:1, silica gel) gave the peptide **19a** as a pale yellow oil (426 mg, 70%); R_f = 0.34 (3:1 hexanes:EtOAc, UV, CAM); $[\alpha]^{25}_D$ −22.8 (*c* 1.14, CH_2Cl_2); IR (thin film) 3289, 2929, 2858, 1717, 1634 cm^{-1}; ^{1}H and ^{13}C NMR spectra are extremely complex due to amide and carbamate rotamers. See the rt ($CDCl_3$) and 373 K (DMSO-d_6) ^{1}H spectra and rt ($CDCl_3$) ^{13}C spectra in the Supporting Information; HRMS(ESI/APCI+) *m/z* calcd for $C_{58}H_{68}N_2O_{11}NaSi$ $(M + Na)^+$ 1019.4485, found 1019.4499.

Compound 19b. Fmoc (OBn) peptide **19a** (146 mg, 0.146 mmol) was dissolved in a 20% v/v solution of Et_2NH in CH_2Cl_2 [CH_2Cl_2 (2.5 mL) and diethylamine (0.6 mL]. After stirring for 6 h, the solution was concentrated and then reconcentrated from toluene and dried under high vacuum. The crude material was dissolved in EtOH:CH_2Cl_2 (2:0.5 mL) to which was added Boc_2O (370 mg, 10 equiv). After stirring for 12 h, the reaction was concentrated and immediately purified by flash chromatography (9:1 to 5:1 hexanes: EtOAc, silica gel) to provide **19b** as a clear colorless oil (115 mg, 90% over 2 steps): R_f = 0.43 (3:1 hexanes:EtOAc, UV, CAM); $[\alpha]^{25}_D$ −26.6 (*c* 1.0, CH_2Cl_2); IR (thin film) 3319, 2930, 2858, 1711, 1646 cm^{-1}; ^{1}H and ^{13}C NMR spectra are extremely complex due to amide and carbamate rotamers; see the ^{1}H spectra ($CDCl_3$, rt) and (DMSO-d_6, 373 K) and ^{13}C spectrum ($CDCl_3$, rt) in the Supporting Information; HRMS(ESI/APCI+) *m/z* calcd for $C_{48}H_{66}N_2O_{11}NaSi$ $(M + Na)^+$ 897.4328, found 897.4310.

Compounds 21 and 22. Boc (OBn) peptide **19b** (115 mg, 0.132 mmol) was dissolved in dry MeOH (5 mL), and Dowex 50W-X8 cationic resin (100 mg) was added (the resin was first rinsed with dry methanol and dried under a stream of argon). After 65 h, the reaction was complete by TLC and a single streak was observed (during the course of the reaction, two streaks initially arise due to a mixture of diol and methyl ether/alcohol products). The reaction was filtered through a plug of Celite, eluting with dry MeOH, and the filtrate was combined to provide the methyl ether as clear, colorless oil (100 mg, 90% yield): R_f = 0 to 0.35 streak (3:1 hexanes:EtOAc, UV, CAM); HRMS(FAB+) *m/z* calcd for $C_{46}H_{65}N_2O_{11}Si$ $(M + H)^+$ 849.4358, found 849.4354. The methyl ether (100 mg) was dissolved in THF (3 mL), and TBAF (1 M in THF, 125 μL, 1.06 equiv) was added in one portion. After 20 min, the reaction was concentrated by rotary evaporation and passed through a silica plug (eluting with 3:1 to 1:1 hexanes:EtOAc) to provide the free phenol as a clear, colorless oil (82 mg, 95% yield): R_f = 0 to 0.43 streak (3:1 hexanes:EtOAc, UV, CAM); HRMS-(FAB+) *m/z* calcd for $C_{40}H_{51}N_2O_{11}$ $(M + H)^+$ 735.3493, found 735.3490. Oxalyl chloride (15 μL 1.5 equiv) was added carefully to a solution of DMSO (25 μL, 3.2 equiv) in CH_2Cl_2 (1 mL) previously cooled to −78 °C. A solution of the above alcohol (82 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and the resulting mixture was stirred at −78 °C for 40 min. The reaction was quenched with Et_3N (125 μL, 8 equiv) and then allowed to warm to rt. The reaction was diluted with CH_2Cl_2 and washed with brine, and then the combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. The crude material was passed through a silica gel plug (eluting with hexanes:EtOAc 1:1) to provide a yellow oil/foam (82 mg, quant.) of hemiaminal **20** which was used without further purification: R_f = 0.5 (hexanes:EtOAc 1:1, UV, CAM). Hemiaminal **20** (232 mg, 0.32 mmol) was dissolved in CH_2Cl_2 (3 mL) to which were added TFA (3 mL) and anisole (0.350 mL) at rt. The reaction was stirred for 14 h and then concentrated to remove TFA, then redissolved in CH_2Cl_2 and washed with saturated aq $NaHCO_3$. The organic fraction was dried (Na_2SO_4), filtered, and concentrated. Crude ^{1}H NMR shows 0.72:1 *ortho* (**21**) to *para* (**22**) regioisomers. Purification by PTLC (2% MeOH in

EtOAc) provided the *ortho* (63 mg) and *para* products (69 mg) for a combined yield of 72%. Data for **21**: $R_f = 0.61$ (EtOAc:MeOH 95:5, UV, CAM); $[\alpha]^{25}_D$ −18.0 (*c* 1.0, CH_2Cl_2); IR (thin film) 3295, 2932, 1672, 1632, 1455, 1428 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14−7.30 (m, 3H), 6.98 (s, 1H), 6.97 (s, 1H), 6.24 (s, 1H), 6.19 (s, 1H), 6.12 (dddd, J = 16.0, 11.0, 5.4, 5.4 Hz, 1H), 6.05 (dd, J = 7.2, 5.0 Hz, 1H), 5.85 (br s, 1H), 5.82 (br s, 1H), 5.78 (v br s, 1H), 5.45 (app dd, J = 17.1, 1.1 Hz, 1H), 5.29 (app dd, J = 10.3, 0.8 Hz, 1H), 4.9 (s, 1H), 4.30 (app d of AB quartet, J = 12.3, 5.4 Hz, 2H), 4.03 (d, J = 6.1 Hz, 1H), 3.87 (AB quartet, J = 12.1 Hz, 2H), 3.63 (s, 3H), 2.95−3.2 (m, 5H), 2.11 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 147.6, 145.6 (×2), 143.4, 139.7, 138.7, 134.5, 133.9, 129.4, 128.8, 128.0 (×2), 127.1, 126.8 (×2), 122.5, 119.3, 117.7, 117.5, 113.0, 108.7, 101.5, 100.2, 75.3, 72.6, 70.0, 60.8, 54.4, 50.0, 46.9, 33.4, 15.9, 9.4. HRMS(ESI/APCI+) *m/z* calcd for $C_{34}H_{35}N_2O_7$ $(M + H)^+$ 583.2439, found 583.2441. Data for **22**: $R_f = 0.5$ (EtOAc:MeOH 95:5, UV, CAM); $[\alpha]^{25}_D$ +47.8 (*c* 1.45, CH_2Cl_2); IR (thin film) 3298, 2931, 1671, 1631, 1430, 1409 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11−7.22 (m, 3H), 6.94 (s, 1H), 6.92 (s, 1H), 6.41 (s, 1H), 6.11 (dddd, J = 16.1, 10.6, 5.5, 5.5 Hz, 1H), 6.08 (s, 1H), 6.03 (dd, J = 6.6, 5.1 Hz, 1H), 5.86 (br s, 1H), 5.83 (br s, 1H), 5.45 (app dd, J = 17.1, 1.1 Hz, 1H), 5.30 (app dd, J = 10.4, 0.8 Hz, 1H), 4.65 (s, 1H), 4.36 (app d of A of AB quartet, J = 12.5, 5.5 Hz, 1H), 4.24 (app d of B of AB quartet, J = 12.5, 5.5 Hz, 2H), 4.01 (d, J = 6.0 Hz, 1H), 3.91 (AB quartet, J = 12.2 Hz, 1H), 3.56 (s, 3H), 2.95−3.24 (m, 5H), 2.27 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 148.0, 147.6, 145.9, 144.3, 139.7, 138.4, 134.6, 133.7, 129.6, 128.7, 128.1 (×2), 127.2, 126.9 (×2), 124.9, 117.8, 117.1, 113.8, 113.0, 108.8, 101.5, 100.5, 75.4, 72.8, 70.1, 61.0, 54.3, 52.6, 46.8, 35.4, 12.0, 9.4; HRMS (ESI/APCI+) *m/z* calcd for $C_{34}H_{35}N_2O_7$ $(M + H)^+$ 583.2439, found 583.2429.

Preparation of Compound 29. The desired *ortho*-regioisomer **21** (55 mg, 0.095 mmol) was dissolved in CH_2Cl_2 (2 mL) and pyridine (11 μL, 0.14 mmol, 1.5 equiv) at 0 °C. TrocCl (13.5 μL, 0.1 mmol, 1.0 equiv) was added and the reaction maintained at 0 °C for 2 h, and then diluted with CH_2Cl_2 and washed with saturated aq NH_4Cl. The organic layer was dried (Na_2SO_4), filtered, and then concentrated. The crude oil was passed through a plug of silica gel eluting with EtOAc, and then concentrated and dried under vacuum. The resulting oil was dissolved in CH_2Cl_2 (600 μL), and MeOH (200 μL) and K_2CO_3 (52 mg, 0.38 mmol, 4 equiv) were added followed by benzyl bromide (22 μL, 0.19 mmol, 2 equiv) and a catalytic amount of tetrabutylammonium iodide. The resulting mixture was stirred at rt for 13.5 h then filtered through a pad of Celite, rinsing with CH_2Cl_2. Flash chromatography (5:1 hexanes:EtOAc) provided the *N*-Troc/*O*-benzyl product as a pale yellow oil (68 mg, 85% over 2 steps): $R_f = 0.46$ (hexanes:EtOAc 3:1, UV, CAM); $[\alpha]^{25}_D$ +58.1 (*c* 1.7, CH_2Cl_2); IR (thin film) 2927, 1724, 1681, 1434, 1371 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of carbamate rotamers) δ 7.30−7.56 (m, 3H), 7.14−7.25 (m, 4H), 6.92−7.00 (m, 2H), 6.45 (d, J = 9.9 Hz, 1H), 6.22 (d, J = 4.1 Hz, 1H), 6.12 (J = 16.1 Hz, 1H), 6.01−6.08 (m, 1H), 5.79−5.90 (m, 3H), 4.98−5.29 (m, 5H), 4.85 (d, J = 12.0, 2.8 Hz, 1H), 4.60 (d, J = 11.9, 6.5 Hz, 1H), 3.97−4.11 (m, 3H), 2.85 (app d, J = 12.1 Hz, 1H), 3.70 (s, 3H), 3.04−3.30 (m, 4H), 2.10 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of carbamate rotamers) δ 166.1/166.0, 151.5/151.4, 149.9, 148.9, 148.4, 148.3/148.2, 146.2, 139.6, 138.5, 137.6/137.5, 133.8/133.7, 132.6/132.5, 131.3/131.2, 128.9 (×2), 128.3, 128.1 (×2), 128.0, 127.2, 126.8, 126.6/126.5, 125.4/125.0, 117.6, 117.3, 116.9, 113.3/113.3, 108.6/108.4, 103.3, 102.9, 101.6, 95.3/95.2, 75.4/75.3, 75.2/75.0, 74.6/74.4, 72.6, 69.9/69.8, 60.5, 54.4/53.7, 50.9/50.1, 47.3/47.2, 32.8/32.4, 16.0, 9.5; HRMS(ESI/APCI+) *m/z* calcd for $C_{44}H_{42}N_2O_9Cl_3$ $(M + H)^+$ 847.1950, found 847.1949.

The allyl-protected pentacycle obtained above (20 mg, 0.024 mmol) was dissolved in CH_2Cl_2 (400 μL), and pyrrolidine (6 μL, 3 eq) was added, followed by $Pd(PPh_3)_4$ (2 mg, 0.002 mmol) under Ar. After 16 h, the reaction was still not complete, so additional portions of pyrrolidine and palladium catalyst were added. After stirring an additional 4 h (20 h total), the dark green reaction was applied directly to flash chromatography (silica gel, hexanes:EtOAc 3:1). The pure fractions were combined to provide the phenol as yellow oil (11 mg 56%), used without characterization: $R_f = 0.26$ (hexanes:EtOAc 3:1, UV, CAM). Phenol (11 mg, 0.014 mmol) was dissolved in CH_2Cl_2 (200 μL) to which were added iPr$_2$NEt (12 μL, 0.07 mmol, 5 equiv) and MOMBr (3.3 μL, 0.042 mmol, 3 equiv). The mixture was stirred for 30 min at rt and then quenched with water and extracted with CH_2Cl_2 (×3). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (hexanes:EtOAc 3:1) provided the protected pentacycle **29** (11.5 mg, quant.): $R_f = 0.41$ (hexanes:EtOAc 3:1, UV, CAM); $[\alpha]^{25}_D$ +45.4 (*c* 0.8, $CHCl_3$) [lit. +50 (*c* 1.0, $CHCl_3$)]; IR (thin film) 2932, 1723, 1681, 1654, 1432, 1371 cm^{-1}. ^1H and ^{13}C NMR spectra perfectly match the data provided by the Danishefsky group for this intermediate in their formal synthesis (copies of their spectra included in the Supporting Information):[7] ^1H NMR (400 MHz, $CDCl_3$, mixture of carbamate rotamers) δ 7.56−7.31 (m, 5H), 7.13−7.23 (m, 3H), 6.96 (app br d, J = 6.9 Hz, 2H), 6.46 (d, J = 9.4 Hz, 1H), 6.01−6.15 (m, 3H), 5.86 (app d, J = 3.0 Hz, 2H), 5.82 (br s, 1H), 4.97−5.19 (m, 4H), 4.86 (d, J = 11.9 Hz, 1H), 4.79 (A of AB quart, J = 12.0 Hz, 1H), 4.68 (B of AB quart, J = 11.9 Hz, 1H), 4.49−4.60 (m, 2H), 4.43 (app d, J = 6.1 Hz, 1H), 4.01 (d of A of AB quart, J = 11.8, 4.4 Hz, 1H), 3.85 (B of AB quart, J = 12.1 Hz, 1H), 3.71 (app d, J = 10.6 Hz, 3H), 3.38 (rotomeric s, 3H), 3.03−3.29 (m, 5H), 2.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of carbamate rotamers) δ 166.0/165.9, 151.6/151.4, 149.9, 148.7/148.2, 147.3, 146.2/146.1, 139.8, 138.4/138.4, 137.8/137.7, 132.6/132.5, 131.1/131.1, 128.8, 128.2, 127.9, 127.2, 126.8, 126.6/126.5, 125.2/125.0, 117.0/116.8, 113.7/113.6, 108.5/108.4, 103.3/102.7, 101.6, 100.4/100.4, 95.3/95.2, 75.4/75.3, 74.4/74.0, 72.6/72.6, 69.9/69.9, 60.4, 57.6/57.5, 54.4/53.7, 50.8/50.1, 47.4/47.3, 32.7/32.3, 16.0, 9.9; HRMS(ESI/APPI+) *m/z* calcd for $C_{43}H_{42}N_2O_{10}Cl_3$ $(M + H)^+$ 851.1900, found 851.1897.

Acknowledgment. This paper is fondly dedicated to the memory of the late Professor A.I. Meyers. We gratefully acknowledge financial support from the National Institutes of Health (Grant CA85419). We are grateful to Prof. Samuel J. Danishefsky of the Memorial Sloan-Kettering Cancer Research Institute for kindly providing characterization data for compound **29**.

Note Added after ASAP Publication. Reference 6 contained an incorrect publication date and the description of the conditions used by Zhu et al. (below Scheme 4) was erroneous in the version published ASAP August 8, 2008; the corrected version was published ASAP September 17, 2008.

Supporting Information Available: Complete experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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EXHIBIT 19

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Further Studies of the *Daphniphyllum* Alkaloid Polycyclization Cascade

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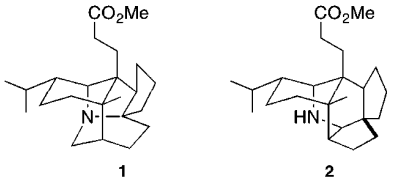
The scope of the 2-azadiene intramolecular Diels−Alder cyclization, previously employed for synthesis of the *Daphniphyllum* alkaloids, has been further investigated. Through a series of 1,5-diol cyclization precursors the substitution pattern of both the dienophile and the 2-azadiene were examined. From these studies it was shown that the cascade reaction is tolerant toward a variety of alkyl-substituted dienophiles. However, it was also demonstrated that this reaction is very sensitive to the substitution pattern of the 2-azadiene. Alterations made to the structure of the 2-azadiene cause either competing side reactions or complete failure of the reaction cascade.

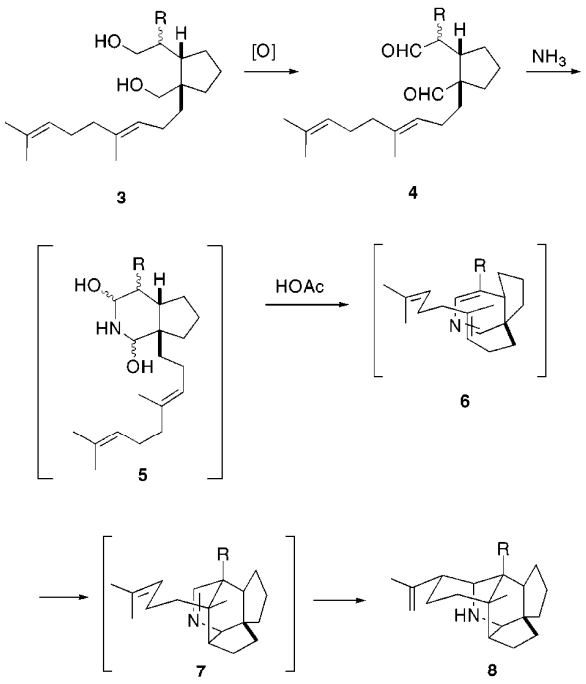
The *Daphniphyllum* alkaloids are a group of polycyclic natural products first isolated from the deciduous tree Yuzuriha (*Daphniphyllum macropodum*) in 1909.[1] Since then, over 30 *Daphniphyllum* alkaloids have been isolated and structurally characterized.[2] Methyl homodaphniphyllate (**1**) and methyl homosecodaphniphyllate (**2**) are representative members of this group of natural products and illustrate two of the pentacyclic core structures that are found.



1 **2**

During the 1980s, we developed the biomimetic approach to these alkaloids that is illustrated in Scheme 1.[3,4] This one-pot procedure begins with the oxidation of a 1,5-diol (**3**) to a dialdehyde (**4**). Treatment of the crude oxidation mixture with ammonia, followed by acetic acid and ammonium acetate, leads to the formation of an azadiene (**6**), which undergoes an intramolecular Diels−Alder cyclization to form imine **7**. Heating the acetic acid solution of imine **7** facilitates an intramolecular aza-Prins cyclization to provide pentacyclic amine **8**. This remarkable process, which forms three carbon−carbon bonds and two nitrogen−carbon bonds and establishes six stereocenters, has been used as the key step in the synthesis of five of the *Daphniphyllum* alkaloids.[3,5,6]

Scheme 1



3 **4** **5** **6** **7** **8**

In this paper, we report further studies that explore the scope and generality of the intramolecular 2-azadiene Diels−Alder cyclization.[7] By studying the cyclizations of diols **9**−**16** we hoped to examine the effect of both the

† The Center for New Directions in Organic Synthesis is supported by Bristol-Myers Squibb as Sponsoring Member.

(1) Yagim S. *Kyoto Igaku Zasshi.* **1909**, *6*, 208.

(2) For reviews on the *Daphniphyllum* alkaloids see: (a) Yamamura, S.; Hirata, Y. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. 15, p 41. (b) Yamamura, S.; Hirata, Y. *Int. Rev. Sci.: Org. Chem., Ser. Two* **1976**, *9*, 161. (c) Yamamura, S. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 29, p 265.

(3) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2544.

(4) We have also reported a classical approach to these alkaloids: Heathcock, C. H.; Davidsen, S. K.; Mills, S. G.; Sanner, M. A. *J. Org. Chem.* **1992**, *57*, 2531.

(5) Heathcock, C. H.; Stafford, J. *J. Org. Chem.* **1992**, *57*, 2566.

(6) Heathcock, C. H.; Rugerri, R. B.; McClure, K. F. *J. Org. Chem.* **1992**, *57*, 2585.

(7) For references on 2-aza dienes, see: (a) Eddaif, A.; Mison, P.; Laurent, A.; Pellissier, N.; Carrupt, P.-A.; Vogel, P. *J. Org. Chem.* **1987**, *52*, 5548. (b) Cheng, Y.-S.; Ho, E.; Mariano, P. S.; Ammon, H. L. *J. Org. Chem.* **1985**, *50*, 5678. (c) Boger, D. L.; Weinreb, S. M. In *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987; pp 255−260. (d) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.

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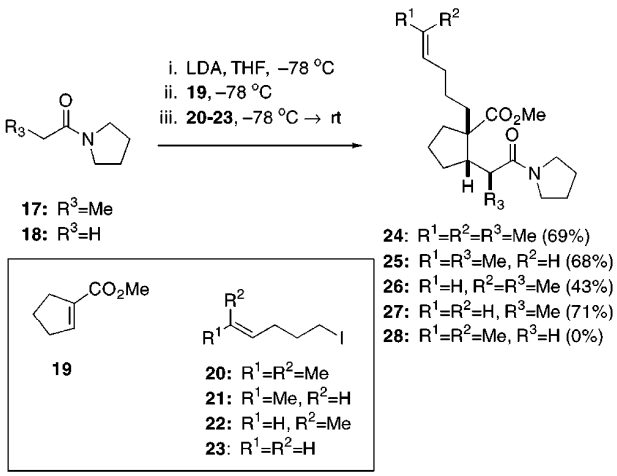
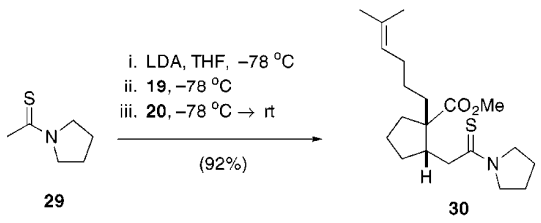
Published on Web 12/23/2000

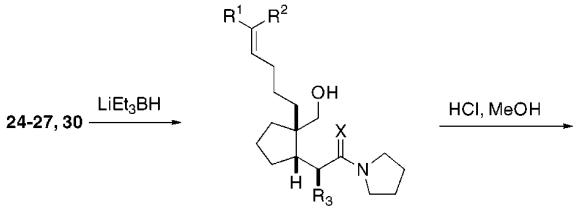
Scheme 2



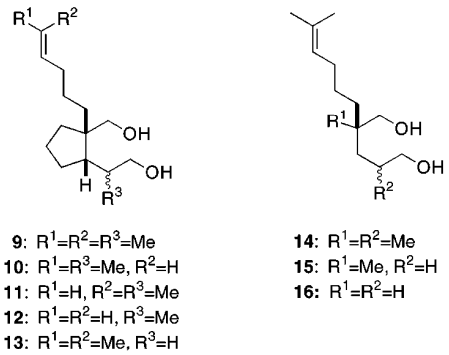
Scheme 3

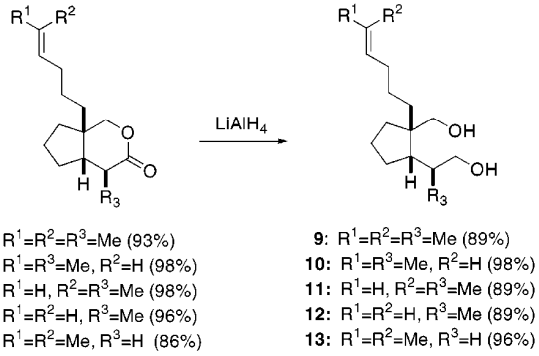


Scheme 4



substitution pattern of the 2-azadiene as well as the pendent dienophile. In addition, the dienophile tether was extended by one carbon, such that six-membered rings would be formed during the Diels–Alder cyclizations.





Results and Discussion

Synthesis of Diols 9–16. The synthesis of diols **9**–**13** began with the three-component coupling of amides **17** and **18**[8] with enoate **19**[9] and iodides **20**–**23** (Scheme 2).[6] The lithium enolate of amide **17** or **18** was treated with enoate **19**, and the corresponding Michael addition adduct was trapped with iodides **20**–**23**.[10] The desired products could be isolated in good to moderate yields in all cases except for ester-amide **28**. The stereochemical assignment of the ester-amides **24**–**27** is based on literature precedent of similar Michael reactions of amide enolates.[9,11]

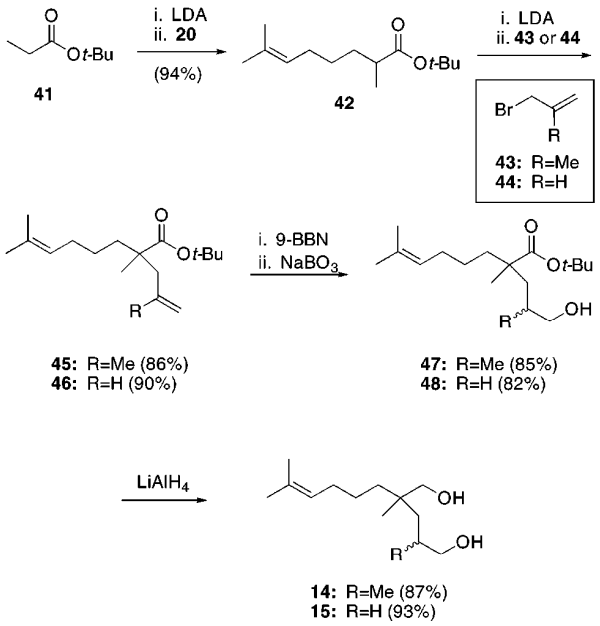
The failure to obtain ester-amide **28** by this method was not unexpected, in light of earlier work in these laboratories.[9] Although none of the desired ester-amide **28** was isolated from the reaction of the lithium enolate of **18** with enoate **19** followed by trapping with iodide **20**, products resulting from 1,2-addition were observed. However, the lithium enolate of thioamide **29**,[12] a softer nucleophile,[4,13] reacts smoothly with enoate **19**. Treatment of the resulting adduct with iodide **20** provided the desired adduct **30** in 92% yield (Scheme 3).

The conversion of amides **24**–**27** and **30** to their corresponding diols is shown in Scheme 4. Lithium triethylborohydride chemoselectively reduced the ester moiety of these substrates to provide alcohols **31**–**35** in good yields. Acid-catalyzed lactonization followed by lithium aluminum hydride reduction efficiently provided the desired diols **9**–**13**.

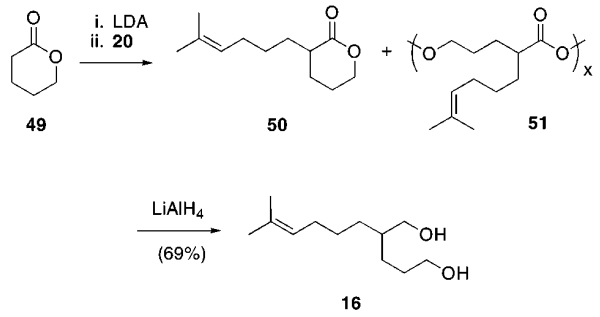
Attempts to prepare diols **14**–**16** through the three-component-coupling method described above lead to intractable mixtures of products. Rather than pursue this method, we developed the alternate approaches to these diols shown in Schemes 5 and 6. The synthesis of diols **14** and **15** began with the alkylation of the lithium enolate of *tert*-butylpropionate (**41**) with iodide **20** to provide ester **42** in high yield. Subsequent allylation of the lithium enolate of ester **42** with either 2-methylallyl bromide or allyl bromide provided esters **45** and **46**, respectively. Selective hydroboration of the terminal olefins in esters **45** and **46**, followed by oxidation lead to

(8) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132–157.
(9) Ruggeri, R. B.; Hansen, M. M.; Heathcock, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 8734.
(10) Millar, J. G.; Underhill, E. W. *J. Org. Chem.* **1986**, *51*, 4726.
(11) Yamaguchi, M. *Yuki Gosei Kagaka.* **1986**, *44*, 405.
(12) (a) Oare, D. A. Doctoral Thesis, University of California at Berkeley, 1988. (b) Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S. O. *Org. Synth.* **1984**, *62*, 158.
(13) (a) Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 581, 643. (b) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (c) Deschamps, B.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron Lett.* **1973**, *14*, 527.

Scheme 5



Scheme 6



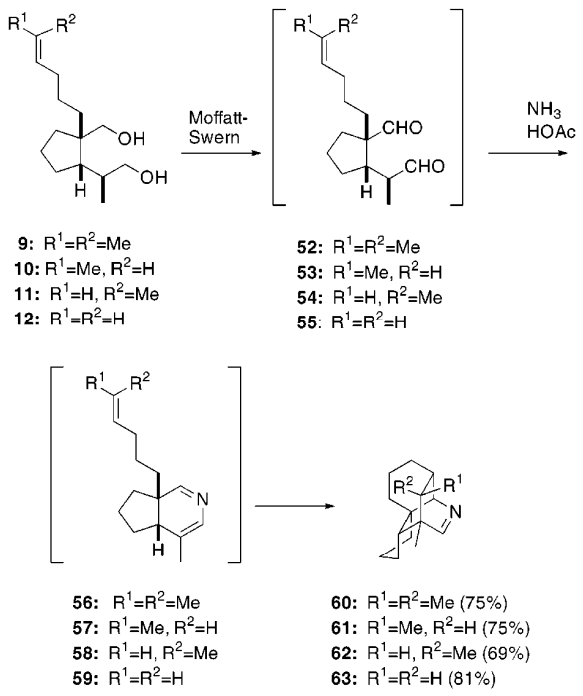
the primary alcohols **47** and **48**. Reduction of the ester function in **47** and **48** gave access to the desired diols **14** and **15**.

The synthesis of diol **16** was carried out in two steps as shown in Scheme 6. Alkylation of the lithium enolate of δ-valerolactone with iodide **20** provided lactone **50** in low and variable yields (25−50%). We believe that ring-opening of the lactone **50** and oligomerization to polyester **51** was responsible for the low and variable yields of **50**. Support for this hypothesis came from the observation that reduction of the crude reaction mixture with LAH provided the desired diol **16** in a reproducible 69% yield.

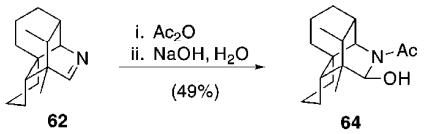
Exploration of the Azadiene Diels−Alder Cylization. With diols **9**−**16** in hand, we were prepared to commence with our studies of the scope and generality of the *Daphniphyllum* alkaloid azadiene Diels−Alder cyclization. From the onset of this project, we planned to use the biomimetic reaction protocol developed during the *Daphniphyllum* alkaloid synthesis, rather than attempting to optimize the reaction conditions for each substrate. This protocol involves Moffatt−Swern[14] oxidation of the 1,5-diol to the dialdehyde, treatment of the crude methylene chloride solution with ammonia followed by solvent exchange from methylene chloride to a buffered acetic acid solution. Following an aqueous workup,

(14) Mancusco, A. J.; Swern, D. *Synthesis* **1981**, 165.

Scheme 7



Scheme 8



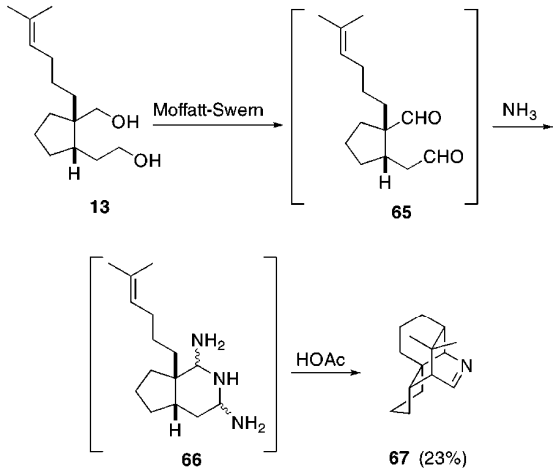
the imine products were isolated by column chromatography on silica gel. The cyclization sequences of diols **9**−**12** are shown in Scheme 7.

Oxidation of diols **9**−**12** led smoothly to the 1,5-dialdehydes **52**−**55**. These delicate molecules can be observed in the crude form by ^{1}H NMR, following an aqueous workup of the Moffatt−Swern oxidation. However, as noted above, the reaction mixtures were more routinely treated directly with ammonia, followed by solvent exchange to acetic acid. Following an aqueous workup, imines **60**−**63** were isolated in yields ranging from 69 to 81% by column chromatography on silica gel that had been pretreated with triethylamine. The structures of imines **60**−**63** were determined through ^{1}H NMR, ^{13}C NMR, ^{13}C DEPT, IR, and elemental analysis. In addition to the spectral and analytical evidence that supported the assigned structures of tetracyclic imines **60**−**63**, the structure of **62** was further confirmed by conversion into derivative **64**, the structure of which was rigorously determined by X-ray crystallography (Scheme 8).[15]

In the course of performing the cyclizations of diols **9**−**12**, we noted a definite trend in the reaction rates of these substrates (imines **60** and **61** can be formed at room temperature, whereas imines **62** and **63** require heating at 80 °C). Qualitatively, the rates of these azadiene

(15) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 147538. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Scheme 9

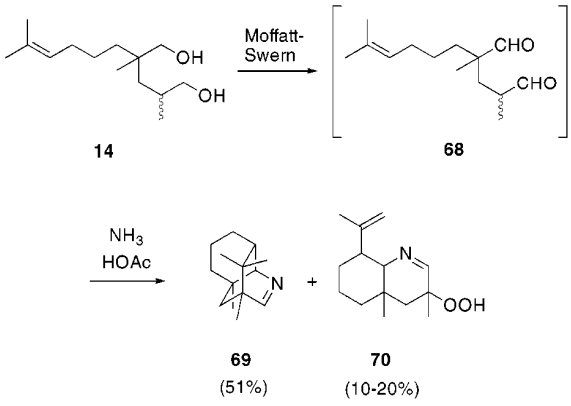


13 65 66 67 (23%)

cyclizations follow the order **56** > **57** > **58** > **59**. This observation supports a rate-limiting inverse-electron-demand Diels–Alder reaction mechanism in which the more electron-rich dienophiles provide faster reaction rates. However, it was also noted that azadiene **57** cyclizes at a faster rate than azadiene **58**, even though both substrates have disubstituted dienophiles. We believe the steric congestion associated with cyclizing the *Z*-olefin of azadiene **58** is the cause of this marked decrease in reaction rate. In addition, it was noted that the olefin geometry of diols **10** and **11** is conserved during the reaction providing imines **61** and **62** respectively, further supporting a concerted mechanism for the Diels–Alder step of the cascade. These experiments also demonstrate that the cascade cyclization works well when the tether length is such that a six-membered ring is formed (the examples previously demonstrated in our *Daphniphyllum* alkaloid syntheses all give rise to five-membered rings). These cyclizations also show that the cascade succeeds with substrates having various alkyl substitution patterns on the dienophile, ranging from mono- to trisubstituted. At this point we turned our attention to the structure of the aza-diene intermediate.

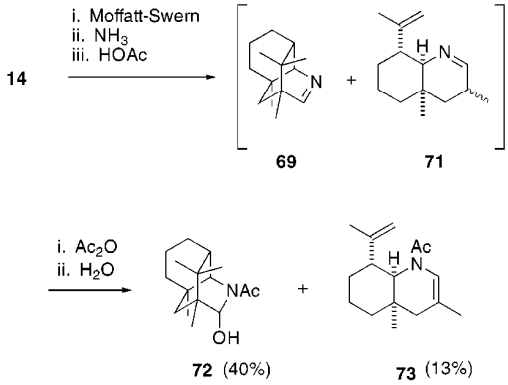
The cyclization sequence of diol **13** is shown in Scheme 9. Treatment of diol **13** under the standard cyclization conditions provided imine **67** in a rather disappointing 23% yield. This was intriguing because the only difference between diol **13** and previous diols is the methyl stereocenter alpha to one of the aldehydes. At this point attempts were then made to determine at which stage the reaction cascade was faltering. Oxidation of diol **13** under Moffatt-Swern conditions followed by an aqueous work up provided the crude 1,5-dialdehyde **65**, verifying the efficiency of this step of the cascade. Repeating the cyclization protocol and stopping after treatment of dialdehyde **65** with ammonia provided a complex mixture of products that has been assigned as the various bisaminal and bishemiaminal structural isomers related to compound **66**. Treatment of this mixture with acetic acid and ammonium acetate again provided imine **67** in low yield, along with intractable polymeric material. To check the stability of imine **67** to the reaction conditions it was taken up in D-4 acetic acid and heated for 50 h at 80 °C, at which time there was no sign of decomposition as judged by ^{1}H NMR. From these data we believe inefficient azadiene formation is responsible for the low yield in the cyclization of diol **13**.

Scheme 10



14 68 69 (51%) 70 (10-20%)

Scheme 11



69 71 72 (40%) 73 (13%)

We next turned our attention to the cyclization of diols **14**–**16**, in which the five-membered ring of diols **9**–**13** is absent. Treatment of diol **14** under the standard cyclization conditions provided the desired tricyclic imine **69** in 51% yield along with bicyclic imine-hydroperoxide **70** in 10–20% yield (Scheme 10). The structure of imine-hydroperoxide **70** was tentatively assigned on the basis of ^{1}H NMR, IR, and mass spectroscopy. This compound was very sensitive; partially decomposing when exposed to silica gel chromatography as well as on storage at 0 °C under a nitrogen atmosphere. We believe that imine-hydroperoxide **70** arises from autoxidation of the corresponding imine on exposure to air during the workup of the reaction.[16] This cyclization was particularly interesting because we had not previously been able to isolate and identify any side products from the reaction cascade.

Because of the sensitive nature of imine-hydroperoxide **70** we decided to modify the cyclization protocol in order to produce a more stable product. Attempts to treat **70** with reducing agents such as trimethyl phosphite or triphenylphosphine in order to reduce the peroxide moiety were unsuccessful, resulting in either no reaction or decomposition of the starting material. Based on these results, we decided to investigate the alternative approach shown in Scheme 11. The idea was that it may be possible to intercept the precursor to **70** by acylation of the imine nitrogen,[17] thus producing an enamide that would be less prone to autoxidation. In the event, treatment of the crude cyclization reaction mixture with

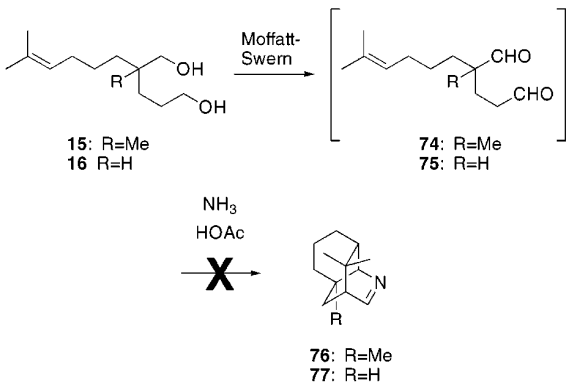
(16) Kleinman, E. F. Doctoral Thesis, University of California at Berkeley, 1980.
(17) Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1* **1984**, *6*, 1173–1182.

an excess of acetic anhydride provided a mixture of amides **72** (40%) and **73** (13%). As expected, enamide **73** was not prone to autoxidation and was fully characterized. The relative stereochemistry of **73** was established by 1D and 2D (NOESY) ^{1}H NMR spectroscopy. In addition, amide **72** is a crystalline solid and its structure was unambiguously determined by X-ray crystallography.[18]

With the structures of **72** and **73** firmly established we considered the factors governing their competing formation. Initial experiments were performed to determine whether imines **69** and **71** can be interconverted. Because imine **69** was isolable it was easily resubjected to the reaction conditions and shown to be stable. As noted above, imine **71** was not easily isolable. To circumvent this difficulty the cyclization reaction was carried out for various times and the ratio of amides **72** and **73** was measured. Extending the reaction time had little effect on either the yield or ratio of amides **72** and **73**. From these data we conclude that imines **69** and **71** are both kinetic products of this reaction. Interestingly, removal of the five-membered ring of diol **9** generates a system in which the aza-Diels–Alder cyclization is only slightly more favorable than the aza-Prins cyclization. Through our efforts it has been possible to observe the 1,5-dialdehyde **68**, but we have been unable to observe the corresponding azadiene intermediate in this reaction. Therefore, it is presently unclear at which point in the cyclization cascade the paths leading to imines **69** and **71** diverge.

We also attempted the cascade cyclization with diols **15** and **16** (Scheme 12). Both of these substrates failed to produce any tractable products. This was not unexpected based on the results gained from diol **13**. Again, aldehydes **74** and **75** could be observed in their crude form, confirming the efficiency of the oxidation step in the cascade reaction. As previously discussed, we believe

Scheme 12



that inefficient aza-diene formation is responsible for the failure of these reactions.

Conclusion

From the above studies we have been able to expand the scope of the *Daphniphyllum* alkaloids cyclization, while defining some of the limitations of this cascade reaction. The cyclization is very permissive to various alkyl substitution patterns of the dienophile, but a marked decrease in rate is noted when relatively electron deficient dienophiles are employed. In addition, it has been demonstrated that the structure of the 2-azadiene is crucial. The cyclopentyl ring, quaternary carbon and tertiary carbon centers in the diol starting material all play a role in providing a selective and high-yielding cyclization.

Acknowledgment. This work was supported by a research grant from the United States Public Health Service Institute of General Medical Studies (GM46057). We are also grateful to Elf Atochem for a predoctoral fellowship supporting G.A.W.

Supporting Information Available: Experimental procedures and characterization for all new compounds reported in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001145R

(18) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 147539. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Further Studies of the *Daphniphyllum* Alkaloid Polycyclization Cascade

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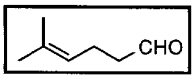
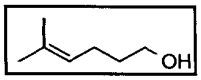
Supporting Information; Experimental Procedures

General. Unless otherwise noted, all reactions were carried out in a flame dried round bottom flask equipped with a magnetic stirring bar, under an atmosphere of N_2. Unless otherwise noted all reagents where purchased from commercial suppliers and used without purification. Ether and tetrahydrofuran (THF) were distilled under N_2 from Na/benzophenone immediately prior to use. Methylene chloride (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine (*i*-Pr_2NH) and Hünig's base (*i*-Pr_2EtN) were distilled under N_2 from CaH_2 immediately prior to use. Dimethyl sulfoxide (DMSO) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) were distilled under N_2 from CaH_2 and stored over 3-Å molecular sieves. Silica gel chromatography was carried out using INC silitech 32-62 D 60-Å silica gel according to the procedure described by Still.[1] Thin layer chromatography (TLC) was performed with Merck Silica Gel 60 plates. When necessary, the density of compounds that were oils were determined by weighing, three separate times, from 50 to 100 µL of the oil in a 100-µL syringe, averaging the results. In this manner the density of the following frequently used compounds were determined (g/mL): enoate **19**, 1.03 and iodide, **20**, 1.43. The concentration of commercially available *n*-butyllithium in hexanes was checked periodically by titration with diphenylacetic acid.[2] Unless otherwise noted, extracts were dried over $MgSO_4$ and solvents were removed with a rotary evaporator at aspirator pressure. Unless otherwise noted, IR spectra were recorded as films on NaCl plates and NMR spectra were measured in $CDCl_3$. Unless otherwise noted ^1H NMR were recorded on a 500 MHz spectrometer and ^{13}C NMR were recorded on a 100 MHz spectrometer. *J* values are in Hertz. In some cases distortionless enhancement by polarization transfer (DEPT)[3] was used to assign the ^{13}C NMR resonances as CH_3, CH_2, CH or C. Elemental analysis was performed by the Microanalytical Laboratory operated by the UCB College of Chemistry.

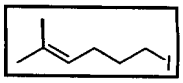
5-Methyl-4-hexenal. Following the procedure of Saucey,[4] 5-Methyl-4-hexenal was provided in 52% yield after distillation (71-76 °C, 50 torr), IR: 2952, 2857, 1715, 1630, 1436, 1355, 1297, 1266, 1090, 741 cm^{-1}. The ^1H and ^{13}C NMR spectral data obtained for this compound was consistent with that reported in the literature.[5]



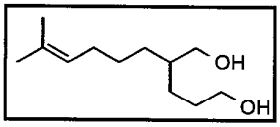
5-Methyl-4-hexen-1-ol. A stirring suspension of $LiAlH_4$ (7.32 g, 193 mmol) in 190 mL of Et_2O was cooled to 0 °C. To this suspension was added a solution of the 5-Methyl-4-hexenal (21.66 g, 193 mmol) in 325 mL of Et_2O dropwise via teflon cannula. The flask containing the aldehyde solution and teflon cannula were rinsed through with 30 mL of Et_2O. The gray reaction mixture was allowed to slowly warm to room temperature (3 h). Stirring continued at rt for an additional 10 h. The reaction mixture was cooled to 0 °C and 7.32 mL of water, 7.32 mL 15% NaOH and 22 mL of water were added sequentially.[6] Following these additions the reaction mixture was allowed to warm to rt at which time a white precipitate formed. The reaction mixture was dried, filtered and the solvent was removed. Distillation of the crude product provided 22.78 g (99%) of the desired alcohol.[7] IR:



3337, 2965, 2929, 2867, 1449, 1376, 1059 cm^{-1}. The ^1H and ^{13}C NMR spectral data obtained for this compound was consistent with that reported in the literature.[8]

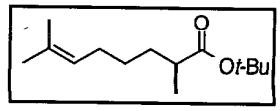


5-Iodo-2-methyl-2-hexene (20). A dry 250 mL round bottom flask was charged with 5-methyl-4-hexen-1-ol (3.0 g, 26.3 mmol) and 55 mL of CH_2Cl_2. To this stirring solution was added triphenylphosphine (7.13 g, 27.2 mmol) and imidazole (2.15 g, 31.5 mmol). After complete dissolution the reaction mixture was cooled to 0 °C and iodine (9.0 g, 35.5 mmol) was added in small portions (approx 2 g). A dark brown color developed along with a precipitate during the iodine addition. Stirring of the solution continued for a total of 4 h at 0 °C. To the dark brown solution was added 25 mL of saturated sodium thiosulfate. After the reaction mixture turned clear it was extracted with CH_2Cl_2 (3 x 25 mL). The combined extracts were dried and concentrated to afford a slightly yellow oil. The crude product was purified by flash chromatography on silica gel eluting with pet ether/ether (4 : 1) to provide 5.21 g (88%) of the pure iodide **20** . The iodide was stored under an atmosphere of nitrogen and over copper wire and 3 Å molecular sieves. Immediately prior to use the iodide was passed through basic alumina. The IR and ^1H NMR spectral data obtained for this compound was consistent with that reported in the literature.[9] ^{13}C NMR (100 MHz): δ 6.8, 17.9, 25.7, 28.7, 33.6, 122.3, 133.1.

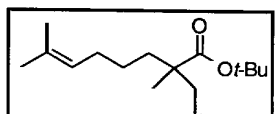


4-Hydroxymethyl-9-methyl-8-decene-1-ol (16). To a stirring solution of diisopropyl amine (1.20 mL, 8.56 mmol) in 15 mL of THF at -78 °C was added dropwise a solution of *n*-butyllithium (3.60 mL, 8.46 mmol). The resulting mixture was warmed to 0 °C for 10 min and cooled to -78 °C. A solution of δ-valerolactone **49** (826 µL, 8.90 mmol) in 15 mL of THF was added via teflon cannula over 90 min and stirred for an additional 15 min. The iodide **20** (140 µL, 0.89 mmol) was added slowly followed by 15 mL of DMPU. The resulting yellow solution was stirred at -78 °C for 1 h and -45 °C for 3 h. The reaction flask was removed from the cold bath and 10 mL of saturated ammonium chloride and 10 mL water were added. After warming to room temperature the mixture was extracted with ether (3 x 30 mL). The combined organic layers were washed with water (3 x 10 mL) and brine (10 mL), dried and the solvent was removed to afford 700 mg of a yellow oil. Without further purification the yellow oil was dissolved in 2 mL ether and added via teflon cannula to a solution of $LiAlH_4$, (133 mg, 3.5 mmol) in 7 mL of ether at 0 °C. An exothermic reaction occurred as evidenced by rapid bubbling of the solvent. The addition flask and cannula were rinsed with ether (2 x 2 mL). After 1 h the reaction mixture was allowed to warm to 25 °C. After 2 h 133 µL of water, 133 µL of a 15% aqueous solution of NaOH and 330 µL of water were added sequentially.[6] After 5 min a scupula of $MgSO_4$ was added to the fine white suspension and the mixture was filtered through a fine glass frit and concentrated. Silica gel chromatography eluting with EtOAc/hexanes (9:1) afforded 123 mg (69%) of the desired diol **16**. IR: 3550-3400, 1673 cm^{-1}. ^1H NMR (500 MHz): δ 1.23-1.36 (m, 6), 1.39-1.49 (m, 2), 1.52-1.58 (m, 1), 1.56 (d, 3, *J*=0.7), 1.65 (d, 3, *J*=1.0), 1.93 (m, 2), 2.17 (bs, 1), 2.22 (bs, 1), 3.46-3.49 (m, 1), 3.54-3.56 (m, 1), 3.61 (m, 2), 5.07 (m, 1). ^{13}C NMR (100 MHz): δ 17.7 (CH_3), 25.7 (CH_3), 26.9 (CH_2), 27.1 (CH_2), 28.3 (CH_2), 29.7 (CH_2), 30.6 (CH_2), 40.1 (CH), 63.1 (CH_2), 65.3 (CH_2), 124.5 (CH), 131.5 (C). Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.59; H, 12.20.

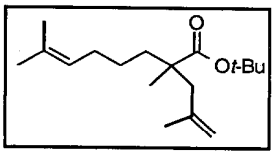
***t*-Butyl 2,7-dimethyl-6-octenoate (42).** To a solution of diisopropylamine (900 µL, 6.42 mmol) in 13.5 mL THF at -78 °C was added 2.73 mL (6.41 mmol) of a 2.34 M solution of *n*-butyllithium in hexanes dropwise. The resulting mixture was warmed to 0 °C for 10 min and then cooled to -78 °C. A solution of *t*-butyl propionate (1.02 µL, 6.75 mmol) in 6.75 mL THF was added slowly (15 min) via teflon cannula. The resulting mixture was stirred for 45 min following the addition. The iodide **20** (702 µL, 4.5 mmol) was added via syringe followed by 5 mL of DMPU. After 1h of stirring at -78 °C the reaction mixture was warmed to -45 °C. After 1.5 h, 15 mL of satd ammonium chloride and 5 mL of water were added and the reaction mixture was allowed to warm to room temperature. The mixture was extracted with ether (4 x 20 mL). The combined extracts were washed with water (2 x 30 mL), brine (30 mL), dried and concentrated. Silica gel chromatography of the crude product with EtOAc/hexanes (1 : 19) provided 953 mg (94%) of the pure ester **42**. IR: 2974, 2932, 2876, 1730, 1456, 1366, 1256, 1217, 1148, 1068, 848. ^{1}H NMR (500 MHz): δ 1.07 (d, 3, *J*=7.0), 1.28-1.35 (m, 4), 1.42 (s, 9), 1.57 (s, 3), 1.67 (d, 3, *J*=1.1), 1.94 (m, 2), 2.26-2.30 (m, 1), 5.06-5.09 (m, 1). ^{13}C NMR (100 MHz): δ 17.2 (CH_3), 17.7 (CH_3), 25.7 (CH_3), 27.4 (CH_2), 27.9 (CH_2), 28.1 (CH_3), 33.5 (CH_2), 40.4 (CH), 79.7 (C), 124.4 (CH), 131.5 (C), 176.3 (C). Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 73.91; H, 11.58.



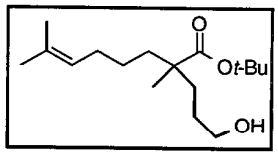
***t*-Butyl 2,7-dimethyl-2-(2-allyl)-6-octenoate (46).** To a solution of diisopropylamine (594 µL, 4.24 mmol) in 9.0 mL THF at 0 °C was added dropwise 1.75 mL (4.12 mmol) of a 2.35 M solution of *n*-butyllithium in hexanes. The mixture was stirred at 0 °C for 30 min then was cooled to -78 °C and a solution of the ester **42** (622 mg, 2.75 mmol) in 2.75 mL THF was added slowly via teflon cannula. The flask and cannula were rinsed with 2 mL of THF. Stirring was continued for 2 h, at which time allyl bromide (476 µL, 5.5 mmol) was added dropwise. The slightly yellow solution was stirred at -78 °C for 1.5 h, warmed to 25 °C and poured onto 20 mL of saturated NH_4Cl and 10 mL of water. This mixture was extracted with ether (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried and the solvents were removed to afford 879 mg of a yellow oil. Silica gel chromatography ether/hexanes (1:99) provided 658 mg (90%) of the desired ester **46**. IR: 3074, 2974, 2932, 2364, 1725 cm^{-1}. ^{1}H NMR(500 MHz): δ 1.05 (s, 3), 1.18-1.24 (m, 1), 1.27-1.43 (m, 2), 1.42 (s,9), 1.48-1.59 (m, 1), 1.58 (s, 3), 1.67 (s, 3), 1.94 (m, 2), 2.11 (dd, 1, *J*=7.71, 13.67), 2.33 (dd, 1, *J*=7.06, 13.63), 5.01 (s, 1), 5.03-5.04 (m, 1), 5.07-5.10 (m, 1), 5.67-5.76 (m, 1). ^{13}C NMR (100 MHz): δ 17.7, 21.2, 24.9, 25.7, 28.1, 28.4, 38.8, 43.6, 46.1, 79.8, 117.5, 124.4, 131.4, 134.4, 176.2. Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.46, H; 11.33.



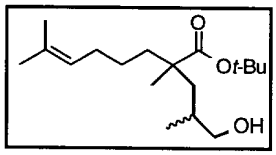
***t*-Butyl 2,7-dimethyl-2-(2-methyl-2-propenyl)-6-octenoate (45).** The foregoing procedure was followed with 334 µL (2.38 mmol) of diisopropyl amine, 959 µL (2.32 mmol) of a 2.42 M solution of *n*-butyllithium in hexanes, 263 mg (1.16 mmol) of ester **42** and 352 µL (3.49 mmol) of 1-bromo-2-methyl-2-propene. The crude product was purified by flash chromatography on silica gel eluting with a gradient of benzene/pet. ether (from 3:1 to 1:1) to provide 279 mg (86 %) of the desired ester **45** as a clear slightly yellow oil. IR: 3074, 2974, 2932, 2364, 1723 cm^{-1}. ^{1}H NMR(500 MHz): δ 1.03 (s, 3), 1.13-1.21 (m, 1), 1.26-1.38 (m, 2), 1.42 (s, 9), 1.45-1.67 (m, 10), 1.91 (q, 2, *J*=7.1),



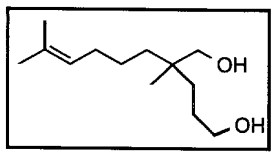
2.04 (d, 1, *J*=13.8), 2.46 (d, 1, *J*= 13.7), 4.64 (s, 1), 4.76-4.77 (m, 1), 5.06-5.09 (m, 1). ^{13}C NMR (100 MHz): δ 17.7, 20.8, 23.9, 24.8, 25.7, 28.0, 28.4, 40.5, 45.9, 47.5, 79.9, 114.0, 124.4, 131.6, 142.8, 176.6. Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 76.98, H; 11.64.



***t*-Butyl 2,7-dimethyl-2-(3-hydroxypropyl)-6- octenoate (48).** To a solution of 9-borabicyclo[3.3.1]nonane (9-BBN) (43 mg, 0.35 mmol) in 450 µL of THF at 25 °C was added a solution of **46** (60 mg, 0.23 mmol) in 500 µL of THF, via syringe. The flask containing the solution of the ester and the syringe were rinsed through with 2 x 500 µL THF. After stirring for 1.75 h, water (2.3 mL), sodium perborate (120 mg, 0.78 mmol) and 130 µL (0.26 mmol) of a 2N aqueous solution of NaOH was added. After 2 h the suspension was diluted with 5 mL of water and 10 mL ether. The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried and concentrated to afford 126 mg of an oil. Silica gel chromatography eluting with EtOAc/hexanes (1:4) provided 53.6 mg (82 %) of the desired alcohol **48**. IR: 3350, 2973, 2931, 2863, 1723 cm^{-1}. ^1H NMR (500 MHz): δ 1.05 (s, 3), 1.17-1.21 (m, 2), 1.25-1.46 (m , 4), 1.41 (s, 9), 1.51-1.56 (m, 2), 1.56 (s, 3), 1.63 (dd, 1, *J*=3.5, 11.7), 1.65 (d, 3, *J*=1.0), 1.91 (m, 2), 3.56-3.59 (m, 2), 5.05-5.08 (m, 1). ^{13}C NMR (100 MHz): δ 17.6, 21.1, 24.7, 25.6, 27.8, 27.9, 28.3, 35.2, 39.2, 45.8, 63.0, 79.8, 124.3, 131.5, 176.7. Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.98, H, 11.52.

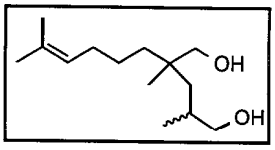


***t*-Butyl 2,7-dimethyl-2-(2-methyl-3-hydroxypropyl)-6-octenoate (47).** The foregoing procedure was followed with 161 mg (1.32 mmol) of 9-BBN, and 295 mg (1.05 mmol) of ester **45**. The crude product was purified by flash chromatography on silica gel eluting with EtOAc/hexanes (3:1) to provide 300 mg of the desired ester **47** contaminated by a small amount of an unidentified 9-BBN by product. IR: 3437, 2974, 2932, 2873, 1722 cm^{-1}. ^1H NMR (500 MHz): δ 0.89 (d, 1.2, *J*=6.8), 0.93 (d, 1.8 *J*=6.8), 1.00-1.09 (m, 1), 1.05 (s, 1.2), 1.09 (s, 1.8), 1.10-1.80 (m , 6), 1.42 (s, 9), 1.56 (s, 3), 1.65 (s, 3), 1.82-1.91 (m, 2.4), 2.18 (bs, 0.6), 3.34-3.41 (m, 2), 5.02-5.11 (m, 1). ^{13}C NMR (100 MHz): δ 17.7, 17.9, 19.3, 21.3, 21.5, 24.6, 25.7, 28.0, 28.4, 32.4, 32.6, 40.0, 41.4, 41.6, 42.2, 45.6, 46.0, 67.4, 68.8, 80.1, 80.5, 124.3, 124.4, 131.7, 176.6. Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found: C, 72.17, H, 11.66.

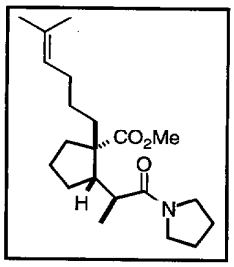


4,9-Dimethyl-4-(hydroxymethyl)-8-decen-1-ol (15). To a solution of the ester **48** (691 mg, 2.43 mmol) in 5.0 mL ether at 0 °C was added $LiAlH_4$ (182 mg, 4.8 mmol) slowly. The flask was flushed with N_2 and stirred at 0 °C for 30 min then allowed to warm to 25 °C while stirring continued for 12 h. The reaction mixture was cooled to 0 °C and 182 µL of water, 182 µL of a 15 % aqueous solution of NaOH and 540 µL of water were added sequentially. After 5 min. $MgSO_4$ (0.3 g) and celite (1 g) were added to the fine white suspension and the mixture was filtered through a fine glass frit and concentrated to provide 565 mg of a clear oil. Silica gel chromatography, eluting with 500 mL of EtOAc/hexanes (8 : 1) followed by 500 mL of EtOAc/hexanes (9 : 1) provided 484 mg (93 %) of the desired diol **15**. IR: 3337, 2927,

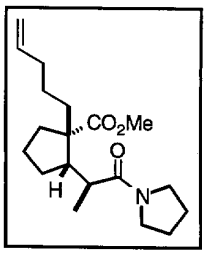
2873, 1671, 1451, 1376, 1037 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.82 (s, 3), 1.18-1.32 (m, 6), 1.47-1.53 (m, 4), 1.58 (s, 3), 1.67 (d, 3, *J*=1.0), 1.92 (m, 2), 3.33-3.36 (m, 2), 3.61 (m, 2), 5.07-5.10 (m, 1). ^{13}C NMR (100 MHz): δ 17.7, 21.8, 23.7, 25.7, 26.5, 28.8, 32.1, 36.2, 37.1, 63.6, 69.3, 124.6, 131.5.



4-Hydroxymethyl-2,4,9-Trimethyl-8-decen-1-ol (14). The foregoing procedure was followed with 300 mg (1.0 mmol) of ester **47** and 56.1 mg (1.5 mmol) of LAH. The crude product was purified by flash chromatography on silica gel, eluting with a gradient of EtOAc/hexanes (from 3:1 to 1:1) to provide 198 mg (87%) of the desired diol **15** as a colorless oil. IR: 3324, 2928, 2872, 1454 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.75 (s, 1.8), 0.86 (s, 1.2), 0.89 (d, 3, *J*=6.2), 0.90-1.39 (m, 5), 1.48-1.54 (m, 1), 1.57 (s, 3), 1.58-1.76 (m , 1), 1.66 (s, 3), 1.83-1.92 (m, 2), 3.15-3.24 (m, 2), 3.39-3.80 (m, 2), 3.52 (bs, 2), 5.10-5.18 (m, 1). ^{13}C NMR (100 MHz): δ 17.5, 17.6, 19.6, 19.9, 20.4, 23.4, 23.5, 23.8, 25.6, 28.7, 28.8, 30.1, 30.2, 35.5, 37.7, 37.9, 38.8, 39.3, 40.3, 67.6, 68.8, 69.0, 124.5, 124.7, 131.0, 131.3.

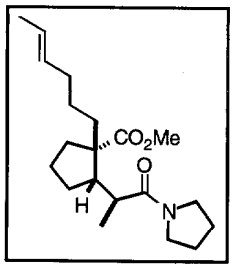


Methyl 1-(5-methyl-4-hexenyl)-2-[1-(1-pyrrolidinylcarbonyl)-ethyl]- cyclopentanecarboxylate (24). To a solution of the diisopropylamine (230 µL, 1.64 mmol) in 1.6 mL THF at 0 °C was added 641 µL (1.59 mmol) of a 2.48 M solution of *n*-butyllithium in hexanes dropwise. The mixture was stirred at 0 °C for 30 min cooled to -78 °C and a solution of the *N*-propionylpyrrolidine (**17**) (200 µL,1.59 mmol) in 0.8 mL THF was added slowly via teflon cannula. This solution was stirred at -78 °C for 0.5 h at which time a solution of enoate **19** (200 mg, 1.59 mmol) in 1.6 mL THF was added slowly via teflon cannula. After 15 min the iodide **20** (167 µL, 1.06 mmol) was added. The yellow solution was allowed to warm slowly to 25 °C over 15 h. To the reaction mixture was added 10 mL of saturated NH_4Cl and 5 mL of saturated $Na_2S_2O_3$. The resulting mixture was extracted with ether (3 x 15 mL). The organic extracts were combined and washed with brine (40 mL). The aqueous wash was back extracted with ether (50 mL). The combined organic extracts were dried and concentrated to afford 516 mg of a yellow oil. Repeated silica gel chromatography with EtOAc/hexanes (1:1) provided 256 mg (69 %) of the desired amide-ester **24** as a clear colorless oil. IR: 2951, 2872, 1721, 1641, 1430, 1161 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.00 (d, 3, *J*=6.91), 1.03-1.12 (m, 1), 1.18-1.30 (m, 2), 1.35-1.61 (m, 4), 1.55 (s, 3), 1.64 (s, 3), 1.71-1.99 (m, 8), 2.13-2.18 (m, 1), 2.28-2.33 (m, 1), 2.51-2.56 (m, 1), 3.31-3.48 (m, 3), 3.62-3.67 (m, 1), 3.62 (s, 3), 5.02-5.05 (m, 1). ^{13}C NMR (100 MHz): δ 16.7, 17.7, 21.6, 24.6, 25.7, 26.2, 26.6, 28.3, 28.6, 34.6, 37.8, 38.2, 45.8, 46.1, 51.3, 51.7, 57.0, 124.6, 131.3, 174.8, 177.0. Anal. Calcd for $C_{21}H_{35}NO_3$: C, 72.17; H, 10.09; N, 4.01. Found: C, 72.07; H, 10.16; N, 4.10.

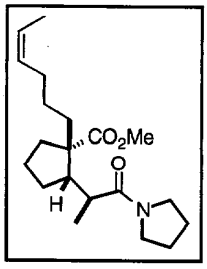


Methyl 1-(4-pentenyl)-2-[1-(1-pyrrolidinylcarbonyl)-ethyl]-cyclopentane-carboxylate (27): The foregoing procedure was followed with 1.11 ml (7.91 mmol) of diisopropylamine, 3.28 ml of a 2.33M solution of *n*-butyllithium in hexanes, 1.15g (8.93 mmol) of *N*-propionylpyrrolidine (**17**), 942 µL (7.65 mmol) of enoate **19**, and 1.0 g (5.1 mmol) of iodide **23**. The crude product was purified by flash

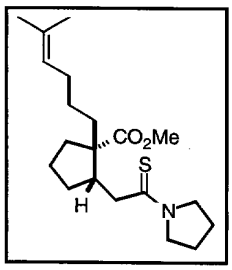
chromatography on silica gel (25% EtOAc/Hex) to provide 1.17 g (71%) of the desired ester **27** as a clear colorless oil. IR: 2965, 2872, 1721, 1640, 1430 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.00 (d, 3, *J*=7.0), 1.13-1.25 (m, 2), 1.32-1.61 (m, 5), 1.73-2.00 (m, 8), 2.14-2.19 (m, 1), 2.30-2.36 (m, 1), 2.50-2.56 (m, 1), 3.33 (ddd, 1, *J*=6.2, 6.2, 9.9), 3.38-3.47 (m, 2), 3.63-3.67 (m, 1), 3.63 (s, 3), 4.88-4.90 (m, 1), 4.93-4.97 (m, 1), 5.74 (dddd, 1, *J*=6.6, 6.6, 10.2, 17.0). ^{13}C NMR (100 MHz): δ 16.7, 21.6, 24.4, 25.5, 36.1, 28.3, 34.2, 34.5, 37.4, 38.2, 45.7, 46.0, 51.3, 51.7, 56.9, 114.3, 138.8, 174.8, 177.0. Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72; N, 4.36. Found: C, 70.78; H, 10.09; N, 4.18.



Methyl 1-(E-4-hexenyl)-2-[1-(1-pyrrolidinylcarbonyl)-ethyl]-cyclo-pentanecarboxylate (25). The foregoing procedure was followed with 1.03 ml (7.38 mmol) of diisopropylamine, 3.05 ml of a 2.34M solution of *n*-butyllithium in hexanes, 899 µL (7.14 mmol) of *N*-propionylpyrrolidine (**17**), 879 µL (7.14 mmol) of enoate **19**, and 1.0 g (4.76 mmol) of iodide **21**. The crude product was purified by flash chromatography on silica gel (30-40% EtOAc/Hex) to provide 1.09 g (68%) of the desired ester **25** as a clear colorless oil. IR: 2950, 1721, 1641, 1431 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.99 (d, 3, *J*=7.0), 1.08-1.12 (m, 1), 1.17-1.29 (m, 2), 1.36-1.43 (m, 1), 1.45-1.49 (m, 1), 1.52-1.59 (m, 1), 1.59 (d, 3, *J*=4.0), 1.71-1.76 (m, 1), 1.79-1.98 (m, 8), 2.15 (ddd, 1, *J*=5.1, 9.2, 13.1), 2.30 (ddd, 1, *J*=8.6, 8.6, 12.0), 2.53 (dq, 1, *J*=6.9, 6.9), 3.31 (ddd, 1, *J*=6.7, 9.9, 13.6), 3.36-3.46 (m, 2), 3.61 (s, 3), 3.63-3.66 (m, 1), 5.30-5.39 (m, 2). ^{13}C NMR (100 MHz): δ 16.7, 17.9, 21.6, 24.4, 26.1, 26.3, 28.3, 33.1, 34.5, 37.5, 38.2, 45.7, 46.0, 51.3, 51.7, 56.9, 124.7, 131.3, 174.8, 177.0. Anal. Calcd for $C_{20}H_{33}NO_3$: C, 71.60; H, 9.91; N, 4.17. Found: C, 71.47; H, 10.04; N, 4.17.

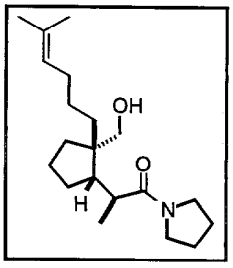


Methyl 1-(Z-4-hexenyl)-2-[1-(1-pyrrolidinylcarbonyl)-ethyl]-cyclo-pentanecarboxylate (26). The foregoing procedure was followed with 1.03 ml (7.38 mmol) of diisopropylamine, 3.05 ml of a 2.34 M solution of *n*-butyllithium in hexanes, 899 µL (7.14 mmol) of *N*-propionylpyrrolidine (**17**), 879 µL (7.14 mmol) of enoate **19**, and 1.0 g (4.76 mmol) of iodide **22**. The crude product was purified by flash chromatography on silica gel (30-40% EtOAc/Hex) to provide 681 mg (43%) of the desired ester **26** as a clear colorless oil. IR: 2951, 2871, 1721, 1641, 1431 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.00 (d, 3, *J*=6.9), 1.10-1.16 (m, 1), 1.21-1.32 (m, 2), 1.37-1.46 (m, 1), 1.48-1.62 (m, 2), 1.57 (d, 3, *J*=5.4), 1.74-1.78 (m, 1), 1.82-1.89 (m, 4), 1.91-2.00 (m, 4), 2.17 (dddd, 1, *J*=4.8, 4.8, 8.7, 8.7), 2.33 (ddd, 1, *J*=8.6, 7.2, 12.0), 2.52-2.58 (m, 1), 3.32-3.37 (m, 1), 3.39-3.48 (m, 2), 3.63-3.68 (m, 1), 3.64 (s, 3), 5.29-5.34 (m, 1), 5.37-5.42 (m, 1). ^{13}C NMR (100 MHz): δ 12.8, 16.7, 21.6, 24.4, 26.2, 26.2, 27.4, 28.3, 34.5, 37.6, 38.2, 45.8, 46.1, 51.3, 51.7, 57.0, 123.8, 130.5, 174.8, 177.0. Anal. Calcd for $C_{20}H_{33}NO_3$: C, 71.60; H, 9.91; N, 4.17. Found: C, 71.49; H, 10.09; N, 4.25.

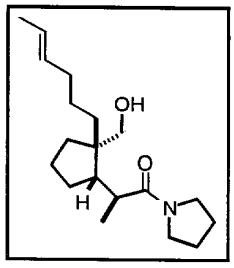


1-(5-Methyl-hex-4-enyl)-2-(2-pyrrolidin-1-yl-2-thioxo-ethyl)-cyclopentanecarboxylic acid methyl ester (30): The foregoing procedure was followed with 1.28 ml (9.15 mmol) of diisopropylamine, 3.83 ml of a 2.33M solution of *n*-butyllithium in hexanes, 1.15g (8.93 mmol) of *N*-pyrrolidine-thioacetamide (**29**),[10] 1.10 ml (8.93 mmol) of enoate **19**, and 702 µL (4.46 mmol) of iodide **20**. The crude product was purified by flash chromatography on silica gel (20-30% EtOAc/hexanes) to provide 1.44 g (92%) of the

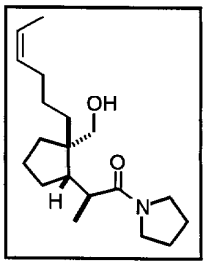
desired thioamide **30** as a clear colorless oil. IR: 2964, 2872, 1722, 1471, 1446 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.13-1.22 (m, 1), 1.25-1.40 (m, 3), 1.46-1.52 (m, 1), 1.55 (s, 3), 1.56-1.62 (m, 1), 1.64 (s, 3), 1.72-1.80 (m, 1), 1.89-2.05 (m, 8), 2.19 (ddd, 1, *J*=5.2, 9.13, 14.2), 2.40-2.49 (m, 2), 2.79 (d, 1, *J*=11.5), 3.55-3.67 (m, 2), 3.62 (s, 3), 3.77-3.87 (m, 2), 5.05 (dd, 1, *J*=7.1, 7.1). ^{13}C NMR (100 MHz): δ 17.7, 21.9, 24.2, 25.7, 26.2, 26.3, 28.5, 30.2, 33.4, 37.5, 44.8, 49.8, 50.6, 51.3, 54.0, 56.9, 124.3, 131.6, 176.5, 199.7. Anal. Calcd for $C_{20}H_{33}NO_2S$: C, 68.33; H, 9.46; N, 3.98. Found: C, 68.60; H, 9.68; N, 4.04.



1-Hydroxymethyl-1-(5-methyl-4-hexenyl)-2-[1-(1-pyrrolidinyl-carbonyl)-ethyl]-cyclopentane (31). To a solution of the ester-amide **24** (137 mg, 0.39 mmol) in 3.9 mL of THF at 0 °C was added 2.34 mL (2.34 mmol) of a 1.0 M solution of lithium triethylborohydride in THF. The reaction mixture was stirred at 25 °C for 1 h and returned to 0 °C at which time 10 mL of water and 5 mL of brine were added slowly. The mixture was extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried with K_2CO_3 and the solvents and triethylborane were removed with heating (30-40 °C) using a N_2 flushed rotary evaporator at aspirator pressure for 0.5 h to provide 130 mg of a clear oil. Silica gel chromatography with EtOAc/hexanes (1:1) provided 109 mg (87 %) of the desired alcohol **31** as a white solid, mp 68-69 °C. IR: 3387, 2947, 2872, 1618, 1439, 1047 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.03 (d, 3, *J*=6.9), 1.10-1.19 (m, 1), 1.20-1.52 (m, 9), 1.53 (s, 3), 1.62 (s, 3), 1.77-1.92 (m, 6), 2.10 (m, 1), 2.32 (bs, 1), 2.55-2.61 (m, 1), 3.51-3.56 (m, 1), 3.26- 3.41 (m, 5), 5.05-5.13 (m, 1). ^{13}C NMR (100 MHz): δ 17.5, 17.6, 21.7, 24.2, 24.7, 25.6, 26.1, 28.9, 29.3, 33.5, 35.9, 38.3, 45.8, 46.3, 48.4, 48.8, 66.1, 125.0, 131.0, 176.1. Anal. Calcd for $C_{20}H_{35}NO_2$: C, 74.72; H, 10.97; N, 4.36. Found: C, 74.74; H, 11.21; N, 4.57.

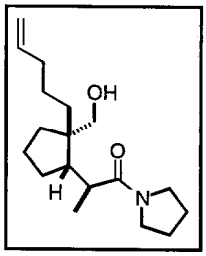


E-1-Hydroxymethyl-1-(4-hexenyl)-2-[1-(1-pyrrolidinylcarbonyl)-ethyl]- cyclopentane (32). The foregoing procedure was followed with 454 mg (1.35 mmol) of amide **25** and 4.1 ml of a 1.0 M solution of lithium triethylborohydride in THF. The crude product was purified by flash chromatography on silica gel (50% EtOAc/ Hex) to provide 378 mg (91%) of the desired alcohol **32** was a clear colorless solid, mp 121-131°C. IR: 3428, 2946, 2871, 1616 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.07 (d, 3, *J*=6.9), 1.14-1.20 (m, 1), 1.26-1.41 (m, 4), 1.47-1.54 (m, 4), 1.61 (d, 3, *J*=4.4), 1.81-1.97 (m, 7), 1.99-2.02 (m, 1), 2.12-2.18 (m, 1), 2.59 (dddd, 1, *J*=7.0, 7.0, 7.0, 10.0), 3.29-3.41 (m, 3), 3.44 (dd, 2, *J*=7.0, 7.0), 3.53-3.57 (m, 1), 5.39-5.41 (m, 2). ^{13}C NMR (100 MHz): δ 17.5, 17.9, 21.7, 24.2, 24.5, 26.1, 29.4, 33.4, 33.6, 35.8, 38.4, 45.8, 46.3, 48.4, 48.8, 66.1, 124.5, 131.7, 176.1. Anal. Calcd for $C_{19}H_{33}NO_2$: C, 74.23; H, 10.82; N, 4.56. Found: C, 73.93; H, 10.80; N, 4.51.

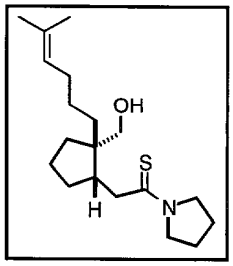


Z-1-Hydroxymethyl-1-(4-hexenyl)-2-[1-(1-pyrrolidinylcarbo nyl)-ethyl]- cyclopentane (33). The foregoing procedure was followed with 680 mg (2.0 mmol) of amide **26** and 6.1 ml of a 1.0 M solution of lithium triethylborohydride in THF. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/hexanes (1:1) to provide 512 mg (83%) of the desired alcohol **33** as a clear colorless oil. IR: 3401, 2948, 2872, 1719, 1618 cm^{-1}. ^{1}H

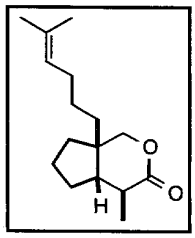
NMR (500 MHz): δ 1.06 (d, 3, *J*=6.9), 1.18-1.22 (m, 1), 1.24-1.41 (m, 5), 1.41-1.58 (m, 7), 1.79-2.02 (m, 6), 2.05-2.18 (m, 2), 2.57 (dq, 1, *J*=6.9, 9.9), 3.27-3.43 (m, 5), 3.54 (ddd, 1, *J*=6.9, 6.9, 9.9), 5.35-5.42 (m, 2). Anal. Calcd for $C_{19}H_{33}NO_2$: C, 74.23; H, 10.82; N, 4.56. Found: C, 74.26; H, 11.07; N, 4.34.



1-Hydroxymethyl-1-(4-pentenyl)-2-[1-(1-pyrrolidinylcarbonyl)-ethyl]- cyclopentane (34). The foregoing procedure was followed with 1.17g (3.64 mmol) of amide **27** and 10.9 ml of a 1.0 M solution of lithium triethylborohydride in THF. The crude product was purified by flash chromatography on silica gel, eluting with a gradient of EtOAc/hexanes (from 1:1 to 3:5) to provide 960 mg (90%) of the desired alcohol **34** as a clear colorless solid, mp 56-58°C. IR: 3331, 2951, 2864, 1609 cm $^{-1}$. ^{1}H NMR (500 MHz): δ 1.05 (d, 3, *J*=6.9), 1.15 (ddd, 1, *J*=4.7, 12.8, 12.8 Hz), 1.27-1.53 (m, 8), 1.77-2.00 (m, 7), 2.13 (q, 1, *J*=9.31), 2.55-2.61 (m, 1), 3.27-3.43 (m, 6), 3.52-3.56 (m, 1), 4.88 (d, 1, *J*=10.2), 4.95 (dd, 1, *J*=1.5, 17.1), 5.78 (dddd, 1, *J*=6.7, 6.7, 10.2, 16.9). ^{13}C NMR (100 MHz): δ 17.6, 21.7, 23.8, 24.3, 26.2, 29.4, 33.6, 34.6, 35.7, 38.5, 45.9, 46.4, 48.3, 48.9, 66.2, 114.2, 139.3, 176.2. Anal. Calcd for $C_{18}H_{31}NO_2$: C, 73.67; H, 10.65; N, 4.77. Found: C, 73.73; H, 10.46; N, 4.80.



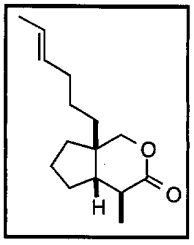
2-[2-Hydroxymethyl-2-(5-methyl-hex-4-enyl)-cyclopentyl]-1-pyrrolidin-1-yl-ethanethione (35). The foregoing procedure was followed with 254.3 mg (0.723 mmol) of thioamide **30** and 1.81 ml of a 1.0 M solution of lithium triethylborohydride in THF. The crude product was purified by flash chromatography on silica gel eluting with EtOAc/hexanes (2:5) to provide 186.3 mg (80%) of the desired alcohol **35** as a clear colorless oil. IR: 3407, 2942, 2871, 1487, 1448 cm $^{-1}$. ^{1}H NMR (500 MHz): δ 1.21 (ddd, 1, *J*=4.2, 12.8, 16.9 Hz), 1.28-1.51 (m, 8), 1.56 (s, 3), 1.56-1.61 (m, 1), 1.64 (s, 3), 1.74 (bs, 1), 1.91-1.96 (m, 4), 2.02 (ddd, 2, *J*=6.8, 6.8, 6.8), 2.22-2.28 (m, 1), 2.70 (dd, 1, *J*=10.5, 13.8), 2.87 (dd, 1, *J*=3.9, 13.7), 3.44 (q, 2, *J*=11.1), 3.64 (t, 2, *J*=6.9), 3.83 (t, 2, *J*=7.0), 5.07-5.10 (m, 1). ^{13}C NMR (100 MHz): δ 17.7, 22.1, 24.2, 24.9, 25.7, 26.3, 28.8, 31.1, 33.6, 36.0, 44.4, 47.3, 48.2, 50.8, 53.9, 66.0, 124.6, 131.5, 200.9. Anal. Calcd for $C_{19}H_{33}NOS$: C, 70.53; H, 10.28; N, 4.33. Found: C, 70.13; H, 10.23; N, 4.51.



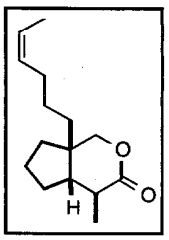
[5-Methyl-4-hexenyl]-hexahydro-4-(methyl)cyclopenta[c]pyran-3 (1H)- one (36). To a solution of the amide alcohol **31** (117 mg, 0.363 mmol) in 3.6 mL MeOH was added 726 µL of a 5.0 M aqueous solution of HCl. This solution was stirred at 25 °C, under an air atmosphere, for 4 h. The reaction mixture was diluted with 20 mL ether and 20 mL brine. The organic layer was separated and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried and concentrated to provide a colorless oil. Silica gel chromatography, eluting with EtOAc/hexanes (1:4) provided 84 mg (93 %) of the desired lactone **36**, as a colorless oil. IR: 2933, 2862, 1746 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.17 (d, 3, *J*=6.52), 1.19-1.35 (m, 4), 1.43-1.57 (m, 4), 1.55 (s, 3), 1.59-1.68 (m, 2), 1.64 (s, 3), 1.90-2.01 (m, 3), 2.19-2.25 (m, 1), 3.85 (d, 1, *J*=11.39), 4.07 (d, 1, *J*=11.41), 5.03-5.06 (m, 1). ^{13}C NMR (100 MHz): δ 14.6 (CH_3), 17.7 (CH_3), 24.7 (CH_2), 25.3 (CH_2), 25.7 (CH_3), 28.4 (CH_2), 33.6 (CH_2), 35.1 (CH_2), 38.4 (CH, CH_2), 45.7 (C), 50.0

(CH), 71.5 (CH_2), 124.1 (CH), 131.7 (C), 176.0 (C). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.68; H, 10.79.

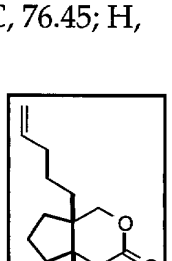
[E-4-hexenyl]-hexahydro-4-(methyl)cyclopenta[c]pyran-3(1H)-one (37). The foregoing procedure was followed with 378 mg (1.23 mmol) of alcohol **32** and 2.46 ml of a 5 M aqueous HCl solution. The crude product was purified by flash chromatography on silica gel, eluting with a gradient of EtOAc/hexanes (from 1:10 to 1:5) to provide 284 mg (98%) of the desired lactone **37** as a clear colorless oil. IR: 2935, 1745 cm^{-1}. ^1H NMR (500 MHz): δ 1.18 (d, 3, *J*=6.5), 1.20-1.29 (m, 3), 1.31-1.40 (m, 1), 1.40-1.58 (m, 5), 1.59-1.68 (m, 4), 1.88-2.02 (m, 3), 2.23 (dq, 1,*J*=6.6, 10.4), 3.86 (d, 1, *J*=11.4), 4.08 (d, 1, *J*=11.4), 5.33-5.43 (m, 2). ^{13}C NMR (100 MHz): δ 14.6, 17.9, 24.5, 25.3, 33.0, 33.6, 35.1, 38.3, 38.5, 45.7, 50.0, 71.6, 125.3, 130.9, 175.5. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.51; H, 10.51.



[Z-4-hexenyl]-hexahydro-4-(methyl)cyclopenta[c]pyran-3(1H)-one (38). The foregoing procedure was followed with 510 mg (1.66 mmol) of alcohol **33** and 3.3 ml of a 5 M aqueous HCl solution. The crude product was purified by flash chromatography on silica gel, eluting with a gradient of EtOAc/hexanes (from 1:10 to 1:5) to provide 385 mg (98%) of the desired lactone **38** as a clear colorless oil. IR: 2936, 1745, 1453, 1265 cm^{-1}. ^1H NMR (500 MHz): δ 1.19 (d, 3, *J*=6.7), 1.21-1.29 (m, 3), 1.33-1.40 (m, 1), 1.43-1.58 (m, 4), 1.56 (d, 3, *J*=7.7), 1.61-1.69 (m, 2), 1.94-2.01 (m, 3), 2.23 (dq, 1,*J*=6.5, 10.5), 3.86 (d, 1, *J*=11.4), 4.08 (d, 1, *J*=11.4), 5.29-5.34 (m, 1), 5.39-5.45 (m, 1). ^{13}C NMR (100 MHz): δ 12.7, 14.6, 24.3, 25.3, 27.1, 33.6, 35.1, 38.3, 38.4, 45.7, 50.0, 71.5, 124.2, 130.0, 176.0. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.45; H, 10.47.

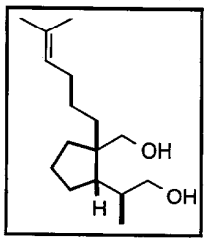


[4-pentenyl]-hexahydro-4-(methyl)cyclopenta[c]pyran-3(1H)-one (39). The foregoing procedure was followed with 960 mg (3.27 mmol) of alcohol **34** and 6.5 ml of a 5 M aqueous HCl solution. The crude product was purified by flash chromatography on silica gel eluting with EtOAc/hexanes (1:5) to provide 700 mg (96%) of the desired lactone **39** as a clear colorless oil. IR: 2935, 1745 cm^{-1}. ^1H NMR (500 MHz): δ 1.18 (d, 3, *J*=6.5), 1.24-1.35 (m, 3), 1.37-1.57 (m, 6), 1.60-1.70 (m, 2), 1.93-2.12 (m, 2), 2.20-2.29 (m, 1), 3.85 (d, 1, *J*=11.2), 4.11 (d, 1, *J*=11.3), 4.90 (d, 1, *J*=10.2), 5.01 (dd, 1, *J*=1.5, 17.0), 5.78 (dddd, 1, *J*=6.7, 6.7, 10.2, 16.8). ^{13}C NMR (100 MHz): δ 14.2, 23.3, 24.9, 33.1, 33.7, 34.6, 37.8, 37.9, 45.2, 49.6, 71.0, 114.3, 137.9, 175.5. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.58; H, 10.32.

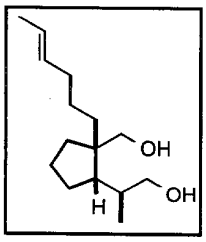


[5-Methyl-4-hexenyl]-hexahydro-cyclopenta[c]pyran-3(1H)- one (40). To a stirring solution of alcohol **35** (407 mg, 1.26 mmol) in MeOH (12.6 ml) was added a 5 M aqueous solution of NaOH (2.5 ml, 12.6 mmol). The resulting mixture was heated to 80 °C for 2 h and cooled to rt. To the mixture was added a 5 M aqueous solution of HCl (3.8 ml, 18.9 mmol). The resulting mixture was stirred for 15 min, diluted with H_2O (10 ml) and extracted with Et_2O (3 x 20 ml). The combined extracts were dried, filtered and concentrated. The crude material was purified by flash

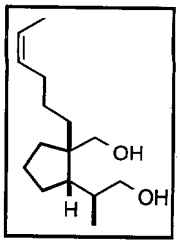
chromatography on silica gel eluting with EtOAc/hexanes (1:5) to provide 255 mg (86%) of the desired lactone **40** as a clear colorless oil. IR: 2933, 2861, 1753 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.23-1.29 (m, 4), 1.35-1.41 (m, 1), 1.46-1.62 (m, 4), 1.56 (s, 3), 1.64 (s, 3), 1.87-1.93 (m, 3), 2.01 (ddd, 1, *J*=6.7, 6.7, 6.7), 2.26 (dd, 1, *J*=6.8, 15.1), 2.49 (dd, 1, *J*=6.6, 15.1), 3.88 (d, 1, *J*=11.4), 3.99 (d, 1, *J*=11.5), 5.02-5.05 (m, 1). ^{13}C NMR (100 MHz): δ 17.6, 24.6, 24.7, 25.6, 28.4, 34.3, 34.5, 35.2, 38.4, 41.3, 44.5, 73.5, 123.9, 131.9, 173.7. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.57; H, 10.36.



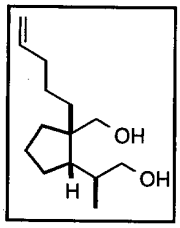
1-Hydroxymethyl-1-(5-methyl-4-hexenyl)-2-(1-methyl-2-hydroxy-ethyl)-cyclopentane (9). To a solution of the lactone **36** (65.1 mg, 0.26 mmol) in 2.6 mL ether at 0 °C was slowly added $LiAlH_4$ (10 mg, 0.26 mmol). The flask was flushed with N_2 and stirred at 0 °C for 10 min, then allowed to warm to rt and stirred for another 12 h. The reaction mixture was cooled to 0 °C and 10 μL of water, 10 μL of a 15 % aqueous solution of NaOH and 30 μL of water were added sequentially. After 5 min. a scupula of $MgSO_4$ and a scupula of celite was added to the fine white suspension and the mixture was filtered through a fine glass frit and concentrated to provide 63 mg of a clear oil. Silica gel chromatography, eluting with EtOAc/hexanes (1:1) provided 59 mg (89 %) of the desired diol **9** as a colorless oil. IR: 3355, 2930, 2873, 1450, 1375, 1036 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.87 (d, 3, *J*=6.8 Hz), 1.15-1.48 (m, 8), 1.51-1.73 (m, 3), 1.56 (s, 3), 1.61 (s, 3), 1.78-1.82 (m, 1), 1.90-1.92 (m, 2), 2.56 (bs, 2), 3.34 (dd, 1, *J*=6.3, 10.4), 3.41 (d, 1, *J*=11.0), 3.51 (d, 1, *J*=11.0), 3.54 (dd, 1, *J*=4.5, 10.4), 5.07-5.10 (m, 1). ^{13}C NMR (100 MHz): δ 16.1, 17.7, 22.2, 24.9, 25. 6, 28.6, 28.9, 34.8, 35.6, 36.7, 48.4, 48.6, 65.9, 68.4, 124.7, 131.4. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.40; H, 12.10.



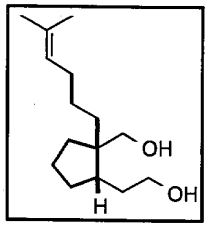
E-1-(4-Hexenyl)-1-hydroxymethyl- 2-(1-methyl-2-hydroxy-ethyl)-cyclopentane (10). The foregoing procedure was followed with 284 mg (1.20 mmol) of lactone **37** and 67 mg (1.77 mmol) of $LiAlH_4$. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/hexanes (2:5) to provide 282 mg (98%) of the pure diol **10** as a colorless oil. IR: 3351, 2934, 2873, 1452 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.85 (d, 3, *J*=6.8), 1.20 (ddd, 1, *J*=4.8, 12.0, 12.0), 1.28-1.42 (m, 6), 1.50-1.61 (m, 3), 1.60 (d, 3, *J*=6.5), 1.69-1.72 (m, 1), 1.78-1.82 (m, 1), 1.90-1.92 (m, 2), 2.93 (bs, 2), 3.30 (dd, 1, *J*=6.4, 10.5), 3.39 (d, 1, *J*=11.0), 3.49 (d, 1, *J*=11.0), 3.53 (dd, 1, *J*=6.0, 10.5), 5.34-5.42 (m, 2). ^{13}C NMR (100 MHz): δ 16.1, 17.8, 22.2, 24.7, 28.5, 33.4, 34.8, 35.6, 36.6, 48.4, 48.6, 65.8, 68.3, 124.7, 131.4. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.84; H, 12.07.



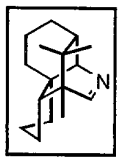
Z-1-(4-Hexenyl)-1-hydroxymethyl-2-(1-methyl-2-hydroxyethyl)-cyclopentane (11). The foregoing procedure was followed with 345 mg (1.46 mmol) of lactone **38** and 82 mg (2.92 mmol) of $LiAlH_4$. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/hexanes (2:5) to provide 311 mg (89%) of the pure diol **11** as a colorless oil. IR: 3359, 2937, 2872, 1454 cm^{-1}. ^1H NMR (500 MHz): δ 0.89 (d, 3, *J*=6.8), 1.23-1.28 (m, 2), 1.31-1.48 (m, 7), 1.58 (d, 3, *J*=6.1), 1.54-1.66 (m, 2), 1.68-1.75 (m, 1), 1.85 (dq, 1, *J*=6.6, 6.6), 1.94 (bs, 2), 2.01 (ddd, 1, *J*=7.2, 7.2, 7.2), 3.39 (dd, 1, *J*=6.3, 10.4), 3.44 (d, 1, *J*=11.0), 3.54 (d, 1, *J*=11.0), 3.57 (dd, 1, *J*=5.9, 10.4), 5.34-5.46 (m, 2). ^{13}C NMR (100 MHz): δ 12.7, 16.1, 22.2, 24.5, 27.6, 28.5, 34.7, 35.7, 36.6, 48.3, 48.6, 65.6, 68.2, 123.7, 130.6. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.14; H, 11.58.



1-(4-Pentenyl)-1-hydroxymethyl-2-(1-methyl-2-hydroxyethyl)-cyclopentane (12). The foregoing procedure was followed with 700 mg (3.15 mmol) of lactone **39** and 219 mg (5.77 mmol) of $LiAlH_4$. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/hexanes (1:1) to provide 635 mg (89%) of the pure diol **12** as a colorless oil. IR: 3348, 2941, 1640, 1458 cm^{-1}. ^1H NMR (400 MHz): δ 0.87 (d, 3, *J*=6.8), 1.20-1.28 (m, 1), 1.34-1.72 (m, 10), 1.84 (dddd, 1, *J*=6.4, 6.4, 12.9, 12.9), 1.99-2.04 (m, 2), 2.57 (bs, 2), 3.36 (dd, 1, *J*=6.3, 10.5), 3.42 (d, 1, *J*=11.0), 3.53 (d, 1, *J*=10.9), 3.55 (dd, 1, *J*=6.0, 10.5), 4.90-4.93 (m, 1), 4.95-5.00 (m, 1), 5.78 (dddd, 1, *J*=6.7, 6.7, 10.2, 17.0). ^{13}C NMR (100 MHz): δ 16.04, 22.25, 24.02, 28.47, 34.60, 34.78, 35.56, 36.51, 48.34, 48.61, 65.97, 68.46, 114.40, 138.99. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.16; H, 11.69.

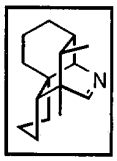


1-Hydroxymethyl-1-(5-methyl-4-hexenyl)-2-(2-hydroxyethyl)-cyclopentane (13). The foregoing procedure was followed with 153.5 mg (0.64 mmol) of lactone **40** and 54 mg (1.42 mmol) of $LiAlH_4$. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/Hex (1:1) to provide 147.8 mg (96%) of the pure diol **13** as a colorless oil. IR: 3349, 2932, 2869, 1451 cm^{-1}. ^1H NMR (500 MHz): δ 1.15-1.36 (m, 4), 1.36-1.59 (m, 7), 1.55 (s, 3), 1.64 (s, 3), 1.74-1.84 (m, 2), 1.91 (q, 2, *J*= 7.2), 2.29 (bs, 1), 2.50 (bs, 1), 3.37 (d, 1, *J*=11.0), 3.43 (d, 1, *J*=11.0), 3.48-3.53 (m, 1), 3.62-3.67 (m, 1), 5.06-5.09 (m, 1). ^{13}C NMR (100 MHz): δ 17.7, 22.4, 24.9, 25.6, 28.9, 31.6, 33.1, 33.8, 36.3, 44.1, 47.8, 62.7, 65.8, 124.7, 131.4. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.02; H, 11.99.

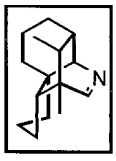


1,14,14-Trimethyl-12-azatricyclo[8.3.1.$0^{2,6}$.$0^{6,11}$]tetradec-12-ene (60). A stirring solution of oxalyl chloride (94 μL, 1.05 mmol) in 2.1 mL CH_2Cl_2 was cooled to -78°C. To this solution was added a solution of dimethyl sulfoxide (DMSO) (149 μL, 2.10 mmol) in 1.3 mL CH_2Cl_2 via teflon cannula. After 5 min a solution of the diol **9** (88.7 mg, 0.35 mmol) in 0.7 mL CH_2Cl_2 was added via teflon cannula. The flask containing the diol and the telfon cannula were rinsed through with 0.5 mL CH_2Cl_2. After 15 min a solution of diisopropylethylamine (Hünig's base) (304 μL, 1.75 mmol) in 1.1 mL of CH_2Cl_2 was added via teflon cannula.

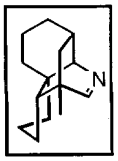
After 10 min the clear solution was warmed to 0 °C and stirring continued for 1 h. The N_2 atmosphere was replaced with NH_3 for five min. The solution turned cloudy as a white precipitate formed during the first min. The NH_3 atmosphere was replaced by N_2 and the reaction mixture was warmed to 25 °C, allowing the excess ammonia to escape. After 0.5 h the stirring bar was removed rinsing it with several mL of benzene and the solvent was removed with a rotary evaporator under aspirator pressure (0.5 h) and high vacuum (10 min). The white solid / oil was placed under a N_2 atmosphere and to it was added a magnetic stirring bar, NH_4OAc (269 mg, 3.49 mmol) and 3.5 mL of HOAc. The white precipitate was dissolved by swirling the solution around the sides of the flask. After 15 h the reaction mixture was diluted with CH_2Cl_2 (20 mL) and poured onto water (20 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2 x 20 mL). The combined organic layers were washed with 2 N NaOH (20 mL), dried with K_2CO_3 and concentrated to provide 65 mg of a colorless oil. Flash chromatography on silica gel (which was rinsed with 200 mL of a 5% solution of triethylamine in EtOAc) eluting with EtOAc/hexanes/triethylamine (50:49:1) provided 61 mg (75%) of the desired imine **60** as a colorless solid, mp 43.5-48 °C. IR: 2950, 1623, 1463, 1448 cm^{-1}. ^1H NMR (500 MHz): δ 0.76 (s, 3), 0.97 (s, 3), 1.04-1.08 (m, 2), 1.08 (s, 3), 1.13-1.16 (m, 1), 1.19-1.28 (m, 8), 1.73 (m, 3), 3.78 (d, 1, *J*=3.7), 8.01 (s, 1). ^{13}C NMR (100 MHz): δ 14.0 (CH_3), 18.0 (CH_3), 19.4 (CH_2), 24.3 (CH_2), 25.6 (CH_2), 31.4 (CH_3), 33.1 (CH_2), 36.9 (CH_2), 37.7 (CH_2), 38.7 (C), 40.4 (CH), 45.6 (CH), 45.7 (C), 47.7 (C), 66.2 (CH), 179.5 (CH). Anal. Calcd for $C_{16}H_{25}N$: C, 83.06; H, 10.89; N, 6.05. Found: C, 83.11; H, 11.20; N, 6.01.



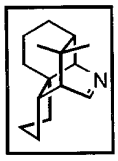
(1*S*,14*S*)-1,14-Dimethyl-12-azatricyclo[8.3.1.0^{2,6}.0^{6,11}]tetradec-12-ene (61). The foregoing procedure was followed with 103 mg (0.43 mmol) of diol **10**, 117 µL (1.31 mmol) of oxalyl chloride, 187 µL (2.63 mmol) of DMSO, 382 µL (2.19 mmol) of Hünig's base and 338 mg (4.38 mmol) of NH_4OAc. After addition of HOAc the reaction mixture was stirred at rt for 15 hrs. The crude product was purified by flash chromatography on silica gel (47:48:5 EtOAc/Hex/Et_3N) to provide 70.0 mg (75%) of the desired imine **61** as a yellow oil. IR: 2927, 1618, 1453 cm^{-1}. ^1H NMR (500 MHz): δ 0.71 (d, 3, *J*=7.0), 0.93-1.02 (m, 1), 1.10-1.29 (m, 5), 1.14 (s, 3), 1.32-1.45 (m, 6), 1.53-1.56 (m, 2), 1.77-1.83 (m, 1), 3.70 (d, 1, *J*=3.2), 7.93 (s, 1). ^{13}C NMR (100 MHz): δ 17.4, 17.5, 19.3, 24.1, 27.1, 33.0, 36.4, 38.0, 40.2, 40.7, 43.4, 47.3, 52.2, 65.4, 177.2. Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.44. Found: C, 82.56; H, 10.57; N, 6.42.



(1*S*,14*R*)-1,14-Dimethyl-12-azatricyclo[8.3.1.0^{2,6}.0^{6,11}]tetradec-12-ene (62). The foregoing procedure was followed with 120 mg (0.50 mmol) of diol **11**, 135 µL (1.51 mmol) of oxalyl chloride, 214 µL (3.02 mmol) of DMSO, 438 µL (2.51 mmol) of Hünig's base and 388 mg (5.03 mmol) of NH_4OAc. After addition of HOAc the reaction mixture was stirred at rt for 100 h. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/hexanes/triethylamine (20:79.5:0.5) to provide 75.2 mg (69%) of the desired imine **62** as a slightly yellow solid, mp 44-49°C. IR: 2927, 1618, 1453 cm^{-1}. ^1H NMR (500 MHz): δ 0.95 (d, 3, *J*=7.5), 1.00-1.10 (m, 1), 1.07 (s, 3), 1.12-1.60 (m, 10), 1.68-1.83 (m, 4), 3.77 (d, 1, *J*=3.7), 8.04 (s, 1). ^{13}C NMR (100 MHz): δ 8.29, 17.8, 20.3, 23.7, 25.4, 31.6, 32.6, 35.8, 36.8, 37.7, 41.8, 43.3, 47.3, 65.3, 179.4. Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.44. Found: C, 82.72; H, 10.97; N, 6.31.

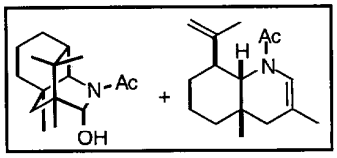


1-Methyl-12-azatricyclo[8.3.1.0^{2,6}.0^{6,11}]tetradec-12-ene (63). The foregoing procedure was followed with 120 mg (0.53 mmol) of diol **12**, 142 µL (1.59 mmol) of oxalyl chloride, 226 µL (3.18 mmol) of DMSO, 462 µL (2.65 mmol) of Hünig's base and 409 mg (5.31 mmol) of NH_4OAc. After addition of HOAc the reaction mixture was heated to 80°C for 50h. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/hexanes/triethylamine (20:79.5:0.5) to provide 86.6 mg (80.4%) of the desired imine **63** as a yellow oil. IR: 2925, 1618, 1449 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.89-0.98 (m, 2), 1.08-1.25 (m, 4), 1.11 (s, 3), 1.31-1.52 (m, 8), 1.72-1.79 (m, 2), 3.69 (d, 1, *J*=3.3), 7.97 (s, 1). ^{13}C NMR (100 MHz): δ 16.5, 20.3, 23.4, 28.2, 30.9, 32.7, 35.2, 36.2, 37.9, 39.2, 47.2, 51.5, 65.1, 177.5. HRMS calc for $C_{14}H_{21}N$: 203.167400. Found: 203.166969.



14,14-Trimethyl-12-azatricyclo[8.3.1.0^{2,6}.0^{6,11}]tetradec-12-ene (67). The foregoing procedure was followed with 91 mg (0.379 mmol) of diol **13**, 101 µL (1.13 mmol) of oxalyl chloride, 161 µL (2.27 mmol) of DMSO, 330 µL (1.89 mmol) of Hünig's base and 292 mg (3.79 mmol) of NH_4OAc. After addition of HOAc the reaction mixture was heated to 80°C for 15h. The crude product was purified by flash chromatography on silica gel, eluting with a gradient of EtOAc/hexanes/triethylamine (from 9:90:1 to 49:50:1) to provide 19.3 mg (23%) of the desired imine **67** as a yellow oil. IR: 2967, 1622, 1461 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.81 (s, 3), 1.08 (s, 3), 1.09-1.17 (m, 2), 1.23-1.52 (m, 8), 1.65-1.74 (m, 2), 1.85-1.89 (m, 1), 1.99 (dd, 1, *J*=7.3, 7.3), 2.10 (dd, 1, *J*=2.2, 4.3), 3.81 (d, 1, *J*=3.7), 8.39 (d, 1, *J*=4.0). ^{13}C NMR (100 MHz): δ 19.9, 21.8, 24.7, 25.1, 34.1, 34.3, 36.4, 36.9, 37.9, 39.1, 40.6, 46.5, 51.4, 67.3, 175.9.

1,3,11,11-Tetramethyl-9-azatricyclo[5.3.1.0^{3,8}]undec-9-ene (69). The foregoing procedure was followed with 102 mg (0.45 mmol) of diol **14**, 120 µL (1.34 mmol) of oxalyl chloride, 190 µL (2.68 mmol) of DMSO, 389 µL (2.24 mmol) of Hünig's base and 345 mg (4.47 mmol) of NH_4OAc. After addition of HOAc the reaction mixture was stirred for 15h at rt. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/hexanes/triethylamine (20:79:1) to provide 47.1 mg (51%) of the desired imine **69** as a yellow oil. IR: 2924, 1622, 1453 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.60 (d, 1, *J*=13.6), 0.76 (s, 3), 0.79 (s, 3), 0.96 (s, 3), 1.05 (s, 3), 1.17-1.51 (m, 6), 1.53 (d, 1, *J*=14.1), 1.73-1.78 (m, 1), 3.49 (d, 1, *J*=3.8), 8.00 (s, 1). ^{13}C NMR (100 MHz): δ 17.1, 17.5, 19.4, 25.5, 29.6, 31.1, 35.3, 37.6, 37.8, 37.9, 39.8, 42.1, 68.7, 177.7. Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.72; H, 11.36; N, 7.02.

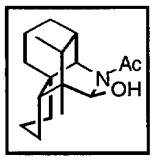


(1*S*,10*R*)-9-Acetyl-10-hydroxy-1,3,11,11-tetramethyl-9-azatricyclo[5.3.1.0^{3,8}]undecane (72) and (4a*S*,8*R*,8a*S*)-1-(8-Isopropenyl-3,4a-dimethyl-4a,5,6,7,8,8a-hexahydro-4*H*-quinolin-1-yl)-ethanone (73). The foregoing procedure was followed with 149 mg (0.65 mmol) of diol **14**, 175 µL (1.96 mmol) of oxalyl chloride, 279 µL (3.93 mmol) of DMSO, 570 µL (3.27 mmol) of Hünig's base and 504 mg (6.54 mmol) of NH_4OAc. After addition of HOAc the reaction mixture was stirred at rt for 3 hrs at which time acetic anhydride (3.1 ml, 32.7 mmol) was added.

The resulting mixture was stirred for an additional 15 hrs. The reaction mixture was cooled to 0 °C and H_2O (10 ml) was added slowly. After 0.5 h the mixture was extracted with $CHCl_3$ (3 x 20 ml). The combined organic layers were washed with 2 N NaOH (60 ml), Brine, dried (K_2CO_3), filtered and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with MeOH/CH_2Cl_2 (1:100) to provide 20.6 mg (13%) of the faster eluting enamide **73** as a yellow oil followed by 69.0 mg (40%) amide **72** as a colorless solid.

1-(8-Isopropenyl-3,4a-dimethyl-4a,5,6,7,8,8a-hexahydro-4*H*-quinolin-1-yl)-ethanone (73). IR: 2928, 1651, 1402 cm^{-1}. ^1H NMR (400 MHz): δ 0.85 (s, 3), 1.20-1.38 (m, 2), 1.43-1.64 (m, 5), 1.66 (s, 3), 1.69 (s, 3), 2.00-2.10 (m, 1), 2.05 (s, 3), 2.29 (d, 1, *J*=18.3), 4.17 (d, 1, *J*=11.3), 4.46 (d, 1, *J*=2.7), 4.57 (dd, 1, *J*=1.4, 2.7), 6.14 (s, 1). ^{13}C NMR (125 MHz): δ 18.8, 20.8, 21.3, 21.6, 28.2, 30.3, 32.8, 35.1, 37.8, 44.7, 57.0, 111.5, 116.0, 118.2, 147.4, 168.1. LRMS cald. for $C_{16}H_{25}NO$, 247. Found 247.

9-Acetyl-10-hydroxy-1,3,11,11-tetramethyl-9-azatricyclo[5.3.1.0^{3,8}]undecane (72). mp 97-100°C IR: 3414, 2962, 1634, 1436 cm^{-1}. ^1H NMR (500 MHz): δ 0.86 (s, 3), 0.87 (s, 3), 0.98 (s, 3), 1.07 (s, 3), 1.10-1.54 (m, 7), 1.65 (q, 1, *J*=4.1), 1.81-1.84 (m, 1), 2.05 (s, 3), 2.97 (d, 1, *J*=4.1), 4.05 (d, 1, *J*=3.0), 5.23 (d, 1, *J*=1.9). ^{13}C NMR (125 MHz): δ 16.5, 19.0, 19.3, 24.5, 26.9, 28.5, 29.2, 32.9, 33.6, 35.5, 39.0, 39.3, 43.9, 61.9, 79.1, 171.3. Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 82.25; H, 10.19; N, 5.47.



(1*S*,13*R*,14*R*)-1,14-Dimethyl-13-hydroxy-12-azatricyclo[8.3.1.0^{2,6}.0^{6,11}] tetradec-12-ene (64). Imine **62** (15.2 mg, 0.070 mmol) was treated with Ac_2O (1 ml) at rt for 15 h. The reaction mixture was poured onto Et_2O (20 ml) and H_2O (20 ml). The organic layer was separated, washed with 2N NaOH (20 ml), brine (20 ml), dried and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/hexanes (2:5) to provide 9.3 mg (48%) on the desired amide **64** as a colorless crystiline solid, mp 126-127°C (hexanes). IR: 3449, 2952, 1636 cm^{-1}. ^1H NMR (400 MHz): δ 0.87 (s, 3), 0.97 (d, 3, *J*=7.7), 1.21-1.23 (m, 2), 1.30-1.64 (m, 10), 1.81-1.87 (m, 2), 2.06 (s, 3), 2.33 (dddd, 1, *J*=3.7, 3.7, 3.7, 11.0), 2.51 (dq, 1, *J*=7.7, 11.1), 3.19 (d, 1, *J*=3.8), 5.13 (s, 1). ^{13}C NMR (125 MHz): δ 8.9, 17.8, 20.0, 21.8, 23.5, 26.8, 26.9, 29.0, 36.0, 37.0, 37.2, 38.5, 41.7, 45.3, 59.5, 79.2, 172.3. HRMS cald. for $C_{17}H_{27}NO_2$ (+ Li^+), 284.220184. found: 284.219670.

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9.Curran, D. P.; Yu, H.; Hongtao, L. *Tetrahedron* **1994**, *50*, 7343.

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EXHIBIT 20

2554 J. Org. Chem. 1992, 57, 2554-2566

Daphniphyllum Alkaloids. 12. A Proposed Biosynthesis of the Pentacyclic Skeleton. *proto*-Daphniphylline[1]

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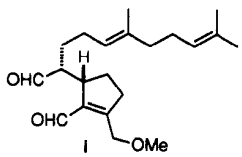
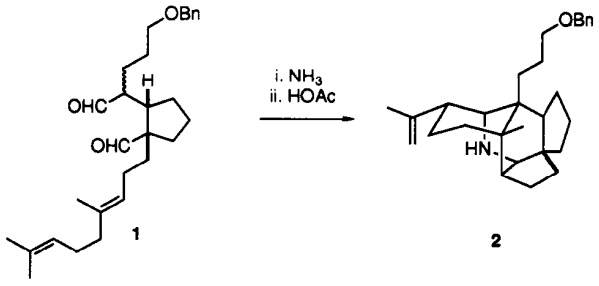
Received August 6, 1991

A biosynthetic proposal for the pentacyclic skeleton of the *Daphniphyllum* alkaloids is put forth (Scheme I) and various ramifications are examined experimentally. *proto*-Daphniphylline (**11**), the putative product of this hypothetical biogenesis, has been prepared by a convergent synthesis that starts with amide **14**, α,β-unsaturated ester **15**, and homogeranyl iodide (Scheme II) and employs a highly efficient tetracyclization process previously used for the synthesis of (±)-methyl homosecodaphniphyllate (**30**) (Scheme III). The structure of *proto*-daphniphylline was confirmed by converting it into **30**. The mechanism of the first stage of the tetracyclization process was investigated with the bis-homoneryl analogues **36**/**37**. Treatment of these aldehydes successively with ammonia and acetic acid provided tetracyclic imine **38**, suggesting that the cyclization reaction is a concerted Diels–Alder reaction rather than a stepwise process. Dialdehydes **27**/**28** were converted into 1,2-dihydro-*proto*-daphniphylline (**29**) by a version of the tetracyclization process wherein methylamine (or glycine) is substituted for ammonia. *proto*-Daphniphylline has also been prepared in a one-pot, two-stage process from the acyclic dialdehydes **51** and **55**. Several versions of this pentacyclization process have been worked out. In the simplest, **51** or **55** is treated successively with ammonia and hot acetic acid to afford **11** in 15 ± 2% yield. A slightly more elaborate protocol, a three-stage process that utilizes NaOH in benzene, ammonia in DMSO, and hot acetic acid, provided **11** in 49.4% overall yield. However, the most efficient pentacyclization process discovered employs successive reactions with methylamine (or glycine) and hot acetic acid. Under these conditions, 17,18-dihydro-*proto*-daphniphylline (**29**) is produced in 65% yield. The latter process is one of the most efficient reaction cascades ever discovered; it results in the formation of five rings, four carbon–carbon bonds, two carbon–nitrogen bonds, and concludes with the selective saturation of one of the three double bonds in *proto*-daphniphylline!

In the preceding paper in this series,[1] we described a simple protocol wherein the monocyclic dialdehyde **1** is converted into the pentacyclic unsaturated amine **2** by successive treatment with ammonia and acetic acid. Because of the exceptional ease with which the "tetracyclization reaction" occurs, it was speculated that the process may actually be biomimetic.[3] A possible biosynthesis is put forth in Scheme I. The rough outlines of this proposal are as follows: Step 1 is an oxidative transformation of squalene into a dialdehyde, **4**.[4] In step 2 it is proposed that some primary amine, perhaps pyridoxamine[5] or an amino acid, condenses with one of the carbonyl groups of **4**, giving imine **5**. Step 3 is the prototopic rearrangement of a 1-aza diene to a 2-aza diene, a process that is well-precedented for the imines formed from α,β-unsaturated carbonyl compounds and benzylamine.[6] Although potassium *tert*-butoxide was used for the prototopic rearrangement of benzylimines, one can imagine that an imine derived from pyridoxamine or an amino acid would rearrange under much milder conditions. Because the 2-aza diene that would result from the foregoing prototopic rearrangement is an enimine, its double bond is not especially nucleophilic. However, if some nucleophilic species adds to the imine double bond, as in step 4, the product **7** is a nucleophilic enamine. The subsequent cyclization to give **8** has an exact in vitro precedent in the work of Schreiber, Meyers, and Wiberg.[7] In steps 6–9 the resulting bicyclic dihydropyran derivative **8** is transformed into a dihydropyridine derivative (**9**) similar to the intermediate in the in vitro conversion of **1** into **2**. Other possible scenarios can be envisioned for the metamorphosis of **8** into **9**. According to our biosynthetic supposition, **9** would then be converted into **10** by a catalyzed Diels–Alder process and the final ring would result from an ene-like cyclization, giving **11**, the putative primordial *Daphniphyllum* alkaloid. Because of the likelihood that **11** is the first pentacyclic substance to occur in the biosynthesis of the *Daphniphyllum* alkaloids, we have named it *proto*-daphniphylline.[8,9]



I



(1) For part 11, see: (a) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.*, preceding paper in this issue.

(2) (a) Present address: Marion Merrel Dow Research Institute; 16, rue d Ankara; B.P. 447 R/9; 67009 Strasbourg, France. (b) Present address: Department of Chemistry, Yale University, New Haven, CT 06511.

(3) Ruggeri, R. B.; Heathcock, C. H. *Pure Appl. Chem.* **1989**, *61*, 289.

(4) Terpenoids have been described in which two methyl groups are in the aldehyde oxidation state. Petrodial (*i*) is one example. Isoe, S.; Ge, Y.; Yamamoto, K.; Katsumura, S. *Tetrahedron Lett.* **1988**, *29*, 4591.

(5) Pyridoxamine is a well-known nitrogen donor in alkaloid biosynthesis: (a) Dalton, D. R. *The Alkaloids, A Biogenetic Approach*; Marcel Dekker: New York, 1976. (b) Akhtar, M.; Emery, V. C.; Robinson, J. A. In *The Chemistry of Enzyme Action*; Page, M. I., Ed.; Elsevier: Amsterdam, 1984; p 303.

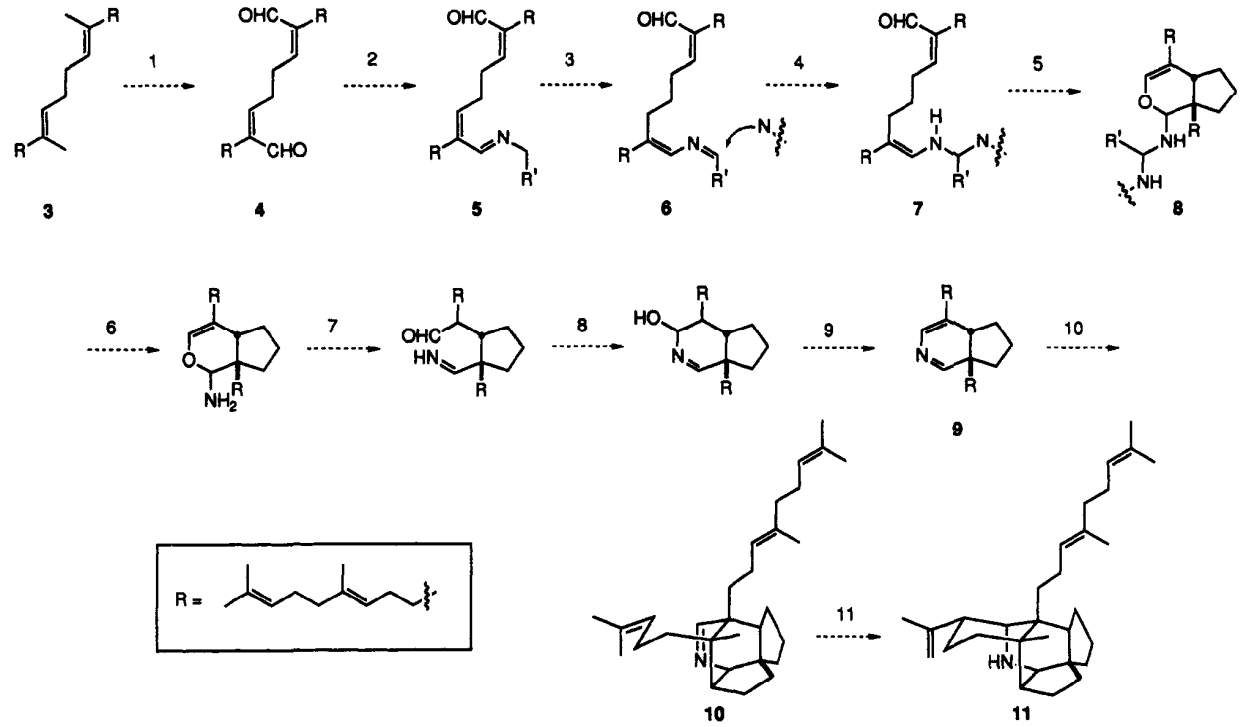
(6) Malhotra, S. K.; Moakley, D. F.; Johnson, F. *J. Am. Chem. Soc.* **1967**, *89*, 2794.

(7) Schreiber, S. L.; Meyers, H. V.; Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 8274.

(8) For a preliminary account of the synthesis of *proto*-daphniphylline, see: Piettre, S.; Heathcock, C. H. *Science (Washington D.C.)* **1990**, *248*, 1532.

0022-3263/92/1957-2554$03.00/0

Scheme I

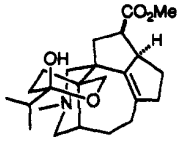


With regard to the proposed biosynthetic scheme, an interesting problem arises with regard to the final ene-type cyclization of **10** to **11**. In this step there are two nucleophilic sites that might interact with the immonium ion, leading to cations **12** or **13**. Closure model "a" gives a six-membered ring and leads to *proto*-daphniphylline. There are no known *Daphniphyllum* alkaloids with the skeleton that would result from the alternative closure mode "b", which would produce a five-membered ring. The selection of closure mode "a" over the alternative "b" might be due to an intrinsic chemical preference of the system, or it might reflect a conformational bias that is imposed by an enzyme. We thought it would be worthwhile to apply the tetracyclization process to an appropriate substrate containing two geranyl units to address this interesting question.

Our first synthesis of *proto*-daphniphylline began with the synthesis of amide **14** by alkylation of the lithium enolate of *N*-acetylpyrrolidine with homogeranyl iodide (**16**)[10] at −78 °C; compound **14** was obtained in 87% yield. Amide **14** was deprotonated with LDA and the resulting enolate treated successively with enoate **15** and halide **16** (Scheme II). There was obtained in a total yield of 94% a mixture of the four diastereomeric ester–amides **17**–**20** in an isomer ratio of 85:10:3:2. The major isomer **17** was isolated in 80% yield after chromatography on silica gel. The results of this convergent assembly of the entire *proto*-daphniphyline skeleton were quite analogous to those obtained in the previously reported synthesis of methyl homosecodaphniphyllate, except that the minor isomer corresponding to **20** was not observed in that reaction.[1]

As shown in Scheme III, amide–ester **17** was reduced with DIBAL in toluene at −78 °C to give hydroxy amide **21** in 86% yield, accompanied by 8% of amino alcohol **22**. The amide function was hydrolyzed with KOH in aqueous ethanol. Acidification of the alkaline hydrolysis mixture provided lactones **23** and **24** as a 1:1 mixture in a total isolated yield of 93%. The lactones were separately reduced to diols **25** and **26**, which were subjected to Swern oxidation conditions to obtain dialdehydes **27** and **28**. Because compounds **27** and **28** are quite fragile and decompose readily, they were always cyclized immediately after their preparation. The two dialdehydes were each subjected to the tetracyclization protocol[1] to obtain *proto*-daphniphylline in 78% yield. Careful examination of the reaction product revealed no trace of a product that would have resulted from closure mode "b".

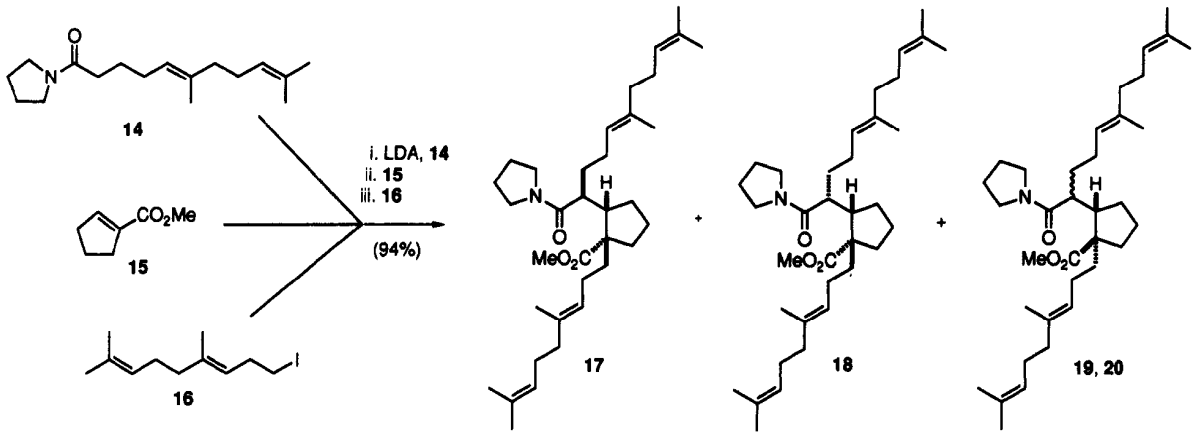
(9) There is a subset of *Daphniphyllum* alkaloids in which the final ene-like cyclization has not occurred. One example of this group is daphnigracine (**ii**): Yamamura, S.; Lamberton, J. A.; Irikawa, H.; Okumura, Y.; Hirata, Y. *Chem. Lett.* **1975**, 923. Yamamura, S.; Lamberton, J. A.; Irikawa, H.; Okumura, Y.; Toda, M.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1836. Thus, the proposed biosynthetic intermediate imine **10** is *proto*-daphnigracine.



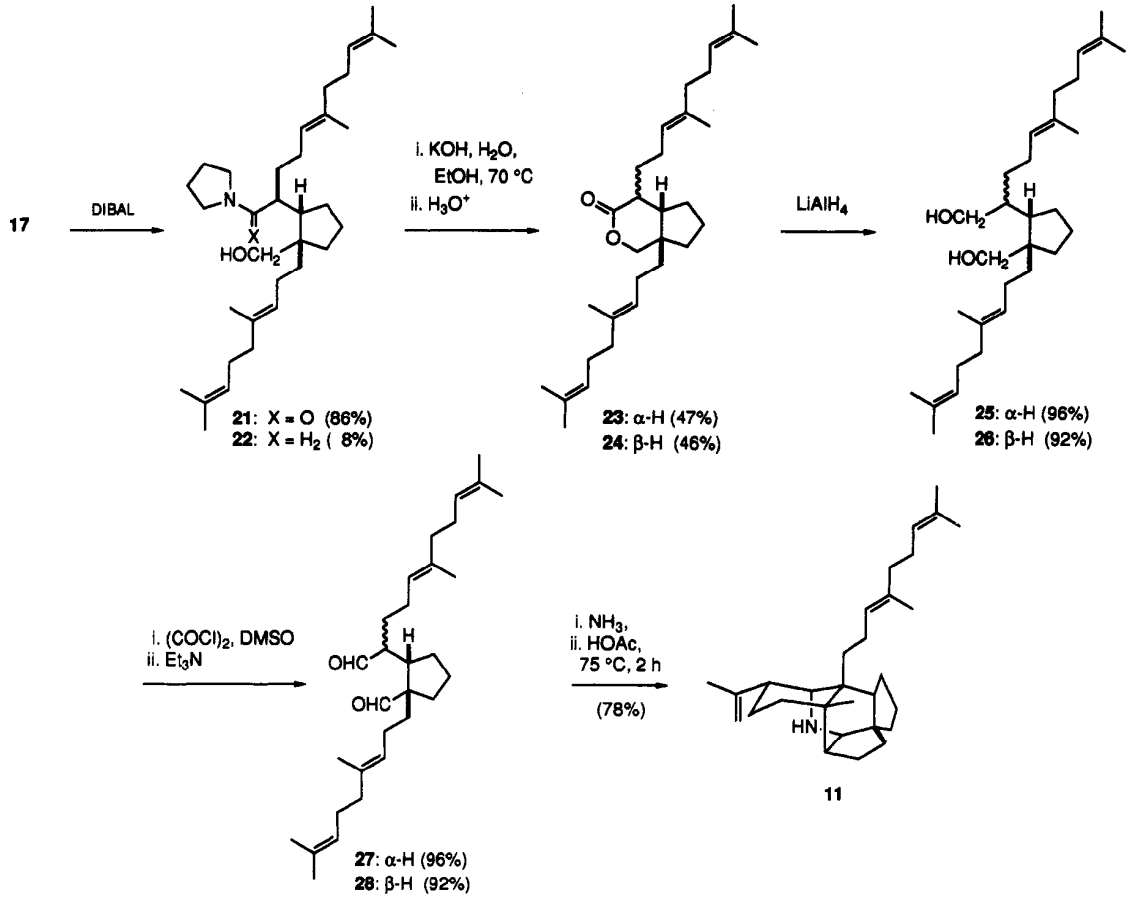
ii

(10) (a) Leopold, E. J. *Org. Synth.* **1985**, *64*, 164. (b) Kocienski, P.; Wadman, S. *J. Org. Chem.* **1989**, *54*, 1215.

Scheme II



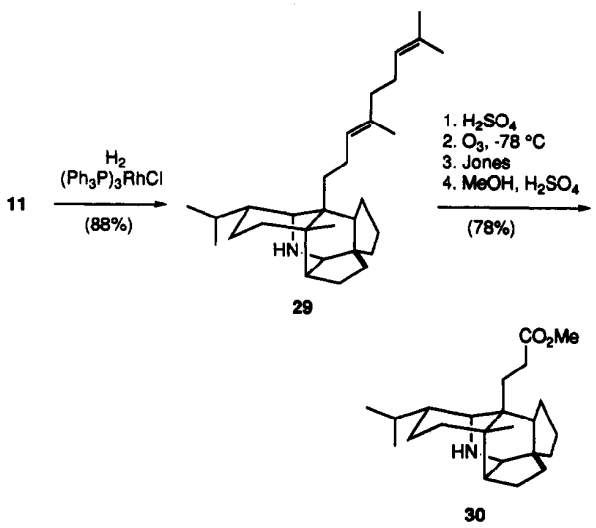
Scheme III



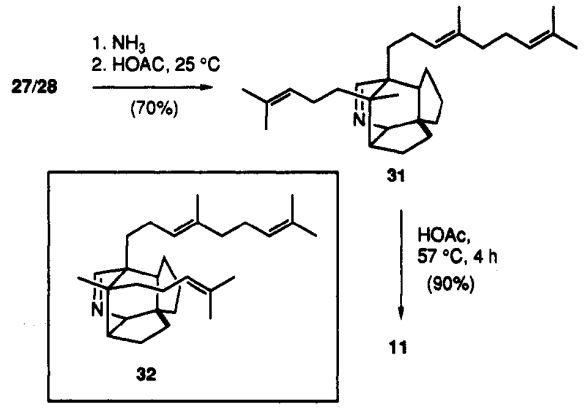
The structure of *proto*-daphniphylline was confirmed by converting it into (±)-methyl homosecodaphniphyllate (**30**). Careful hydrogenation of **11** with Wilkinson's catalyst[11] provided **29**. Ozonolysis of the sulfuric acid salt of this unsaturated amine, Jones oxidation of the resulting aldehyde,[12] and Fischer esterification gave **30** in 78% overall yield. Compound **30** was identified by comparison of its TLC mobility and NMR spectra with a sample prepared by the previously reported method.[1]

proto-Daphnigracine (**31**) was produced in 70% yield by passing gaseous ammonia through a CH_2Cl_2 solution of aldehydes **27** or **28**, removal of the solvent, and dissolution in acetic acid at room temperature. Treatment of **31** with acetic acid at 57 °C for 4 h gave *proto*-daphniphylline (**11**) in 90% yield. Careful examination of the crude product in the formation of **31** permitted the isolation of 4% of the isomeric tetracyclic imine **32**. The presence of this by-product was later traced to a small amount of contami-

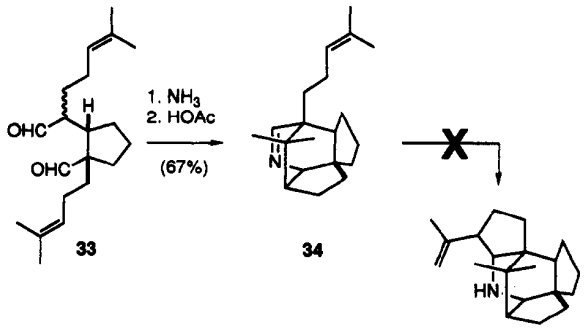
(11) Young, J. F.; Osborn, J. A.; Jardine, F. H.; Wilkinson, G. *J. Chem. Soc., Chem. Commun.* **1965**, 131.
(12) Bowden K.; Heibron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39. (b) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548.



nating nerol in the geraniol used for the preparation of iodide **16** (vide infra).

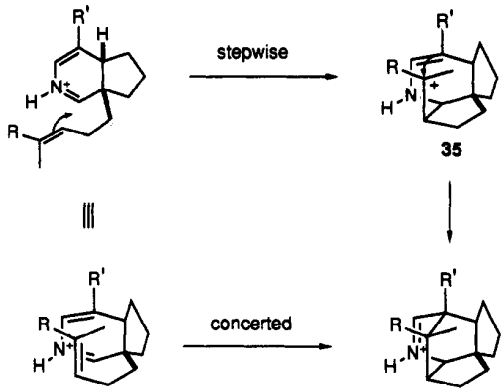


Our failure to observe any of the five-membered ring closure product in cyclization of immonium ion **10**-H^+ shows only that closure mode "a" has a lower activation energy than closure mode "b" by about 3.3 kcal/mol (assuming that we would have found as little as 3% of isomeric product). In order to examine the feasibility of five-membered ring closure more closely, we prepared dialdehyde **33** along the same lines as were used for the preparation of **27/28**.[13] Successive treatment of **33** with ammonia and acetic acid at room temperature gave tetracyclic imine **34**. However, under no conditions were we



(13) Details for this synthesis are given in the supplementary material.

Scheme IV

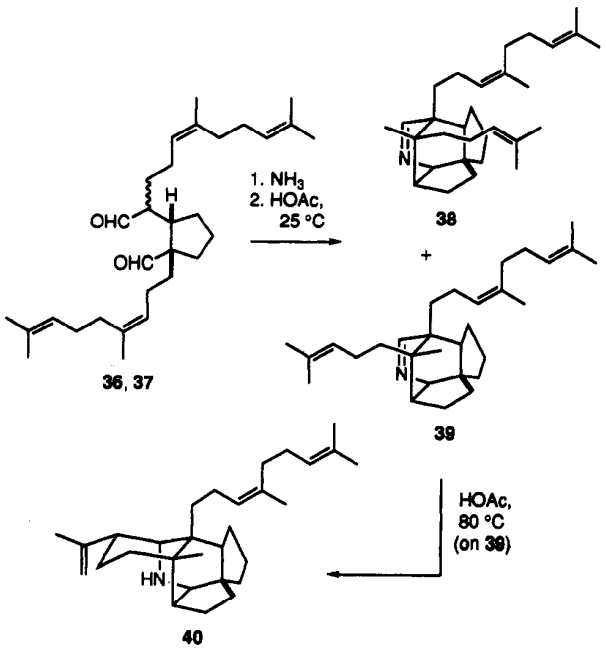


able to induce **34** to undergo a further cyclization. The material was recovered unchanged in 84% yield after being refluxed in acetic acid for 47 h.

The cyclizations of dialdehydes **1**, **27/28**, and **33** proceed through intermediate dihydropyridines.[1] As shown in Scheme IV, the initial cyclization might be two-step, passing through an intermediate tricyclic enamino cation **35**, or concerted. Information on this point can be gained by investigating the stereochemistry of the reaction. To this end, the bis-neryl analogues **36** and **37** were prepared by the same method as has been previously described, starting with nerol instead of geraniol.[13] Because the nerol used was only 97% *Z*, the dialdehydes should be 94% *Z,Z*, 3% *Z,E*, and 3% *E,Z*. Treatment of **36** or **37** successively with ammonia and acetic acid at room temperature gave tetracyclic imine **38** in 79% yield, accompanied by 3.5% of isomer **39**. Isomer **39** presumably results from cyclization of the *E,Z* contaminant. Imine **38** was unchanged after being heated with ammonium acetate in acetic acid at 80 °C for 15 h, but imine **39** was smoothly converted into the pentacyclic product **40** by this treatment.[14] Thus, the cyclization process appears to be concerted and may be viewed as an inverse-electron-demand Diels–Alder reaction of the trisubstituted double bond with the protonated 2-aza diene.

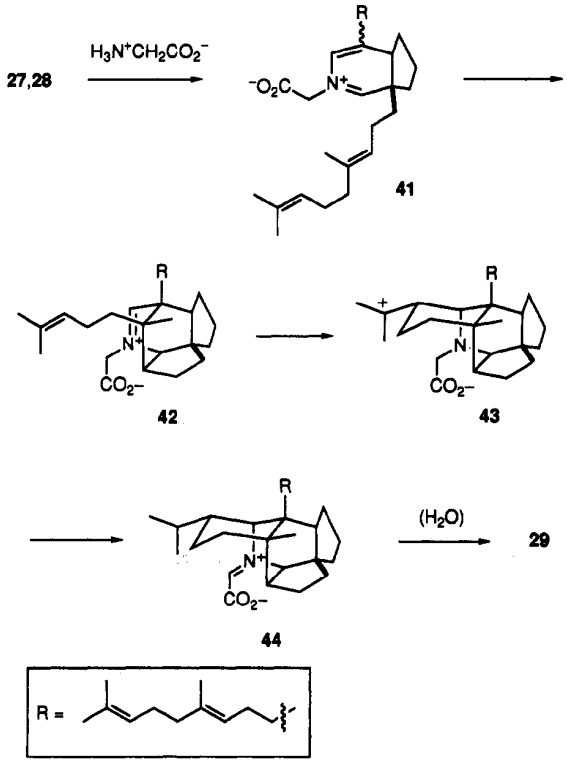
Tetracyclization of dialdehydes **27/28** was readily achieved by the methylamine cyclization previously reported in connection with the total synthesis of methyl homosecodaphniphyllate.[1] Thus, treatment of dialdehydes **27** and **28** successively with methylamine at room temperature and acetic acid at 80 °C for 11 h provided dihydro-*proto*-daphniphylline (**29**) in 66% yield. This remarkable reductive cyclization also occurred when glycine was substituted for methylamine as a nitrogen source, providing **29** in 53% yield. Because the reaction with glycine can proceed through intermediates having no net charge (Scheme V, compounds **41**, **42**, **43**, and **44**), we had anticipated that cyclization might occur under even milder conditions than with ammonia or methylamine. However, subjection of dialdehydes **27** and **28** to several sets of nonacidic conditions (10 equiv of glycine in $CHCl_3$, EtOH, or aqueous EtOH, as well as 0.67 N $H_2NCH_2CO_2Na$ in aqueous EtOH) led only to recovered starting material or decomposition.

(14) Capillary GLC analysis of our synthetic *proto*-daphniphylline (**11**) revealed the presence of 2% of a compound having the same retention time as **40**. Like imine **32**, this isomer probably derives from a small amount (2–4%) of nerol in our starting geraniol.

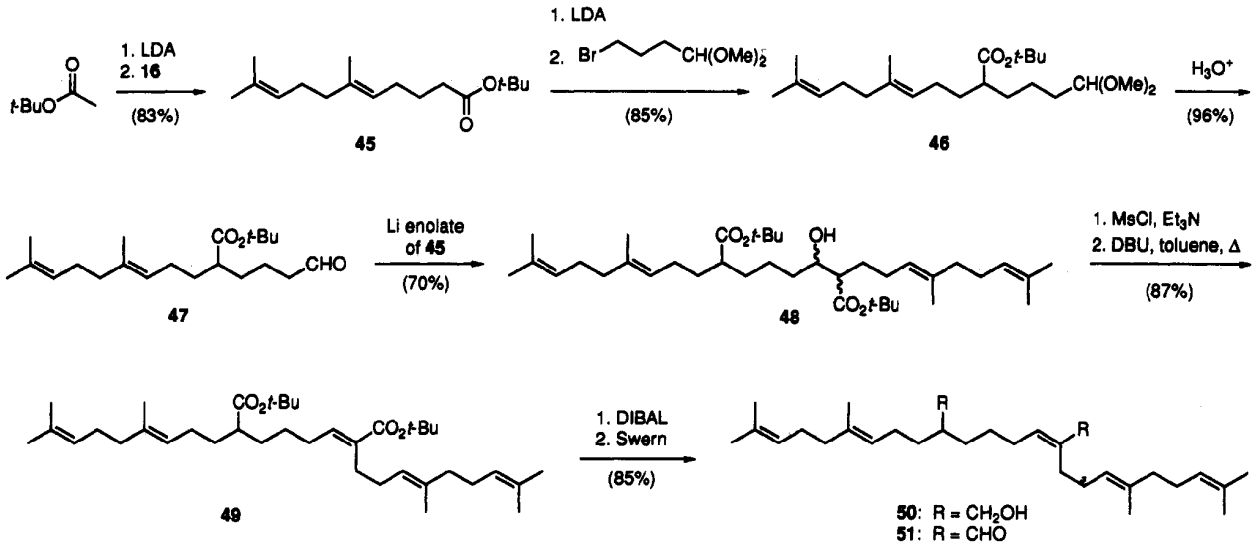


Because of the extraordinary efficiency of the tetracyclization process, we wondered if we could apply the procedure to an acyclic dialdehyde similar to **4** and thereby form all five of *proto*-daphniphylline's rings in one grand, biomimetic operation. To simplify the process somewhat,

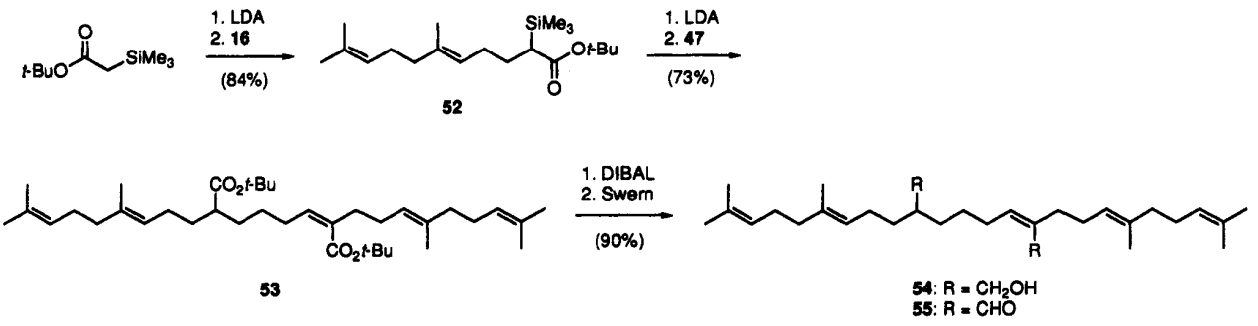
Scheme V

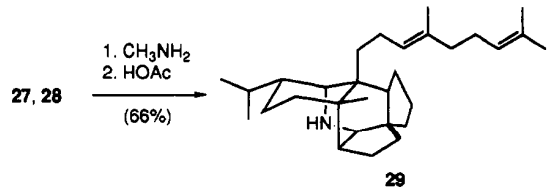


Scheme VI



Scheme VII





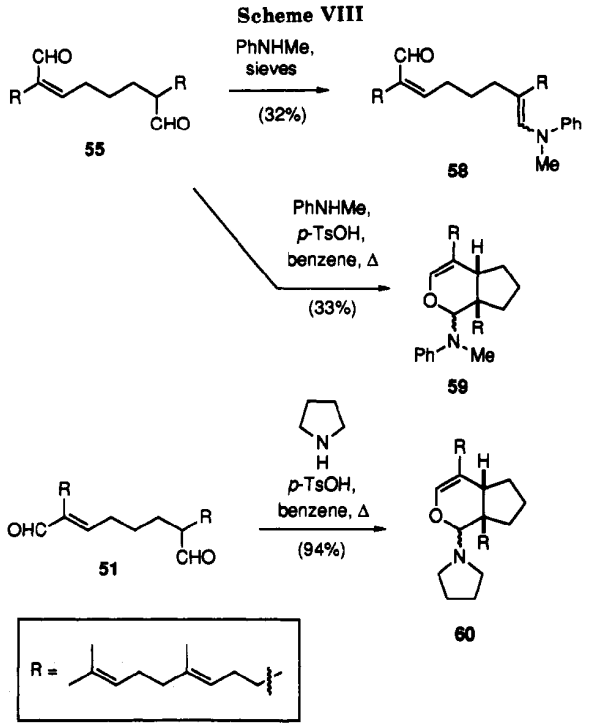
we decided to synthesize a dialdehyde in which one double bond has already been reduced. That is, we elected to intersect with the biosynthesis suggested in Scheme I at step 5. To this end, we prepared the *E* and *Z* isomers of 10,11-dihydrosqualene-27,28-dialdehyde (**51** and **55**) as shown in Schemes VI and VII. Alkylation of the lithium enolate of *tert*-butyl acetate with homogeranyl iodide (**16**) afforded ester **45**, which was alkylated with the dimethyl acetal of 4-bromobutanal[15] to obtain **46**. Hydrolysis of the acetal gave aldehyde **47**, which was condensed with the lithium enolate of **45** to obtain β-hydroxy esters **48** as a mixture of diastereomers. Elimination was accomplished by treatment of the methanesulfonate of **48** with DBU in toluene at 80 °C. Diester **49** was obtained in excellent yield, accompanied by approximately 10% of the *Z* isomer. After chromatographic separation of the stereoisomeric diesters, **49** was converted into the *E* dialdehyde **51** as shown in Scheme VI. To obtain the *Z* isomer in quantity, *tert*-butyl (trimethylsilyl)acetate was alkylated with iodide **16** to obtain the α-trimethylsilyl ester **52**. Treatment of the lithium enolate of **52** with aldehyde **47** afforded mainly the *Z* diester **53** (*Z*:*E* ratio = 7:3). The pure *Z* stereoisomer, obtained by silica gel chromatography of the mixture, was transformed into the *Z* dialdehyde **55** as shown in Scheme VII. Dialdehydes **51** and **55** are readily available by the routes shown; the overall yields are 35–45% from homogeranyl iodide. Both dialdehydes are somewhat labile and were partially destroyed by chromatography on silica gel. In addition, **55** is readily isomerized to **51**. Although we have carried out polycyclization experiments with both isomers, in most of our work we have used the *E* isomer **51**, which is more conveniently available in a pure form.

The pentacyclization process was first investigated using the conditions that had served for the tetracyclization of **27**/**28** to **11**. Thus, treatment of a CH_2Cl_2 solution of either **51** or **55** with ammonia and triethylamine hydrochloride at room temperature for 16 h resulted in disappearance in starting material, as shown by TLC. At this point the solvent was evaporated under vacuum and the resulting residue taken up in acetic acid and heated at 80 °C for 2 h. Workup gave *proto*-daphniphylline (**11**) in 15 ± 2% yield. A large amount of less polar material was also isolated in the chromatographic purification of **11**. This material was shown by NMR to be a complex mixture of compounds containing homogeranyl units; it is believed to consist of oligomers of the starting dialdehydes resulting from Michael or aldol reactions. Although the yield was low, this first pentacyclization was nevertheless very encouraging, as it represented the formation of six σ bonds and five rings in a single, simple process starting with acylic dialdehydes.

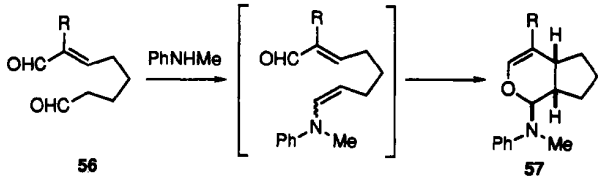
The difference in the yield of **11** obtained in the pentacyclization of **51**/**55** (15%) and the tetracyclization of **27**/**28** (78%) obviously reflects poor selectivity in formation of the first carbon–carbon bond. In an attempt to improve the yield of this part of the cyclization, we investigated various conditions that might accomplish the

(15) (a) Vedejs, E.; Arnost, M. J.; Hagen, J. P. *J. Org. Chem.* **1979**, *44*, 3234. (b) Petersen, J. S.; Tteberg-Kaulen, S.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 2948. (c) Kuehne, M. E.; Bohnert, J. C. *J. Org. Chem.* **1981**, *46*, 3443.

Scheme VIII



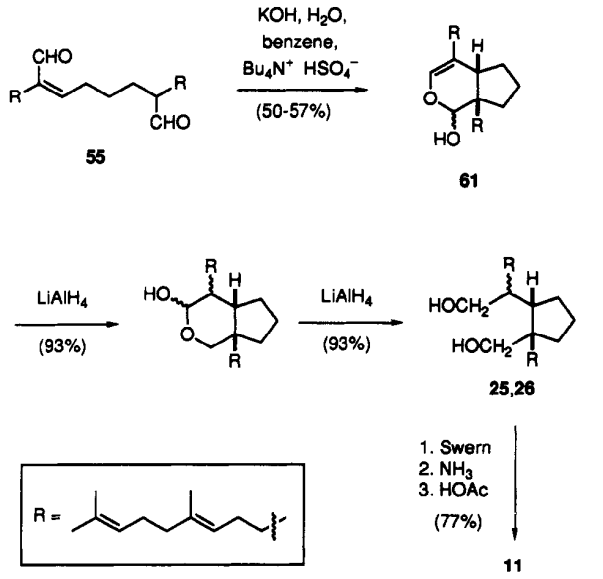
intramolecular Michael cyclization of **51**/**55**. Substituted oct-2-ene-1,8-dials are known to react with secondary amines to give enamines that undergo an overall [4 + 2] cycloaddition reaction to give aminodihydropyrans:[7]



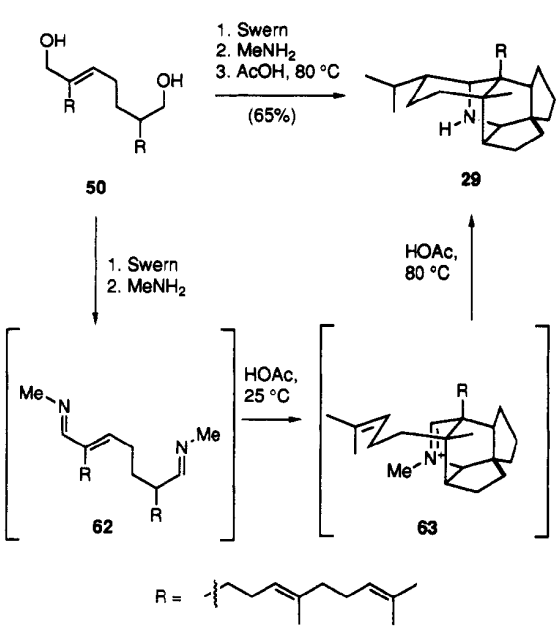
This precedent appears to offer an attractive way to form the first bond in the pentacyclization process, as dialdehyde **56** is but a simple analogue of **51** or **55**; upon treatment with ammonia, aminodihydropyran **59** might enter the pentacyclization manifold leading to **11**. To this end, we investigated the reactions of **51** and **55** with *N*-methylaniline and pyrrolidine. Under the conditions recommended by Schreiber and co-workers, aldehyde **55** was observed to isomerize to its *E* stereoisomer and enamines (*E*)- and (*Z*)-**58** were obtained in low yield (Scheme VIII). However, no aminodihydropyran was obtained. The fact that the enamine is formed but does not cyclize is presumably the result of steric hindrance; in our system the nucleophilic carbon of the enamine is fully substituted. More forcing conditions (*p*-toluenesulfonic acid, refluxing benzene, Dean–Stark trap) afforded aminodihydropyran **59** in an unoptimized yield of 33%. Treatment of dialdehyde **51** with pyrrolidine under similar conditions provided aminodihydropyran **60** in 94% yield. Both **59** and **60** were formed as an approximate 2:1 mixture at the anomeric center. Unfortunately, neither **59** nor **60** turned out to be a viable intermediate for the synthesis of *proto*-daphniphylline. Neither compound gave the tetracyclization reaction when treated successively with ammonia and acetic acid and neither could be hydrolyzed to dialdehydes **27**/**28**.[16]

(16) More details on the hydrolytic chemistry of these compounds are given in the supplementary material.

Scheme IX



Scheme X



While attempting to optimize the foregoing aminodihydropyran synthesis, one run in ether at room temperature unexpectedly gave a 2:1 mixture of hydroxydihydropyrans **61**. These compounds could be isolated by rapid chromatography on silica gel. Two-stage reduction with $LiAlH_4$ provided a mixture of diols **25** and **26**, identical with the compounds prepared from reduction of lactones **23** and **24**. The cis stereochemistry of the 6-5 ring fusion was confirmed by conversion of the diol mixture into *proto*-daphniphylline (Scheme IX). Optimization of this propitious discovery eventually led to a two-phase protocol wherein a benzene solution of the dialdehyde is stirred for 10 min at room temperature with 50% aqueous KOH in the presence of a catalytic amount of tetra-*n*-butylammonium bisulfate. Under these conditions, compounds **61** were obtained in 50–57% yield.

Treatment of a DMSO solution of **61** with NH_3 and NH_4OAc at 80 °C for 3 h and then with acetic acid at the same temperature for 3 h gave *proto*-daphniphylline in 86% yield. The three steps from **51** or **55** to *proto*-daphniphylline were most effectively carried out as a two-stage process, without purification of intermediates. Thus, the heterogeneous transformation to **61** was carried out as described in the previous paragraph. After removal of the benzene, a DMSO solution of the crude hydroxydihydropyrans was placed in a pressure bottle and saturated with ammonia. The solution was heated at 80 °C for 3 h. After brief cooling, acetic acid was added and the solution was heated at 80 °C for an additional 3 h. In this manner, *proto*-daphniphylline was obtained in 49.4% overall yield. The process can also be carried out in "one pot." Thus, a solution of **51** or **55** in DMSO was treated sequentially with (1) 1 molar equiv of powdered NaOH at 25 °C for 3.5 h, (2) saturated NH_3 at 80 °C for 3 h, and (3) acetic acid at 80 °C for 3 h; *proto*-daphniphylline was produced in 44% yield on a scale of 132 mg. It is important that the foregoing process be carried out under strictly anhydrous conditions, as the presence of water seems to have a distinctly adverse effect on yield. For example, use of 1 molar equiv of tetra-*n*-butylammonium hydroxide (10% w/w in water) for the first step gave **11** in only 17% yield, and powdered 85% KOH gave an overall yield of only 35%.

Based on the reductive cyclization of dialdehydes **27** and **28** to dihydro-*proto*-daphniphylline (**29**) with methylamine, we next investigated the pentacyclization of dialdehyde **51** with methylamine. Because the low yield in the pentacyclization of **51** and **55** with ammonia was presumably due to poor selectivity in the formation of the first carbon–carbon bond, we reasoned that the more nucleophilic *N*-methyl enamine derived from methylamine might improve upon the 15% yield observed with ammonia. Indeed, we were gratified to find that subjection of diol **50** to the sequence (i) Swern oxidation, (ii) treatment of the Swern reaction mixture with methylamine for 2–3 h, and (iii) concentration followed by treatment of the residue thus obtained with acetic acid at 80 °C for 11 h provided dihydro-*proto*-daphniphylline (**29**) in 65% yield. Since the tetracyclization of **27** and **28** with methylamine proceeds in essentially the same yield (66%), it would seem that cyclization to form the first five-membered ring is highly efficient in this case.

Although the reductive pentacyclization of **51** was generally performed as described above, an early experiment involved isolation of two of the intermediates (Scheme X). If the residue obtained following Swern oxidation and methylamine treatment was triturated with ether and filtered, concentration of the filtrate provided a clear, pale yellow oil, spectral analysis of which (IR, ^1H and ^{13}C NMR) showed it to be bis(*N*-methylimine) **62**. Treatment of this material with acetic acid at room temperature for 5 h followed by concentration from several portions of toluene provided an oily yellow solid, the ^1H NMR of which was consistent with the *N*-methylimmonium ion **63**, presumably as its acetate salt. Finally, treatment of this material with acetic acid at 80 °C provided dihydro-*proto*-daphniphylline (**29**).

As discussed earlier, we had hoped that amino acids would cause the reductive cyclization to occur under even milder conditions, as the cationic nitrogen would be balanced by a carboxylate anion within the same molecule, providing an overall neutral species (Scheme V). While we were unable to discover neutral or basic conditions which led to cyclization, we did find that glycine is a suitable nitrogen source under the same conditions used with methylamine (i.e. acetic acid, 80 °C). Thus, subjection of diol **50** to the sequence (i) Swern oxidation, (ii) concentration of the Swern reaction mixture, followed by treatment of the residue thus obtained with glycine (10

equivalents) in acetic acid at room temperature, and (iii) warming to 80 °C for 6–8 h provided dihydro-*proto*-daphniphylline (**29**) in 38% isolated yield. The lower yield relative to methylamine (65%) is presumably due to the more hindered nature of glycine, which probably renders several steps in the sequence less selective (especially the final intramolecular hydride transfer).

We also investigated several chiral amines to see what magnitude of asymmetric induction could be realized. Two α-amino acids were used in the sequence described above for glycine: (*S*)-(+)-alanine led to a 32% yield of dihydro-*proto*-daphniphylline (**29**) with only minimal optical activity (1–2% ee) and (*S*)-(+)-valine provided a 13% yield of **29** with moderate optical activity (20–25% ee). (*R*)-(+)-α-Phenylethylamine was also investigated, and although the corresponding bis-*N*-phenylethylimine was formed cleanly, treatment of this material with acetic acid at 80 °C led to no characterizable products. Apparently this amine is simply too sterically hindered to undergo the cyclization sequence.

Finally, an aspect of the temperature dependence of the reductive cyclization warrents mentioning. As described above (Scheme X), treatment of the bis(*N*-methylimine) with acetic acid at room temperature leads to the *N*-methylimmonium ion **63**; the subsequent ene reaction/hydride migration occurs upon heating to 80 °C. It was found that running the sequence in the fashion just described or subjecting the bis(*N*-methylimine) **62** *immediately* to 80 °C acetic acid had no measurable effect on the yield of dihydro-*proto*-daphniphylline (**29**) with methylamine. However, in the tetracyclization of aldehydes **27** and **28** with glycine, a significant temperature dependence was observed: direct treatment with 80 °C acetic acid gave **29** in 32% yield, whereas treatment with room temperature acetic acid for 6–8 h followed by heating to 80 °C for another 6–8 h gave **29** in 53% yield. This observation suggests that at least one of the intermediates derived from glycine is more prone to destructive side reactions in hot acetic acid than are the analogous intermediates derived from methylamine.

Experimental Section

General. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Benzene, diethyl ether, and THF were distilled from Na/benzophenone immediately prior to use. Triethylamine (Et_3N) was distilled from CaH_2 prior to use. Dimethyl sulfoxide (DMSO) and hexamethylphosphoric triamide (HMPA) were sequentially dried[17] and stored over 4-Å molecular sieves. All reactions involving oxygen- or moisture-sensitive compounds were performed under a dry N_2 atmosphere. THF/hexane solutions of lithium diisopropylamide (LDA) were prepared at 0 °C from diisopropylamine (1 mmol), THF (2 mL), and a 1.5 M solution of butyllithium in hexane (1 mmol, 0.667 mL). Unless indicated organic extracts were dried with $MgSO_4$. Unless otherwise stated all chromatography was carried out with E. Merck silica gel 60 (230–400 mesh ASTM) using a described procedure[18] and all products were isolated as colorless oils. Thin layer chromatography (TLC) was performed with Analtech silica gel (SiO_2) GF (250 μm) or Macherey-Nagel Plygram Al_2O_3 (200 μm) TLC plates. ^1H NMR and ^{13}C NMR spectra were measured using $CDCl_3$ as solvent. *J* values are in hertz. Infrared spectra were measured in CH_2Cl_2. All mass spectra (MS) were measured using the electron-impact method; data are reported as *m/z* (relative intensity).

1-[(5*E*)-6,10-Dimethyl-1-oxo-5,9-undecadienyl)pyrrolidine (14). *N*-Acetylpyrrolidine (113.5 mg, 1.0 mmol) was added dropwise to a solution of LDA (1 mmol) in THF (1.5 mL) at −78 °C and the mixture was stirred for 45 min. Homogeranyl iodide (278.3 mg, 1.0 mmol) in 0.5 mL of THF was added dropwise and stirring was continued for 3 h at −78 °C. The resulting mixture was warmed to room temperature, stirred for 12 h, and poured into brine (15 mL). Extraction with CH_2Cl_2, drying of the combined organic layers, and evaporation of the solvents gave a crude material that was chromatographed using a 7:3 mixture of hexanes–EtOAc as eluent to afford 231 mg (88%) of **14** as a colorless liquid, bp 135–140 °C (0.05 Torr). IR: 1645 cm^{-1}. ^1H NMR (400 MHz): δ 1.59 (s, 3), 1.60 (s, 3), 1.67 (s, 3), 1.67–2.07 (m, 12), 2.25 (t, 2, *J* = 7.8), 3.40 (t, 2, *J* = 6.8), 3.46 (t, 2, *J* = 6.9), 5.08 (br t, 1, *J* = 1.4), 5.09 (br t, 1, *J* = 1.4). ^{13}C NMR (125 MHz): δ 15.86, 17.51, 24.27, 24.83, 25.51, 25.98, 26.54, 27.34, 33.95, 36.56, 45.38, 46.41, 123.71, 124.15, 131.12, 135.60, 171.54. HMRS: calcd for $C_{17}H_{29}NO$ 263.2249, found 263.2254.

Tandem Michael Addition–Alkylation of Enoate 15. A solution of amide **14** (263.3 mg, 1.0 mmol) in 0.5 mL of THF was added dropwise to a stirring solution of LDA (1.0 mmol) at −78 °C. After 30 min a solution of ester **15** (126.15 mg, 1.0 mmol) in 1 mL of THF was added and stirring was continued for another 15 min. Homogeranyl iodide (278.3 mg, 1.0 mmol) in 1.0 mL of THF was then added slowly and the resulting mixture was stirred for 1 h at −78 °C, at 0 °C for 3 h, and at room temperature for 12 h. The solution was poured into water (15 mL), extracted with CH_2Cl_2 (3 × 10 mL), and dried. Evaporation of the solvents yielded the crude products as a yellowish oil. Chromatography and elution with a 4:1 mixture of hexane–EtOAc gave 14 mg (2.6%) of an isomer of **17** having a neryl group in place of one of the geranyl groups. IR: 1742, 1630 cm^{-1}. ^1H NMR (400 MHz): δ 1.2–2.26 (m, 27), 1.56 (s, 3), 1.60 (s, 6), 1.66 (s, 3), 1.68 (s, 6), 2.59–2.64 (m, 1), 3.36–3.74 (m, 4), 3.67 (s, 3), 5.03–5.08 (m, 4). ^{13}C NMR (125 MHz): δ 15.83, 17.59, 17.63, 21.58, 23.39, 24.32, 24.72, 25.46, 25.65, 25.68, 26.18, 26.51, 26.68, 27.80, 31.45, 31.95, 34.21, 38.00, 39.65, 42.97, 45.70, 46.26, 51.31, 52.08, 56.75, 124.11, 124.21, 124.30, 124.96, 131.26, 131.50, 135.06, 135.44, 173.94, 176.81. HRMS: calcd for $C_{35}H_{57}NO_3$ 539.4338, found 539.4356.

Further elution gave 432 mg (80%) of ester **17**. IR: 1744, 1629 cm^{-1}. ^1H NMR (400 MHz): δ 1.2–2.24 (m, 27), 1.55 (s, 3), 1.56 (s, 3), 1.59 (s, 6), 1.67 (s, 6), 2.61–2.66 (m, 1), 3.38–3.72 (m, 4), 3.67 (s, 3), 5.04–5.10 (m, 4). ^{13}C NMR (125 MHz): δ 15.78, 15.96, 17.58, 21.56, 24.28, 24.66, 25.59, 26.15, 26.60, 26.62, 27.72, 31.10, 34.17, 37.99, 39.60, 42.88, 45.66, 46.22, 51.25, 52.10, 56.65, 124.06, 124.10, 124.25, 131.17, 131.25, 135.00, 135.27, 173.95, 176.73. HRMS: calcd for $C_{35}H_{57}NO_3$ 539.4338, found 539.4329.

Finally there was isolated 75 mg (14%) of a 2:1 mixture of diastereomeric esters **19** and **20**. IR: 1740, 1632 cm^{-1}. ^1H NMR (400 MHz): δ (major isomer) 1.38–2.28 (m, 45), 2.45–2.55 (m, 1), 3.32–3.50 (m, 4), 3.65 (s, 3), 5.05–5.12 (m, 4); δ (minor isomer) 1.15–2.28 (m, 45), 2.58–2.64 (m, 1), 3.32–3.55 (m, 4), 3.65 (s, 3), 5.05–5.17 (m, 4). HRMS: calcd for $C_{35}H_{57}NO_3$ 539.4338, found 539.4343. Anal. Calcd for $C_{35}H_{57}NO_3$: C, 77.86; H, 10.64; N, 2.59. Found: C, 77.25; H, 10.55; N, 2.56.

DIBAL Reduction of Amide 17. Diisobutylaluminum hydride (DIBAL) (4.0 mmol, 2.67 mL of a 1.5 M solution in toluene) was added dropwise to a stirring solution of amides **17** (1 mmol) in toluene (2 mL) at −78 °C. Stirring was continued for 60 min and 2 M NaOH (7 mL) was then slowly added. The mixture was warmed to room temperature and poured into brine (25 mL). Extraction with CH_2Cl_2 (3 × 15 mL), drying of the extract, and evaporation of the solvents furnished the crude material, which was chromatographed. Elution with a 4:1 mixture of hexane–EtOAc gave 428 mg (86%) of hydroxy amide **21**. IR: 3619, 1639 cm^{-1}. ^1H NMR (400 MHz): δ 1.20–2.14 (m, 28), 1.56 (s, 3), 1.61 (s, 3), 1.60 (s, 6), 1.68 (s, 6), 2.63–2.69 (m, 1), 3.40–3.59 (m, 6), 5.06–5.14 (m, 4). ^{13}C NMR (125 MHz): δ 15.87, 15.94, 17.54, 21.51, 22.99, 24.16, 25.26, 25.56, 26.16, 26.56, 26.65, 29.14, 32.29, 36.37, 39.56, 39.62, 45.73, 46.58, 48.26, 48.90, 53.32, 65.83, 124.13, 124.17, 124.32, 125.08, 131.07, 131.19, 131.50, 135.29, 175.00. HRMS: calcd for $C_{34}H_{57}NO_2$ 511.4515, found 511.4517.

Further elution gave 40 mg (8%) of amino alcohol **22**, resulting from overreduction. IR 3400–2500 cm^{-1}. ^1H NMR (400 MHz): δ 1.17–2.19 (m, 30), 1.60 (s, 9), 1.62 (s, 3), 1.68 (s, 6), 2.38–2.44 (m, 2), 2.60–2.66 (m, 2), 2.82 (dd, 1, *J* = 6.9, 12.7), 3.29 (d, 1, *J* = 11.5), 3.65 (d, 1, *J* = 11.4), 5.07–5.11 (m, 3), 5.17 (t, 1, *J* = 6.8). ^{13}C NMR (125 MHz): δ 15.16, 15.77, 15.95, 17.56, 20.80, 23.08, 23.46, 23.87, 25.58, 26.62, 26.65, 30.75, 35.01, 37.57, 38.37, 38.73,

(17) Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 3966.
(18) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

39.60, 39.61, 49.28, 52.28, 53.77, 60.59, 64.61, 65.73, 124.20, 124.34, 124.41, 131.00, 131.15, 134.41, 134.95. Anal. Calcd for $C_{34}H_{59}NO$: C, 82.03; H, 11.95; N, 2.81. Found: C, 81.73; H, 11.97; N, 2.81.

Preparation of Lactones 23 and 24. A mixture of hydroxy amide **21** and 3.2 mL of 5 M KOH in 12 mL of ethanol was heated at 80 °C for 100 min. After cooling to 0 °C, CH_2Cl_2 (20 mL) was added followed by 2 M HCl until pH = 1. The mixture was stirred for 5 min at 25 °C, poured into brine (40 mL), and extracted with CH_2Cl_2 (3 × 20 mL). Drying of the organic extracts, evaporation of the solvents, and medium-pressure chromatography (MPLC) on silica gel using a 7:3 mixture of hexanes–EtOAc as eluent afforded 207 mg (47%) of lactone **23** and 203 mg (46%) of lactone **24**.

[4α,4aα(*E*),7aβ(*E*)]-(±)-4,7a-Bis(4,8-dimethyl-3,7-nonadienyl)hexahydrocyclopenta[*c*]pyran-3(1*H*)-one (23). IR: 1745 cm^{-1}. ^1H NMR (400 MHz): (400 MHz): δ 1.25–2.23 (m, 24), 1.59 (s, 6), 1.60 (s, 6), 1.68 (s, 6), 3.90 (d, 1, *J* = 11.4), 4.13 (d, 1, *J* = 11.4), 5.06–5.14 (m, 4). ^{13}C NMR (125 MHz): δ 15.87, 15.97, 17.55, 22.99, 25.25, 25.56, 25.88, 26.54, 26.65, 29.54, 33.82, 34.84, 38.48, 39.06, 39.59, 42.96, 45.77, 48.34, 71.04, 123.63, 124.14, 124.18, 124.48, 131.17, 135.27, 136.05, 175.10. Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.62; H, 10.82.

[4α,4aα(*E*),7aα(*E*)]-(±)-4,7a-Bis(4,8-dimethyl-3,7-nonadienyl)hexahydrocyclopenta[*c*]pyran-3(1*H*)-one (24). IR: 1744 cm^{-1}. ^1H NMR (400 MHz): δ 1.03–1.10 (m, 1), 1.33–1.44 (m, 4), 1.60–2.15 (m, 18), 1.60 (s, 9), 1.61 (s, 3), 1.68 (s, 6), 2.47–2.52 (m, 1), 3.97–4.03 (m, 2), 5.07–5.14 (m, 4). ^{13}C NMR (125 MHz): δ 15.84, 15.94, 17.51, 22.75, 24.17, 25.07, 25.53, 26.47, 26.57, 27.58, 30.58, 35.38, 38.89, 39.01, 39.48, 39.55, 40.93, 44.77, 45.69, 73.73, 123.34, 123.60, 124.08, 131.14, 131.20, 135.52, 135.96, 175.54. Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.72; H, 10.96.

Preparation of Diols 25 and 26. To a solution of 440.7 mg (1 mmol) of lactone **23** or **24** in 12 mL of ether was added 114 mg (3 mmol) of $LiAlH_4$. The solution was stirred for 3 h, cooled to 0 °C, and quenched by the dropwise addition of water (0.153 mL), 15% w/w aqueous NaOH (0.153 mL), and water (0.460 mL). The slurry was stirred at 0 °C for 30 min and $MgSO_4$ (1 g) was added. Filtration and evaporation of the solvent furnished the pure diol. The analytical sample was further purified by rapid chromatography and elution with CH_2Cl_2–EtOAc (95:5).

[1α(*S),1α(*E*),2α(*E*)]-β,2-Bis(4,8-dimethyl-3,7-nonadienyl)-2-(hydroxymethyl)cyclopentanemethanol (25)** (1,281 mg, 96%). IR: 3680–3080, 3625, 3050–2750 cm^{-1}. ^1H NMR (400 MHz): δ 1.16–1.23 (m, 1), 1.24–1.34 (m, 1), 1.44–1.79 (m, 10), 1.60 (s, 12), 1.68 (s, 6), 1.96–2.11 (m, 12), 3.49, 3.58 (d, 1 each, *J* = 11.0), 3.58 (dd, 1, *J* = 6.0, 10.7), 3.70 (dd, 1, *J* = 4.0, 10.7), 5.07–5.17 (m, 4). ^{13}C NMR (125 MHz): δ 15.88, 15.92, 17.56, 22.05, 23.24, 25.24, 25.57, 26.65, 28.65, 30.19, 35.16, 37.05, 39.63, 40.34, 48.13, 48.46, 65.37, 65.59, 124.26, 124.29, 124.46, 124.88, 131.14, 131.16, 134.70, 135.03. HRMS: calcd for $C_{30}H_{52}O_2$ 444.3967, found 444.3984.

[1α(*R),1α(*E*),2α(*E*)]-β,2-Bis(4,8-dimethyl-3,7-nonadienyl)-2-(hydroxymethyl)cyclopentanemethanol (26)** (1,227 mg, 92%). IR: 3700–3080, 3621, 3055–2785 cm^{-1}. ^1H NMR (400 MHz): δ 1.13–1.22 (m, 1), 1.30–1.38 (m, 1), 1.39–1.47 (m, 1), 1.48–1.76 (m, 10), 1.60 (s, 12), 1.68 (s, 6), 1.88–1.94 (m, 1), 1.97–2.10 (m, 12), 3.46, 3.58 (d, 1, *J* = 11.5), 3.59 (dd, 1, *J* = 4.6, 10.5), 3.70 (dd, 1, *J* = 7.0, 10.5), 5.07–5.16 (m, 4). ^{13}C NMR (125 MHz): δ 15.90, 16.00, 17.59, 22.08, 23.41, 25.61, 25.71, 26.66, 26.82, 34.18, 34.45, 37.36, 37.63, 39.66, 47.89, 51.00, 64.92, 65.75, 124.88, 124.32, 124.90, 131.18, 134.61, 135.11. HRMS: calcd for $C_{30}H_{52}O_2$ 444.3967, found 444.3961.

General Procedure for Swern Oxidation of Diols. A solution of 381 mg (3 mmol) of oxalyl chloride in 6 mL of dry CH_2Cl_2 was cooled to −78 °C and 469 mg (6 mmol) of DMSO in 2 mL of CH_2Cl_2 was added dropwise. After 5 min a solution of 444.7 mg (1 mmol) of the diol in 2 mL of CH_2Cl_2 was added over a 3-min period. After 15 min, 506 mg (5 mmol) of triethylamine in 3 mL of CH_2Cl_2 was added slowly and stirring continued at −78 °C for 10 min. The clear solution was warmed to 0 °C, stirred for 1 h, and poured into 30 mL of water. Rapid extraction with CH_2Cl_2 (3 × 15 mL), drying of the extract (K_2CO_3), and evaporation of the solvent gave the pure dialdehyde in yields varying from 95 to 99%.

[1α(*S),1α(*E*),2α(*E*)]-β,2-Bis(4,8-dimethyl-3,7-nonadienyl)-2-formylcyclopentaneacetaldehyde (27).** IR: 2725, 1725 cm^{-1}. ^1H NMR (400 MHz): δ 1.25–2.25 (m, 23), 1.56, 1.60, 1.68 (s, 6 each), 2.40–2.52 (m, 1), 5.01–5.10 (m, 4), 9.65 (d, 1), 9.65 (s, 1).

[1α(*R),1α(*E*),2α(*E*)]-β,2-Bis(4,8-dimethyl-3,7-nonadienyl)-2-formylcyclopentaneacetaldehyde (28).** IR: 2738, 1728 cm^{-1}. ^1H NMR (400 MHz): δ 1.40–2.12 (m, 23), 1.57, 1.58 (s, 3 each), 1.60, 1.68 (s, 6 each), 2.48–2.53 (m, 1), 5.05 (t, 1, *J* = 6.5), 5.06–5.10 (m, 3), 9.53 (d, 1, *J* = 3.5), 9.66 (s, 1). ^{13}C NMR (125 MHz): δ 16.01, 16.09, 17.66, 23.41, 23.95, 25.67, 25.71, 26.60, 29.44, 31.78, 36.57, 39.61, 39.64, 50.30, 51.36, 59.01, 122.76, 123.48, 124.16, 124.18, 131.42, 135.99, 136.65, 203.99, 205.68.

[2*E*,2(*E*),7(*E*)]-2,7-Bis(4,8-dimethyl-3,7-nonadienyl)-2-octenedial (51). IR: 2725, 1726, 1685, 1646 cm^{-1}. ^1H NMR (400 MHz): δ 1.48–1.76 (m, 6), 1.57 (s, 6), 1.58 (s, 6), 1.60 (s, 3), 1.68 (s, 3), 1.93–2.08 (m, 12), 2.24–2.39 (m, 5), 5.04–5.12 (m, 4), 5.41 (t, 1, *J* = 7.4), 9.37 (s, 1), 9.59 (d, 1, *J* = 2.7). ^{13}C NMR (125 MHz): δ 15.91, 15.97, 17.61, 24.17, 25.26, 25.62, 26.15, 26.50, 25.60, 25.86, 28.34, 39.60, 39.64, 51.16, 123.03, 123.18, 124.10, 124.18, 131.27, 131.34, 135.99, 136.40, 143.61, 154.01, 194.92, 204.56. Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.24; H, 11.27.

[2*Z*,2(*E*)]-,7(*E*)]-2,7-Bis(4,8-dimethyl-3,7-nonadienyl)-2-octenedial (55). IR: 2725, 1725, 1675 cm^{-1}. ^1H NMR (400 MHz): δ 1.43–1.75 (m, 6), 1.57 (s, 3), 1.58 (s, 3), 1.60 (s, 6), 1.68 (s, 6), 1.94–2.29 (m, 15), 2.55–2.61 (m, 2), 5.05–5.10 (m, 4), 6.41 (t, 1, *J* = 8.1), 9.58 (d, 1, *J* = 2.7), 10.10 (s, 1). ^{13}C NMR (125 MHz): δ 15.86, 15.92, 17.56, 24.12, 25.20, 25.58, 26.10, 26.45, 26.55, 26.81, 28.29, 28.87, 28.89, 39.55, 39.59, 51.09, 122.98, 123.13, 124.06, 124.14, 131.20, 131.27, 135.92, 136.33, 143.54, 154.00, 194.27, 204.51. Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.26; H, 10.68.

Tricyclization Process. Preparation of Imines 31 and 39. Ammonia gas was bubbled through a mixture of 220.4 mg (0.5 mmol) dialdehydes **27**/**28** or **36**/**37** and 137.5 mg (1 mmol) of triethylammonium hydrochloride in 12 mL of CH_2Cl_2 at 0 °C for 3 min. The mixture was allowed to warm to 25 °C and stirred for 1 h. The solvent was then evaporated and 77 mg (1 mmol) of NH_4OAc and 10 mL of acetic acid were added. The solution was stirred at 25 °C for 30 min, poured into 75 mL of water, and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with 50 mL of 2 M NaOH. After separation of the two layers, the basic aqueous phase was extracted with another 15 mL of CH_2Cl_2. The combined extracts were dried over K_2CO_3. Filtration, evaporation of the solvent, and chromatography using hexane–EtOAc (8:2) as eluent afforded the colorless, oily imine. Application of this procedure to dialdehydes **27**/**28** gave 148 mg (70%) of imine **31** and 9 mg (4%) of the isomeric imine **32**.

[3α,3aβ,6α(*E*),6aα,9a*R,10*S**]-(±)-2,3,3a,6,6a,7,8,9-Octahydro-10-methyl-10-(4-methyl-3-pentenyl)-6-(4,8-dimethyl-3,7-nonadienyl)-3,6-methano-1*H*-dicyclopenta[*b*,*c*]pyridine (31).** IR: 1625 cm^{-1}. ^1H NMR (400 MHz): δ 0.86 (s, 3), 1.56 (s, 3), 1.61 (s, 3), 1.63 (s, 3), 1.64 (s, 3), 1.69 (s, 3), 0.88–0.96 (m, 1), 1.04–1.18 (m, 1), 1.22–1.91 (m, 16), 1.98–2.03 (m, 2), 2.06–2.11 (m, 2), 2.17–2.26 (m, 2), 4.11 (d, 1, *J* = 4.6), 4.99 (t, 1, *J* = 7.0), 5.10, 5.15 (t, 1 each, *J* = 6.9), 8.10 (s, 1). ^{13}C NMR (125 MHz): δ 16.02, 16.87, 17.57, 22.03, 23.11, 24.68, 25.53, 25.57, 26.57, 31.16, 32.61, 36.96, 38.49, 39.01, 39.55, 43.02, 43.76, 48.31, 53.81, 54.15, 69.10, 124.14, 124.65, 124.83, 130.97, 131.19, 134.87, 178.39. Anal. Calcd for $C_{30}H_{47}N$: C, 85.44; H, 11.23; N, 3.32. Found: C, 85.33; H, 11.02; N, 3.22.

[3α,3aβ,6α(*E*),6aα,9a*R,10*R**]-(±)-2,3,3a,6,6a,7,8,9-Octahydro-10-methyl-10-(4-methyl-3-pentenyl)-6-(4,8-dimethyl-3,7-nonadienyl)-3,6-methano-1*H*-dicyclopenta[*b*,*c*]pyridine (32).** ^1H NMR (400 MHz): δ 0.78 (s, 3), 0.79–2.12 (m, 24), 1.55, 1.59, 1.63 (s, 3 each), 1.69 (s, 6), 4.12 (d, 1, *J* = 4.9), 5.05–5.18 (m, 3), 8.17 (s, 1). HRMS: calcd for $C_{30}H_{47}N$ 421.3708, found 421.3698.

Application of the procedure to dialdehydes **36**/**37** gave 167 mg (79%) of imine **38** and 7 mg (3%) of imine **39**.

[3α,3aβ,6α(*Z*),6aα,9a*R,10*R**]-(±)-2,3,3a,6,6a,7,8,9-Octahydro-10-methyl-10-(4-methyl-3-pentenyl)-6-(4,8-dimethyl-3,7-nonadienyl)-3,6-methano-1*H*-dicyclopenta[*b*,*c*]pyridine (38).** IR: 1625 cm^{-1}. ^1H NMR (400 MHz): δ 0.77 (s, 3), 1.00–1.07 (m, 1), 1.20–1.41 (m, 4), 1.45–1.83 (m, 11), 1.60 (s, 3), 1.61 (s, 3), 1.71 (s, 3), 1.68 (s, 6), 1.98–2.10 (m, 6), 2.17–2.30 (m, 2), 4.12 (d, 1, *J* = 4.9), 5.06–5.18 (m, 3), 8.16 (s, 1). ^{13}C NMR (125 MHz): δ 17.56, 17.68, 23.30, 23.53, 24.05, 24.78, 24.97, 25.67, 25.56, 31.77, 31.92, 32.03, 33.05, 36.20, 37.53, 44.04, 45.82, 48.63, 52.36, 54.88,

68.39, 124.09, 124.77, 125.72, 131.05, 131.55, 135.16, 178.57. Anal. Calcd for $C_{30}H_{47}N$: C, 85.44; H, 11.23; N, 3.32. Found: C, 85.05; H, 10.97; N, 3.27.

[3α,3aβ,6α(*Z*),6aα,9a*R,10*S**]-(±)-2,3,3a,6,6a,7,8,9-Octahydro-10-methyl-10-(4-methyl-3-pentenyl)-6-(4,8-dimethyl-3,7-nonadienyl)-3,6-methano-1*H*-dicyclopenta[*b*,*c*]pyridine (39).** ^{1}H NMR (400 MHz): δ 0.85 (s, 3), 0.86–0.97 (m, 1), 1.04–1.11 (m, 1), 1.19–1.88 (m, 14), 1.56, 1.61 (s, 3), 1.64 (s, 3), 1.68 (s, 3), 1.71 (s, 3), 1.99–2.10 (m, 6), 2.18–2.24 (m, 2), 4.11 (d, 1, *J* = 4.7), 4.96–5.00 (m, 1), 5.10–5.18 (m, 2), 8.10 (s, 1).

***proto*-Daphniphylline (11). Method A.** The foregoing procedure was followed except that the acetic acid solution of the imine **31** was heated at 75 °C for 2 h prior to the workup. There was thus isolated 329 mg (78%) of *proto*-daphniphylline. IR: 1648 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.81 (s, 3), 1.16–1.22 (m, 1), 1.25–2.12 (m, 26), 1.60 (s, 6), 1.68 (s, 6), 1.78 (s, 6), 2.54 (d, 1, *J* = 4.5), 2.74 (br s, 1), 4.74 (s, 1), 4.86, (s, 1), 5.06–5.12 (m, 2). ^{13}C NMR (125 MHz): δ 16.07, 17.63, 20.19, 21.35, 22.59, 22.81, 23.61, 25.63, 26.64, 26.69, 29.76, 33.11, 36.29, 36.62, 36.87, 38.43, 39.52, 39.64, 42.35, 47.76, 49.22, 50.76, 53.76, 60.07, 110.16, 124.28, 125.30, 131.17, 134.30, 147.65. Anal. Calcd for $C_{30}H_{47}N$: C, 85.44; H, 11.23; N, 3.32. Found: C, 85.08; H, 10.85; N, 3.40.

Method B. Compound **11** was also obtained by heating a solution of 172 mg (0.41 mmol) of imine **31** and 314 mg (4.1 mmol) of NH_4OAc in 8 mL of acetic acid at 75 °C for 2 h. Application of the foregoing workup procedure gave 155 mg (90%) of *proto*-daphniphylline.

Method C. Ammonia gas was bubbled for 3 min through a solution of dialdehyde **55** (110 mg, 0.25 mmol), NH_4OAc (19.3 mg, 0.25 mmol), and triethylamine hydrochloride (34.4 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) at room temperature and the resulting mixture was stirred for 16 h. The solvent was then evaporated and NH_4OAc (193 mg, 2.5 mmol) and AcOH (5 mL) were added. The mixture was heated at 80 °C for 3 h, cooled, and poured into water (25 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with 2 M NaOH. The layers were separated and the aqueous phase was extracted with additional CH_2Cl_2 (10 mL). The CH_2Cl_2 extract was dried and evaporated and the residue chromatographed to give 18 mg (17%) of *proto*-daphniphylline (**11**). The same procedure when applied to dialdehyde **51** gave 12.5 mg (13%) of **11**.

Method D. Dialdehyde **55** (132 mg, 0.31 mmol) in dry DMSO (0.5 mL) was added at 25 °C to a suspension of finely powdered NaOH (98% grade, 12.4 mg, 0.31 mmol) in DMSO (2 mL) in a pressure bottle equipped with a rubber ring and a Teflon screw-cap. The resulting mixture was stirred for 3.5 h, NH_4OAc (48 mg, 0.62 mmol) was added, and ammonia was bubbled through the mixture for 3 min. The bottle was closed and heated at 80 °C in an oil bath for 3 h. Acetic acid (5 mL) was added and the solution heated at 80 °C for 2.5 h. Workup and purification as above gave 58 mg (44%) of *proto*-daphniphylline. Use of KOH instead of NaOH gave the product in only 35% yield.

Method E. Tetra-*n*-butylammonium bisulfate (3.3 mg, 0.0096 mmol) was added to a vigorously stirring mixture of 50% KOH (0.193 mL), dialdehyde **51** or **55** (85 mg, 0.193 mmol), and benzene (3 mL) at 25 °C. After 10 min[19] the mixture was poured into water (3 mL) and extracted with ether (3 × 2 mL). The extract was dried over K_2CO_3, the solvents were evaporated, and the residue was placed in a pressure bottle along with NH_4OAc (92 mg, 1.193 mmol) and DMSO (6 mL). Ammonia gas was bubbled through the solution for 3 min and the flask was closed with a Teflon screw-cap and heated at 80 °C for 3 h. Acetic acid (8 mL) was then added and heating continued for 3 h. Workup and purification as above furnished 40.2 mg (49.4%) of pure **11**.

1,2-Dihydro-*proto*-daphniphylline (29). Method A. Tris(triphenylphosphine)rhodium(I) chloride (160 mg, 0.173 mmol) was suspended in 12 mL of dry benzene that had been degassed (freeze–pump–thaw cycle). The suspension was stirred at 25 °C for 45 min under an atmosphere of H_2 (the catalyst dissolved). *proto*-Daphniphylline (243 mg, 0.576 mmol) in C_6H_6 (1 mL) was added with a syringe and stirring was continued for 8 h. The solvent was evaporated and the residue chromatographed on silica gel using 9:1 hexane–EtOAc as eluent to give 213 mg (88%) of amine **29**, contaminated with a small amount of dihydrogenated product. ^{1}H NMR (400 MHz): δ 0.78 (s, 3), 0.89 (d, 3, *J* = 6.7), 0.91 (d, 3, *J* = 6.7), 0.90–0.97 (m, 1), 1.13–1.18 (m, 1), 1.21–1.78 (m, 19), 1.59 (s, 3), 1.61 (s, 3), 1.68 (s, 3), 1.86–1.91 (m, 2), 1.93–2.00 (m, 2), 2.03–2.10 (m, 2), 2.52 (d, 1, *J* = 4.5), 3.02 (s, 1), 5.03–5.11 (m, 2). ^{13}C NMR (125 MHz): δ 16.05, 17.62, 20.75, 21.00, 21.03, 21.33, 22.89, 23.55, 25.63, 26.65, 26.75, 28.75, 29.91, 33.20, 36.37, 36.49, 36.67, 39.13, 39.65, 39.77, 42.87, 47.75, 48.34, 50.42, 53.49, 60.12, 124.30, 125.46, 131.11, 134.09. Anal. Calcd for $C_{30}H_{49}N$: C, 85.04; H, 11.66; N, 3.31. Found: C, 84.74; H, 11.79; N, 3.31.

Method B. To a −78 °C solution of DMSO (66 μL, 0.93 mmol) in 0.8 mL of CH_2Cl_2 was added 206 μL of a 2.0 M solution of oxalyl chloride in CH_2Cl_2 (0.412 mmol). After 15 min, diols **25** and **26** (45.8 mg, 0.103 mmol) were added via cannula as a solution in 0.8 mL of CH_2Cl_2, followed by a 0.8-mL rinse. The resulting cloudy solution was stirred at −78 °C for 15 min and then treated with triethylamine (0.10 mL, 0.72 mmol). The dry ice bath was replaced with an ice water bath, and the solution was allowed to warm to 0 °C over a period of 80 min. A stream of anhydrous methylamine was then passed over the solution for 3 min. The flask was sealed tightly and allowed to warm to ambient temperature over a period of 2 h. The clear solution was concentrated by passing a stream of dry nitrogen over it for a period of 10 min. The resulting white, oily solid was then placed on a vacuum pump for 4 h. The resulting solid was taken up in 5 mL of acetic acid and stirred at room temperature for 5 h and then placed in an 80 °C oil bath for 11 h. After cooling to 0 °C, the mixture was partitioned between CH_2Cl_2 and 15 mL of 6 N NaOH and stirred vigorously for 15 min. The layers were separated, and the aqueous phase was extracted with three portions of CH_2Cl_2. The combined organic phases were than washed with brine and dried over $MgSO_4$. Filtration and concentration provided 57.5 mg of a brown oil, which was purifed by flash chromatography (gradient elution with 10:1 to 5:1 hexanes/ethyl acetate) to provide the desired product as a clear, pale yellow oil (28.7 mg, 65.8%).

Method C. To a −78 °C solution of DMSO (45 μL, 0.63 mmol) in 1 mL of CH_2Cl_2 was added 140 μL of a 2.0 M solution of oxalyl chloride in CH_2Cl_2 (0.280 mmol). After 10 min, diols **25** and **26** (31.1 mg, 0.0699 mmol) were added via cannula as a solution in 1 mL of CH_2Cl_2, followed by two 0.5-mL rinses. The resulting cloudy solution was stirred at −78 °C for 15 min and then treated with triethylamine (0.070 mL, 0.50 mmol). The dry ice bath was replaced with an ice water bath, and the solution was allowed to warm to 0 °C over a period of 60 min. The solvent was then removed under a stream of dry nitrogen to provide a white, oily solid, which was triturated with ether and filtered through a plug of cotton. Concentration of the resulting colorless solution provided 40.8 mg of a clear, pale yellow oil. The crude bisaldehyde was then treated with 1.5 mL of acetic acid and 51 mg of glycine (0.68 mmol) and stirred for 10 h at room temperature, followed by 16 h in an 80 °C oil bath. After being cooled to room temperature, the solution was partitioned between 5 mL each of CH_2Cl_2 and 2 N NaOH and stirred vigorously for 2 h. The layers were separated, the aqueous phase was extracted with two portions of CH_2Cl_2, and the combined organic phases were dried over K_2CO_3. Filtration and concentration provided 27.3 mg of a pale, orange-brown oil. Flash chromatography of this material (gradient elution with 10:1 to 5:1 hexanes/ethyl acetate) provided the desired product as a clear, pale yellow oil (15.8 mg, 53.4%).

Method D. To a −78 °C solution of DMSO (88 μL, 1.2 mmol) in 1 mL of CH_2Cl_2 was added 276 μL of a 2.0 M solution of oxalyl chloride in CH_2Cl_2 (0.552 mmol). After 20 min, diol **50** (61.3 mg, 0.138 mmol) was added via cannula as a solution in 1 mL of CH_2Cl_2, followed by a 1-mL rinse. The resulting cloudy solution was stirred at −78 °C for 20 min and then treated with triethylamine (0.14 mL, 1.0 mmol). The dry ice bath was removed, and the solution was allowed to warm to ambient temperature over a period of 50 min. After cooling to 0 °C, a stream of anhydrous methylamine was passed over the solution for 3 min. The flask was then sealed tightly and allowed to warm to ambient temperature over a period of 5 h. The clear solution was concentrated by passing a stream of dry nitrogen over it for a period of 10 min. The resulting white, oily solid was triturated with ether, filtered, and concentrated (high vacuum for 4 h) to provide 84.0

(19) The reaction can be monitored by TLC on Al_2O_3 plates with a 9:1 mixture of hexane–EtOAc as eluent.

mg of a clear, pale yellow oil. Although generally utilized immediately in the next reaction, spectral analysis of this material was consistent with the bis(*N*-methylimine) **62**. IR (thin film): 2960, 2920, 2840, 1665, 1640, 1450, 1395, 1345. ^{1}H NMR (400 MHz, selected signals listed): δ 7.72 (s, 1), 7.43 (d, 1), 5.77 (t, 1), 5.15–5.05 (m, 4), 3.35 (s, 3), 3.26 (s, 3). ^{13}C NMR (100 MHz): δ 15.91, 15.95, 16.00, 17.58, 25.41, 25.60, 25.98, 26.70, 26.80, 26.93, 27.09, 28.43, 31.69, 32.40, 39.65, 44.62, 47.82, 47.86, 123.99, 124.23, 124.35, 124.43, 131.10, 131.17, 135.08, 135.31, 139.85, 141.34, 166.12, 169.63.

The crude bisimine was taken up in 1 mL of acetic acid and placed in an 80 °C oil bath for 11 h. After being cooled to 0 °C, the mixture was partitioned between 5 mL each of CH_2Cl_2 and 2 N NaOH and stirred vigorously for 15 min. The layers were separated, and the aqueous phase was extracted with three portions of CH_2Cl_2. The combined organic phases were then washed with brine and dried over $MgSO_4$. Filtration and concentration provided 68.0 mg of a brown oil. Purification by flash chromatography (gradient elution with 10:1 to 5:1 hexanes/ethyl acetate) provided the desired product as a clear, pale yellow oil (38.2 mg, 65.4%).

Method E. To a −78 °C solution of DMSO (60 μL, 0.85 mmol) in 1 mL of CH_2Cl_2 was added 190 μL of a 2.0 M solution of oxalyl chloride in CH_2Cl_2 (0.380 mmol). After 20 min, diol **50** (41.9 mg, 0.0942 mmol) was added via cannula as a solution in 1 mL of CH_2Cl_2, followed by two 0.5-mL rinses. The resulting cloudy solution was stirred at −78 °C for 20 min and then treated with triethylamine (0.10 mL, 0.72 mmol). The dry ice bath was removed, and the solution was allowed to warm to room temperature over a period of 60 min. The solvent was then removed under a stream of dry nitrogen to provide a white, oily solid, which was triturated with ether and filtered through a plug of cotton. Concentration of the resulting colorless solution provided 47.5 mg of a clear, pale yellow oil. The crude bisaldehyde was then treated with 1.5 mL of acetic acid and 70 mg of glycine (0.93 mmol) and stirred for 9 h at room temperature, followed by 9 h in an 80 °C oil bath. After being cooled to room temperature, the solution was partitioned between 15 mL each of CH_2Cl_2 and 2 N NaOH and stirred vigorously for 90 min. The layers were separated, the aqueous phase was extracted with two portions of CH_2Cl_2, and the combined organic phases were dried over K_2CO_3. Filtration and concentration provided 72 mg of a brown, cloudy oil. Flash chromatography of this material (gradient elution with 10:1 to 5:1 hexanes/ethyl acetate) provided the desired product as a clear, colorless oil (15.0 mg, 37.6%).

Attempted Cyclization of Imines 31 and 38. A solution of 4.2 mg (0.01 mmol) of imine **31** or **38** and 7.7 mg (0.1 mmol) of NH_4OAc in 0.2 mL of acetic acid was heated at 80 °C for 15 h. Workup as usual gave a brown oil. Analysis by TLC (SiO_2, hexane–EtOAc (7:3)), GC, or ^{1}H NMR spectrometry indicated no change.

[7(*Z*)]-17,18-Didehydro-7-(4,8-dimethyl-3,7-nonadienyl)-12,16-cyclo-21,22,23-trinor-1,12-secodaphnane (40). A solution of 172 mg (0.41 mmol) of imine **39** and 314 mg (4.1 mmol) of NH_4OAc in 8 mL of acetic acid was heated at 80 °C for 2 h. The normal workup gave 155 mg (90%) of amine **40**. ^{1}H NMR (400 MHz): δ 0.80 (s, 3), 0.81–0.90 (m, 1), 1.16–2.10 (m, 25), 1.55 (s, 3), 1.61 (s, 3), 1.68 (s, 3), 1.77 (s, 3), 2.53 (d, 1, J = 4.5), 3.02 (s, 1), 4.74 (s, 1), 4.86 (s, 1), 5.05–5.12 (m, 2). HRMS: calcd for $C_{30}H_{47}N$ 421.3708, found 421.3707.

(±)-Methyl Homosecodaphniphyllate (30). Ozone was bubbled for 3 min through a solution of 150 mg (0.354 mmol) of amine **29**, 69.4 mg (0.71 mmol) of concd H_2SO_4, 4 mL of CH_2Cl_2, and 4 mL of MeOH, cooled to −78 °C. The blue solution was discolored by bubbling N_2 through it and warmed to 25 °C. The solvents were evaporated and the residue placed under high vacuum for 10 min. Acetone (8 mL) was added followed by 1.59 mL of a 2.67 M solution of CrO_3 in concd H_2SO_4 at 0 °C. The mixture was stirred for 30 min at 0 °C and for 10 min at 25 °C. Filtration through a plug of Celite and washing with acetone (15 mL) afforded a clear solution. Evaporation of the solvent gave an oily residue that was dissolved in 25 mL of methanol and treated with 0.5 mL of concd H_2SO_4. The solution was stirred at 25 °C for 40 h, poured into 50 mL of water, and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$ and dried, and the solvents were evaporated. The residue was purified by chromatography and eluted with a 8:2 mixture of hexane–EtOAc to furnish 99 mg (78%) of **30**, identical by ^{1}H NMR, ^{13}C NMR, and TLC with an authentic sample.[1]

***tert*-Butyl (5*E*)-6,10-Dimethylundeca-5,9-dienoate (45).** A solution of 116.2 mg (1 mmol) of *tert*-butyl acetate in 0.8 mL of dry THF was added dropwise to a stirring solution of 1 mmol of LDA at −78 °C. After 45 min, a mixture of 179.2 mg (1 mmol) of HMPA and 0.2 mL of THF (0.2 mL) was added followed *immediately* by a solution of 250 mg (0.9 mmol) of homogeranyl iodide in 1 mL of THF. After 4 h at −78 °C the mixture was warmed to 25 °C, poured into 20 mL of brine, and extracted with CH_2Cl_2 (3 × 10 mL). Drying of the extracts, filtration, and evaporation of the solvents left a residue that was chromatographed. Elution with hexane–EtOAc (99:1) afforded 213 mg (83%) of ester **45**, bp 74–78 °C (0.1 Torr). IR: 1725 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.42 (s, 9), 1.56 (s, 3), 1.57 (s, 3), 1.56–1.62 (m, 2), 1.65 (s, 3), 1.94–2.07 (m, 6), 2.17 (t, 2, J = 7.5), 5.04–5.08 (m, 2). ^{13}C NMR (125 MHz): δ 15.85, 17.58, 25.10, 25.60, 26.53, 27.10, 28.02, 34.83, 39.65, 79.77, 123.56, 124.23, 131.20, 135.73, 173.16. Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.25; H, 11.32.

Further elution gave 28 mg (9%) of a byproduct resulting from Claisen condensation of **45** with *tert*-butyl acetate. IR: 1735, 1714 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.47 (s, 9), 1.59 (s, 3), 1.60 (s, 3), 1.68 (s, 3), 1.60–1.67 (m, 2), 1.96–2.15 (m, 6), 2.51 (t, 1, J = 7.4), 3.33 (s, 2), 5.06–5.10 (m, 2). ^{13}C NMR (125 MHz): δ 15.71, 17.37, 23.29, 25.41, 26.39, 26.79, 27.65, 39.45, 41.90, 50.34, 81.33, 123.23, 124.03, 130.91, 135.74, 166.19, 202.94. Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 74.09; H, 10.59.

(5*E*)-*tert*-Butyl 2-(4,4-Dimethoxybutyl)-6,10-dimethyl-5,9-undecadienoate (46). A solution of 266.4 mg (1 mmol) of ester **45** in 0.8 mL of THF was added dropwise to a stirring solution of LDA (1.2 mmol) at −78 °C. After 45 min of stirring, a solution of 236.5 mg (1.2 mmol) of 1,1-dimethoxy-4-bromobutane in 1 mL of THF was added dropwise, followed by a mixture of 179.2 mg (1 mmol) of HMPA and 0.2 mL of THF. Stirring was continued for 3 h at −78 °C and the mixture was warmed to 25 °C overnight, poured into 20 mL of water, and extracted with CH_2Cl_2. The combined extracts were dried over K_2CO_3 and the solvents evaporated. The residue was chromatographed and eluted with a 97:3 mixture of hexane–EtOAc and finally distilled under reduced pressure to afford 327 mg (85%) of acetal **46**, bp 119–121 °C (0.01 Torr). IR: 1725 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.13–1.64 (m, 8), 1.46 (s, 9), 1.59 (s, 3), 1.60 (s, 3), 1.68 (s, 3), 1.94–2.10 (m, 6), 2.19–2.27 (m, 1), 3.29 (s, 3), 3.30 (s, 3), 4.34 (t, 1, J = 5.8), 5.06–5.10 (m, 2). ^{13}C NMR (125 MHz): δ 15.82, 17.55, 22.32, 25.57, 25.65, 26.54, 28.00, 32.27, 32.53, 39.59, 45.88, 52.37, 52.47, 79.75, 104.17, 123.65, 124.20, 131.10, 135.37, 175.45. Anal. Calcd for $C_{23}H_{42}O_4$: C, 72.21; H, 11.07. Found: C, 72.40; H, 11.22.

(5*E*)-*tert*-Butyl 6,10-Dimethyl-2-(4-oxobutyl)-5,9-undecadienoate (47). A mixture of 3.826 g (10 mmol) of acetal **46**, 380 mg (2 mmol) of *p*-toluenesulfonic acid, and 3.5 mL of water (3.5 mL) in 24 mL of acetone was stirred for 16 h at 25 °C. The solution was poured into 50 mL of brine and extracted with CH_2Cl_2 (3 × 25 mL). Drying of the extract, filtration, and evaporation of the solvent gave a residue that was purified by chromatography (eluant: CH_2Cl_2) and bulb-to-bulb distillation (117–119 °C at 0.02 Torr) to furnish 3.31 g (98%) of aldehyde **47**. IR: 2726, 1724 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.37–1.47 (m, 2), 1.46 (s, 9), 1.58–1.66 (m, 4), 1.59, 1.60 (s, 3), 1.68 (s, 3), 1.93–2.02 (m, 4), 2.05–2.10 (m, 2), 2.23–2.27 (m, 1), 2.42–2.46 (m, 2), 5.06–5.11 (m, 2), 9.75 (t, 1, J = 1.6). ^{13}C NMR (125 MHz): δ 15.86, 17.56, 19.81, 25.59, 26.55, 28.02, 31.79, 32.52, 39.60, 43.60, 45.72, 80.06, 123.49, 124.18, 131.19, 135.57, 175,17, 202.01. Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.60; H, 10.53.

[2(*E*),7(*E*)]-Di-*tert*-butyl 2,7-Bis(4,8-dimethyl-3,7-nonadienyl)-3-hydroxyoctanedioate (48). To a solution of diisopropylamine (0.46 mL, 3.3 mmol) in 3 mL of THF at 0 °C was added 1.39 mL of a 2.33 M *n*-butyllithium solution. After 20 min, the solution was cooled to −78 °C, and ester **45** (785 mg, 2.95 mmol) was added via cannula in 3 mL of THF, followed by a 2-mL rinse. The solution was stirred at −78 °C for 50 min and then treated with aldehyde **47** (815 mg, 2.42 mmol), which was added via cannula in 3 mL of THF, followed by a 2-mL rinse. The solution was stirred for an additional 50 min and then quenched at −78 °C by the addition of approximately 5 mL of aqueous NH_4Cl

solution. After being warmed to room temperature, the solution was extracted with three portions of ether. The combined organic phases were washed with brine and dried over $MgSO_4$. Filtration and concentration provided 1.783 g of a clear, colorless oil. Purification by flash chromatography (gradient elution with 100 to 50 to 20 to 10:1 hexanes/ethyl acetate) provided recovered ester **45** (204 mg, 0.766 mmol), followed by the desired β-hydroxy ester **48** as a clear, colorless oil (1.199 g, 1.989 mmol, 82%). Anal. Calcd for $C_{38}H_{66}O_5$: C, 75.70; H, 11.03. Found: C, 75.90; H, 10.78.

[2*E*,2(*E*),7(*E*)]-Di-*tert*-butyl 2,7-Bis(4,8-dimethyl-3,7-nonadienyl)-2-octenedioate (49). To a 0 °C solution of β-hydroxy esters **48** (1.643 g, 2.725 mmol) and triethylamine (1.52 mL, 10.9 mmol) in 8 mL of CH_2Cl_2 was added 0.42 mL (5.5 mmol) of methanesulfonyl chloride. The ice bath was removed, and the solution was allowed to stir at room temperature for 3 h. After dilution with 20 mL of CH_2Cl_2, the solution was washed with aqueous $NaHCO_3$ (2×), 0.1 N HCl, and brine. The aqueous phases were extracted once with CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$. Filtration and concentration provided a granular, orange-brown oil, which was taken up in 8 mL of toluene, treated with 1,8-diazabicyclo[5.4.0]undecene (DBU) (1.2 mL, 8.2 mmol), and heated in an 80 °C oil bath for 12 h. After being cooled to room temperature, the solution was diluted with ether, washed with 0.1 N HCl (2×), aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. Filtration and concentration provided 1.701 g of a clear pale yellow oil. Purification by flash chromatography (gradient elution with 40 to 30:1 hexanes/ethyl acetate) provided the 14*Z* isomer **53** (0.134 g, 0.23 mmol, 8.4%) and the 14*E* isomer **49** (1.402 g, 2.397 mmol, 88.0%), both as clear, colorless oils. IR: 1725, 1710 cm^{-1}. ^1H NMR (400 MHz): δ 1.40–1.68 (m, 4), 1.45 (s, 9), 1.49 (s, 9), 1.58 (s, 3), 1.59 (s, 3), 1.60 (s, 6), 1.68 (s, 6), 1.96–2.46 (m, 19), 5.07–5.10 (m, 3), 5.11–5.16 (m, 1), 6.62 (t, 1, J = 7.5). ^{13}C NMR (125 MHz): δ 15.90, 15.91, 17.62, 25.64, 25.71, 26.61, 26.66, 26.97, 27.71, 28.09, 28.10, 28.21, 28.47, 32.31, 32.60, 39.66, 39.69, 45.92, 79.82, 79.90, 123.58, 123.66, 124.25, 124.30, 131.22, 133.65, 135.51, 141.01, 167.21, 175.43. Anal. Calcd for $C_{38}H_{64}O_4$: C, 78.03; H, 11.03. Found: C, 78.20; H, 11.06.

(6*E*,14*Z*,18*E*)-10,11-Dihydrosqualene-27,28-diol (50). A 1.0 M solution of DIBAL in toluene (30 mL, 30 mmol) was added dropwise to a solution of 1.939 g (3.315 mmol) of diester **49** in 16 mL of CH_2Cl_2 at −78 °C. After 3 h, the reaction was quenched by slow addition of 2 mL of methanol. After warming to room temperature, 50 mL each of ether and saturated aqueous sodium potassium tartrate were added, and the resulting solution was stirred vigorously until two clear phases resulted. The layers were then separated, and the aqueous phase was extracted with three portions of ether. The combined organic phases were washed with brine and dried. Filtration and evaporation of the solvents gave a crude mixture of compounds that was resubjected to further reduction by being dissolved in 16 mL of CH_2Cl_2, cooled to −78 °C, and treated with another 30-mL portion of 1.0 M DIBAL in toluene (30 mmol) for 3 h at −78 °C. Workup as before provided a clear, pale yellow oil, which was purified by flash chromatography (gradient elution with 3 to 2:1 hexanes/ethyl acetate) to provide diol **50** as a clear, colorless oil (1.413 g, 96%). IR: 3700–3250, 3615 cm^{-1}. ^1H NMR (400 MHz): δ 1.24–1.58 (m, 7), 1.59 (s, 12), 1.68 (s, 6), 1.95–2.14 (m, 16), 3.45 (dd, 1, J = 5.9, 10.5), 4.06 (d, 1, J = 11.8), 4.13 (d, 1, J = 11.8), 5.06–5.13 (m, 4), 5.29 (t, 1, J = 6.3). ^{13}C NMR (125 MHz): δ 15.83, 15.88, 17.50, 25.13, 25.52, 26.57, 26.59, 26.71, 26.81, 27.50, 30.11, 30.81, 34.91, 39.58, 59.68, 65.09, 123.97, 124.21, 124.40, 128.37, 131.03, 134.83, 135.02, 138.24. Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.78. Found: C, 80.86; H, 11.90.

***tert*-Butyl (5*E*)-2-(Trimethylsilyl)-6,10-dimethylundeca-5,9-dienoate (52).** A solution of 188.4 mg (1 mmol) of *tert*-butyl (trimethylsilyl)acetate[20] in 0.5 mL of THF was added slowly into a stirring solution of 1.1 mmol of LDA in THF/hexane at −78 °C. The resulting mixture was stirred for 30 min at −78 °C and 15 min at −42 °C. The solution was cooled to −78 °C, a solution of 278.3 mg (1 mmol) of iodide **16** in 1 mL of THF was added dropwise, and the solution was stirred for 3 h. The mixture was then warmed to room temperature and stirring continued for 16 h. The crude solution was poured into 25 mL of brine, extracted with CH_2Cl_2 (3 × 15 mL), and dried. Filtration, evaporation of the solvent, and chromatography (95:5 hexane–EtOAc) furnished 286 mg (84%) of **52**. IR: 1705 cm^{-1}. ^1H NMR (400 MHz): δ 0.006 (s, 9), 1.29–1.67 (m, 2), 1.44 (s, 9), 1.60 (s, 6), 1.68 (s, 3), 1.76–2.12 (m, 7), 5.04–5.12 (m, 2). ^{13}C NMR (125 MHz): δ −2.67, 15.88, 17.59, 25.62, 26.61, 26.96, 28.26, 28.44, 38.07, 39.70, 79.20, 123.83, 124.31, 131.10, 135.61, 174.50. Anal. Calcd for $C_{20}H_{38}SiO_2$: C, 70.94; H, 11.31. Found: C, 71.03; H, 11.25.

[2*Z*,2(*E*),7(*E*)]-Di-*tert*-butyl 2,7-Bis(4,8-dimethyl-3,7-nonadienyl)-2-octenedioate (53). A solution of 2.71 g (8 mmol) of ester **52** in 8 mL of THF was added dropwise to a solution of 8 mmol of LDA in THF/hexane at −78 °C. After 3.5 h, 2.69 g (8 mmol) of aldehyde **47** was added over a 5-min period and stirring was continued for 15 min. The solution was warmed to 0 °C, stirred for an additional 10 min, and quenched with 100 mL of water. Extraction with CH_2Cl_2, drying of the combined organic extracts, filtration, and evaporation of the solvents gave a crude oil. Chromatographic purification, eluting with 95:5 hexane–EtOAc, gave 2.42 g of 14*Z* isomer **53**, followed by 1.39 g of 14*E* isomer **49** (total yield, 73%). IR: 1720 cm^{-1}. ^1H NMR (400 MHz): δ 1.37–1.68 (m, 6), 1.45 (s, 9), 1.50 (s, 9), 1.58 (s, 3), 1.59 (s, 3), 1.60 (s, 6), 1.68 (s, 6), 1.93–2.23 (m, 15), 2.35–2.39 (m, 2), 5.07–5.14 (m, 4), 5.70 (t, 1, J = 7.4). ^{13}C NMR (125 MHz): δ 15.86, 15.92, 17.59, 25.61, 25.71, 26.58, 26.66, 27.21, 27.58, 28.05, 28.17, 29.30, 32.19, 32.59, 34.96, 39.64, 45.94, 79.73, 80.16, 123.46, 127.71, 124.26, 131.12, 133.53, 135.38, 135.44, 139.30, 167.49, 175.51. Anal. Calcd for $C_{38}H_{64}O_4$: C, 78.03; H, 11.03. Found: C, 78.13; H, 11.21.

(6*E*,14*E*,18*E*)-10,11-Dihydrosqualene-27,28-diol (54). The procedure described for the preparation of diol **50** was followed with 935 mg (1.6 mmol) of diester **53** to obtain 700 mg (87%) of diol **54**. IR: 3720–3240, 3620 cm^{-1}. ^1H NMR (400 MHz): δ 1.28–1.75 (m, 7), 1.60 (s, 12), 1.68 (s, 6), 1.95–2.16 (m, 16), 3.51–3.57 (m, 2), 4.03 (s, 2), 5.06–5.17 (m, 4), 5.43 (t, 1, J = 6.6). ^{13}C NMR (125 MHz): δ 15.95, 17.63, 25.20, 25.64, 26.62, 26.65, 26.92, 26.98, 27.79, 28.14, 30.53, 30.91, 39.66, 40.00, 65.32, 67.14, 123.87, 124.25, 124.28, 124.43, 127.08, 131.27, 131.32, 135.08, 135.47, 138.98. Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.78. Found: C, 80.76; H, 11.76.

1,5-Bis(4,8-dimethylnona-3,7-dienyl)-2-hydroxy-3-oxabicyclo[4.3.0]-4-nonenes (61). Tetra-*n*-butylammonium bisulfate (8.5 mg, 0.025 mmol) was added to a vigorously stirring mixture of dialdehyde **55** (220 mg, 0.5 mmol), C_6H_6 (7.75 mL), and 50% w/w aqueous KOH (0.5 mL) at room temperature. The reaction was monitored by TLC (Al_2O_3; 9:1 mixture of hexane–EtOAc). After about 10 min the mixture was quenched with water (25 mL) and extracted with ether (3 × 15 mL). Drying over K_2CO_3 and evaporation of the solvents gave a residue containing about 57% of the desired products. Chromatography on Al_2O_3 and elution with 93:7 hexane–EtOAc afforded 48 mg (22%) of hydroxydihydropyran **61** as a 2:1 mixture of epimers (extensive decomposition occured upon chromatography). IR: 3585, 1727, 1667 cm^{-1}. ^1H NMR (400 MHz): δ (major isomer) 1.31–1.68 (m, 6), 1.60 (s, 12), 1.68 (s, 6), 1.86–2.18 (m, 17), 4.75 (d, 1, J = 6.6), 5.06–5.15 (m, 4), 6.06 (s, 1); δ (minor isomer) 4.98 (d, 1, J = 6.7), 6.02 (s, 1). ^{13}C NMR (125 MHz): δ 15.95, 15.96, 16.08, 17.65, 22.35, 23.03, 23.33, 23.42, 25.65, 26.53, 26.63, 26.70, 30.81, 30.93, 30.98, 31.11, 31.76, 32.27, 32.38, 38.16, 39.66, 43.47, 43.51, 46.45, 47.68, 96.55, 96.81, 117.09, 117.64, 123.89, 123.92, 124.29, 124.33, 124.49, 124.75, 131.27, 131.29, 133.88, 134.94, 134.97, 135.05, 135.21, 135.31. Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.50; H, 11.00.

(*E*,*E*)-1,5-Bis(4,8-dimethylnona-3,7-dienyl)-2-(methylphenylamino)-3-oxabicyclo[4.3.0]-4-nonenes (59). A mixture of *N*-methylaniline (32.4 mg, 0.302 mmol), dialdehyde **51** (133 mg, 0.302 mmol), and 3 mg of *p*-toluenesulfonic acid in benzene (3 mL) was refluxed for 35 min in a flask equipped with a Dean–Stark apparatus containing molecular sieves. The solvent was evaporated and the oily residue was chromatographed on Al_2O_3. Elution with a 9:1 mixture of hexane and ether delivered 53 mg (33%) of colorless products. ^1H NMR (CD_2Cl_2): δ (major isomer) 1.39–2.26 (m), 2.70–2.71 (m, 1), 2.96 (s, 3), 5.00–5.18 (m, 5), 6.21 (s, 1), 6.82 (t, 1, J = 7.2), 6.95 (d, 2, J = 8.0), 7.21–7.26 (m, 2); δ (minor isomer) 2.30–2.33 (m, 1), 3.01 (s, 1), 6.27 (s, 1). ^{13}C NMR (125 MHz, CD_2Cl_2): δ (major isomer) 151.73, 138.94, 135.59, 135.42, 131.63, 131.55, 129.29, 124.73, 124.70, 124.68, 124.50, 119.56, 116.63, 116.02, 90.02, 49.98, 45.70, 40.16, 40.03, 37.08, 35.43, 34.62, 31.26, 30.32, 27.26, 27.05, 26.94, 25.80, 22.89, 22.85, 17.78, 16.27 15.72;

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δ (minor isomer) 152.02, 138.76, 135.57, 135.24, 131.60, 131.58, 125.13, 124.54, 119.28, 116.41, 115.53, 89.12, 47.94, 44.53, 40.09, 35.14, 34.19, 32.29, 31.59, 27.11, 27.08, 25.54, 22.95, 22.54, 17.75, 16.20, 15.96.

(*E*,*E*)-1,5-Bis(4,8-dimethylnona-3,7-dienyl)-2-pyrrolidino-3-oxabicyclo[4.3.0]-4-nonenes (60). A 10-mL round-bottom flask equipped with a Dean–Stark trap and reflux condenser was charged with bisaldehyde **51** (31.2 mg, 0.071 mmol), pyrrolidine hydrochloride (20 mg, 0.186 mmol), and 1 mL of benzene. The solution was treated with 3 drops of triethylamine and heated to reflux for 2 h. After being cooled to room temperature, the solution was diluted with ether and washed with aqueous NH_4Cl. The layers were separated, and the organic phase was washed with brine. The aqueous phases were then back-extracted with two portions of ether, and the combined organic phases were dried over $MgSO_4$. Filtration and concentration provided 33.1 mg of a clear, yellow oil, which ^1H NMR showed to be the desired aminodihydropyrans (0.067 mmol, 94%). An analytical sample was obtained by filtration through a plug of basic alumina in 10:1 hexanes/ethyl acetate. IR (thin film): 3045, 2960, 2925, 2910, 2870, 2845, 1660, 1450, 1440, 1140 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) (signals for the minor isomer are in parentheses): δ 6.17 (6.24) (s, 1), 5.15–5.09 (m, 4), 4.52 (4.23) (s, 1), 2.94–2.87 (m, 4), 2.53 (br d, J = 5.7, 1), 2.15–1.90 (m, 14), 1.69 (s, 6), 1.61 (s, 12), 1.80–1.20 (m, 12). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major isomer) 138.89, 135.04, 134.90, 134.59, 131.28, 125.16, 124.91, 124.41, 124.37, 115.48, 90.84, 49.06, 47.98, 44.23, 39.75, 39.71, 37.61, 34.34, 30.61, 30.16, 26.81, 26.76, 26.72, 26.68, 25.69, 24.70, 22.56, 22.47, 17.67, 16.10, 15.84, 15.66; δ (minor isomer) 138.58, 135.02, 124.39, 124.27, 124.25, 92.2, 49.71, 46.60, 43.82, 39.69, 34.65, 31.40, 25.95, 24.66, 22.50. Anal. Calcd for $C_{34}H_{55}NO$: C, 82.70; H, 11.23; N, 2.84. Found: C, 82.88; H, 11.55; N, 2.85.

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Registry No. (±)-**11**, 138409-27-5; **14**, 138409-29-7; **15**, 25662-28-6; **16**, 22339-13-5; (±)-**17**, 138512-25-1; (±)-**18**, 138512-26-2; (±)-**19**, 138512-27-3; (±)-**20**, 138512-28-4; (±)-**21**, 138409-30-0; (±)-**22**, 138513-32-3; (±)-**23**, 138409-31-1; (±)-**24**, 138512-29-5; (±)-**25**, 138409-32-2; (±)-**26**, 138512-30-8; (±)-**27**, 138409-33-3; (±)-**28**, 138512-31-9; (±)-**29**, 138409-34-4; (±)-**30**, 118099-25-5; (±)-**31**, 138409-35-5; (±)-**32**, 138512-32-0; (±)-**34**, 138409-36-6; (±)-**36**, 138512-33-1; (±)-**37**, 138512-34-2; (±)-**38**, 138512-35-3; (±)-**39**, 138512-36-4; (±)-**40**, 138409-37-7; **45**, 131938-67-5; **45** (α-acetyl derivative), 138409-53-7; (±)-**46**, 138409-38-8; (±)-**47**, 138409-39-9; **48**, 131979-62-9; (±)-**49**, 138409-40-2; (±)-**50**, 138409-41-3; (±)-**51**, 138409-42-4; (±)-**52**, 138409-43-5; (±)-**53**, 138409-44-6; (±)-**54**, 138409-45-7; (±)-**55**, 138409-46-8; (±)-**59** (isomer 1), 138409-47-9; (±)-**59** (isomer 2), 138512-37-5; (±)-**60** (isomer 1), 138409-48-0; (±)-**60** (isomer 2), 138512-38-6; (±)-**61** (isomer 1), 138409-49-1; (±)-**61** (isomer 2), 138512-39-7; (±)-**62**, 138409-50-4; S1, 138409-22-0; (±)-S3, 138409-23-1; (±)-S4, 138409-24-2; (±)-S5 (isomer 1), 138409-25-3; (±)-S5 (isomer 2), 138512-22-8; (±)-S6 (isomer 1), 138409-26-4; (±)-S6 (isomer 2), 138512-23-9; S10, 69405-40-9; S11, 138409-51-5; (±)-S12, 138409-28-6; (±)-S13, 138512-24-0; (±)-S14, 138512-40-0; (±)-S14 amino-alcohol, 138409-52-6; (±)-S15, 138513-33-4; (±)-S16, 138513-34-5; (±)-s17, 138512-41-1; (±)-S18, 138512-42-2; *t*-BuO-$COCH_3$, 540-88-5; $Br(CH_2)_3CH(OMe)_2$, 24157-02-6; *t*-$BuOCOCH_2SiMe_3$, 41108-81-0; *N*-acetylpyrrolidine, 4030-18-6.

Supplementary Material Available: Descriptions of the preparation of dialdehydes **33**, **36**, and **37** and a more detailed discussion of the hydrolytic chemistry of aminodihydropyran **60**, including 13 additional experimental procedures, mass spectral data for compounds **14**, **17**, **21**, **25**, **26**, **32**, and **40**, and ^1H NMR spectra of compounds **14**, **17**, **25**, **26**, **27**, **28**, **32**, **39**, **40**, **59**, and **62** (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

Daphniphyllum Alkaloids. 13. Asymmetric Total Synthesis of (−)-Secodaphniphylline[1]

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Received August 6, 1991

(−)-Secodaphniphylline (1) has been prepared by total synthesis. The early stages of the synthesis were an asymmetric version of the previously published synthesis of methyl homosecodaphniphyllate (**2**). The necessary chirality was secured by an asymmetric Michael addition reaction of the lithium enolate of the C_2-symmetric amide **9** to α,β-unsaturated ester **10** to give ester amide **12**. The conversion of **12** into (−)-**2** was modelled after the previously reported synthesis in the analogous racemic series, although there were quantitative differences in the reaction conditions required for some of the succeeding transformations of the relatively hindered 2,5-dimethylpyrrolidine amides. The (−)-**2** produced in this synthesis was of 84% ee, which represents the enantioselectivity of the initial Michael addition. Recrystallization of this material provided (−)-**2** of 90% ee. The required 2,8-dioxabicyclo[3.2.1]octanecarboxylic acid chloride **5** was assembled in an eight-step synthesis starting with acid **18**. The necessary chirality was acquired by an asymmetric reduction of acetylenic ketone **19** with the $LiAlH_4$–Darvon alcohol complex. Alcohol **20**, of 92% ee, was obtained and was isomerized to isomer **21** without loss of enantiomeric purity. Concomitant hydration of the triple bond, hydrolysis of the ketal, and cyclization of the resulting keto triol provided a 5:1 mixture of alcohols **23** and **24**. After conversion to a similar mixture of methyl esters **25** and **26**, the isomers were separated and the major carboxylic acid **27** was converted into acid chloride **5**. Ester (−)-**2** and acid chloride **5** were joined by a mixed Claisen condensation and the resulting diastereomeric β-keto esters demethylated and decarboxylated by treatment with NaCN in hot DMSO to obtain (−)-secodaphniphylline (1). Although the two components in the Claisen reaction were enantiomerically enriched only to a modest extent (90% ee and 92% ee), the product alkaloid was >99% ee.

Secodaphniphylline (1) is the parent member of one of the five major structural classes of *Daphniphyllum* alkaloids, a family of secondary metabolites that now has 37 known members.[3] First described in 1969,[4] secodaphni-

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EXHIBIT 21

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Communications

An Air-Stable Catalyst System for the Conversion of Esters to Alcohols

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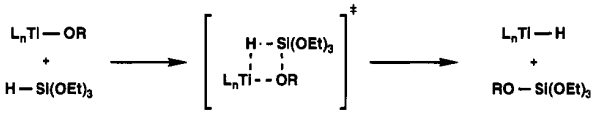
Received April 29, 1992

Summary: The combination of 5 mol % of Ti(O-*i*-Pr)$_4$ with 2.5–3.0 equiv of (EtO)$_3$SiH cleanly hydrosilylates esters to silyl ethers at 40–55 °C, which can be converted to the corresponding primary alcohols via aqueous alkaline hydrolysis in excellent overall yield. The reaction can be carried out in the air, without solvent, and displays a high level of functional group compatibility.

We recently reported the conversion of esters to alcohols[2a] using a novel titanocene-based catalyst system in which a silane served as the stoichiometric reductant.[3] The active catalyst system was generated by the addition of 2 equiv of *n*-BuLi to Cp_2TiCl_2 under an inert atmosphere. We now report a second-generation catalyst system for ester hydrosilylation *which is self-activating, needs no added solvent, and can be generated and utilized in the air.* Moreover, this system displays an enhanced level of functional group compatibility.

A key step in the proposed catalytic cycle described in our initial report was the conversion of a titanium alkoxide into a titanium hydride by a silane via a σ-bond metathesis process.[4] We reasoned that an active titanium hydride species might be generated directly from an appropriate titanium alkoxide and the silane used in the reduction, eliminating the need for the *n*-BuLi activation step (Scheme I). Indeed, we have found that the combination of a catalytic amount of Ti(O-*i*-Pr)$_4$, an extremely inexpensive, air-stable liquid, and (EtO)$_3$SiH generates an effective and mild system for the reduction of a variety of esters (Scheme II). Our results to date are shown in Table I. Except where noted, these reactions were carried out by *simply mixing the ester with 2.5–3.0 equiv of (EtO)$_3$SiH in a test tube, adding 5 mol % of Ti(O-i-Pr)$_4$, and then heating the reaction mixture to 40–55 °C for 4–22 h.*[5a] Product isolation can be accomplished simply

Scheme I



(1) National Science Foundation Predoctoral Fellow, 1989–92.

(2) (a) Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 5093. (b) Esters can be reduced using catalytic Cp_2TiCl_2 and stoichiometric *i*-PrMgBr: Sato, F.; Jinbo, T.; Sato, M. *Tetrahedron Lett.* **1980**, *21*, 2175. (c) For other methods to convert esters to alcohols, see: LaRock, R. C. *Comprehensive Organic Transformations: A Guide To Functional Group Preparations*; VCH Publishers: New York, 1989 and references cited therein.

(3) For other methods to effect the hydrosilylation of esters, see: (a) Calas, R. *Pure Appl. Chem.* **1966**, *13*, 61 and references cited therein. (b) Corriu, R. J. P.; Perz, R.; Reyé, C. *Tetrahedron* **1983**, *39*, 996. (c) For a recent review of the hydrosilylation reaction, see: Ojima, I. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1989.

(4) (a) Woo, H.-G.; Tilley, T. D. *J. Am. Chem. Soc.* **1989**, *111*, 3757. Woo, H.-G.; Tilley, T. D. *J. Am. Chem. Soc.* **1989**, *111*, 8043. (b) We note that Nicolaou has recently described the reduction of an oxime *O*-benzyl ether to a hydroxylamine *O*-benzyl ether using an excess of both Ti(O-*i*-Pr)$_4$ and Ph_2SiH_2: Nicolaou, K. C.; Screiner, E. P.; Stahl, W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 585.

(5) (a) **Typical Procedure.** Triethoxysilane (1.7 mL, 9 mmol) and methyl 10-undecenoate (594 mg, 3 mmol) were added to a test tube. Titanium(IV) isopropoxide (45 μL, 0.15 mmol) was then added, and the test tube was fitted with a drying tube packed with DrieRite to exclude excess moisture. The vessel was then heated in an oil bath at 50 °C. After being stirred for 16 h, the reaction mixture was washed into a 100-mL round-bottom flask with 10 mL of THF. Then, 20 mL of 1 N NaOH was added slowly with stirring. **NOTE:** Vigorous bubbling was observed. After 4 h, the mixture was added to 50 mL each of ether and water. After shaking, the layers were separated, and the aqueous layer was extracted with an additional 50 mL of ether. The combined organic extracts were then washed with two 50-mL portions of 1 N HCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 443 mg (87% yield) of 10-undecen-1-ol as a clear oil. The product was >95% pure as determined by GC and ^{1}H NMR analysis. **CAUTION!!!** Suitable eye protection is required for handling triethoxysilane (vapors can cause blindness); cf. *Silicon Compounds: Register and Review*; Anderson, R., Larson, G. L., Smith, C., Eds.; Hüls America, Inc.; Piscataway, NJ, 1991; pp 5, 190. In the absence of substrate and under an inert atmosphere, (EtO)$_3$SiH is disproportionated by Ti(O-*i*-Pr)$_4$ to form SiH_4, a pyrophoric gas. For a discussion of another titanium-catalyzed disproportionation of (EtO)$_3$SiH, see: Xin, S.; Aikten, C.; Harrod, J. F.; Mu, Y.; Samuel, E. *Can. J. Chem.* **1990**, *68*, 471. (b) An extra equivalent of (EtO)$_3$SiH is required.

0022-3263/92/1957-3751$03.00/0

Table I. Ti(O-*i*-Pr)$_4$ Catalyzed Reduction of Esters

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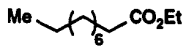
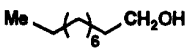
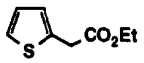
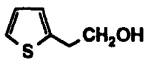
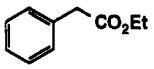
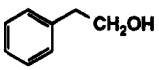
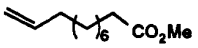
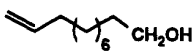
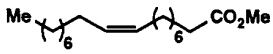
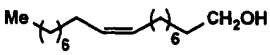
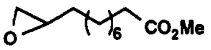
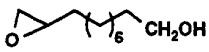
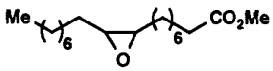
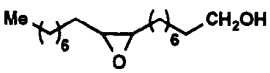
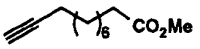
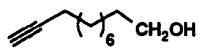
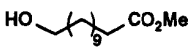
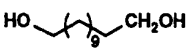
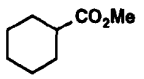
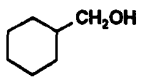
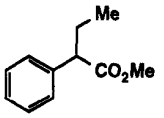
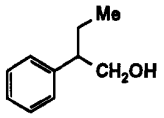
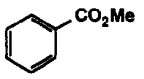
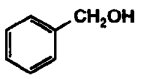
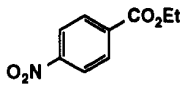
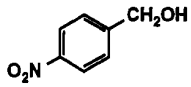
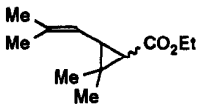
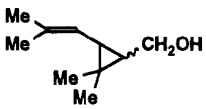
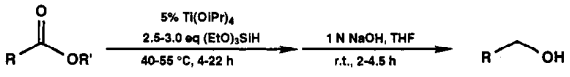
1		10		95
2		4		93[b]
3		4		89
4		6		88
5		16		87
6		5		92
7		21		83[c]
8		18		87[c]
9		18		70[c]
10		7		88[d]
11		16		88
12		14		87
13		10		75[e,f]
14		20		75[c,f]
15		22		80[c,f]

[a] All products were >95% pure and were characterized by GLC, ^{1}H NMR, and IR spectroscopy. They are all known compounds. [b] 50 mmol scale. [c] Purified by flash chromatography or recrystallization. [d] Using 3.75 equiv of HSi(OEt)$_3$. [e] 37 mmol scale, distilled yield. [f] 1.3 equiv of HSi(OEt)$_3$ and 1.4 equiv of H$_3$SiPh are required for complete conversion.

Scheme II



by adding the reaction mixture to a small amount of THF and 1 N NaOH and stirring (2–4.5 h). Conventional workup generally provides the alcohol in >95% purity; the bulk of the silicon- and titanium-containing species go into the aqueous layer or remain at the boundary between the aqueous and organic layers and are easily separated from the product. In the case of epoxides, flash chromatography or recrystallization may be employed to remove traces (less than 5%) of ring-opened products.[6]

The tolerance to other functional groups exhibited by this catalyst system is noteworthy. Halides, olefins, epoxides, alcohols,[5b] and an alkyne (about 5% triple-bond reduction is observed) all survive the reduction protocol. In particular, for entries 4, 5, and 7, the yields are 10–25% better than realized with our previous catalyst system.[2a]

While the simple protocol described above works in many instances, the reduction of aromatic and cyclopropyl

(6) The reaction with methyl 10,11-epoxyundecanoate gave 1% isolated yield of a product whose ^{1}H NMR spectrum is consistent with its formulation as 1,2,11-undecanetriol.

esters stops short of completion. Since methyl cyclohexanecarboxylate (entry 11) and methyl 2-phenylbutyrate (entry 12) react smoothly under the given conditions, this effect cannot be adequately explained by steric factors. However, for these substrates, complete conversion is achieved by the addition of $PhSiH_3$, presumably due to its smaller size and more reactive Si–H bonds.[7] Several other limitations of this method have been discovered to date. For instance, α,β-unsaturated esters react to give mixtures of 1,2 reduction and fully saturated products. In addition, α-bromo esters and ω-cyano esters have not been successfully converted to the desired products.

We are at present unsure as to the nature of the active catalyst in this system. One possibility is that this is a simple Lewis acid-catalyzed hydrosilylation.[3a] However, we have determined that the conversion of ethyl decanoate to decanol is unaffected, in terms of either rate of formation or yield of product, by the addition of 20 equiv (relative to catalyst) of Lewis bases such as pyridine, THF, or PMe_3. A radical mechanism is unlikely since no rearrangement products are found in the reduction of a vinylcyclopropyl ester (Table I, entry 15).[8] An alternate scenario is that the active species in this system is an anionic pentavalent silicon hydride.[9] These species are also known to be electron donors toward organic halides, forming reductive coupling products. However, under our described conditions, ethyl 6-bromohexanoate is converted cleanly to the alcohol with no traces of reductive dimerization (Table I, entry 4). Also, in a control experiment where 1 equiv each of $Ti(O\text{-}i\text{-}Pr)_4$, $(EtO)_3SiH$, and benzyl bromide were combined, and the mixture was heated at 45 °C, no bibenzyl was detected after 2 days. Finally, our working hypothesis involves the initial formation of a titanium hydride species, as we believe occurs in the $Cp_2TiCl_2/2$ *n*-BuLi system. Yet we have found that carrying out the reduction procedure in the presence of 20 equiv of MeI has no effect on the rate or yield of the reaction.[10] A detailed mechanistic study of this intriguing new process is clearly necessary.

In summary, we have developed a new, air-stable catalyst system for the conversion of esters into primary alcohols. The experimental simplicity and mild reaction conditions of this procedure should make it useful to synthetic chemists. We are currently investigating the mechanism of this novel catalyst system and its action on other carbonyl groups and related functionality.

Acknowledgment. We thank the National Science Foundation (CHE-900482) for support of this work. S.L.B. acknowledges additional support as a Fellow of the A.P. Sloan Foundation and as a Camille & Henry Dreyfus Teacher–Scholar. We thank Dr. Alberto Gutiérrez and Dr. Kristina A. Kreutzer for helpful suggestions.

Supplementary Material Available: Detailed experimental procedures for the preparation of and spectroscopic characterization of the products given in Table I (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Why Are Isoxazoles Unreactive in Diels–Alder Reactions? An ab Initio Computational Study

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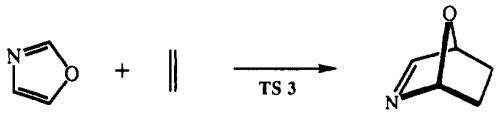
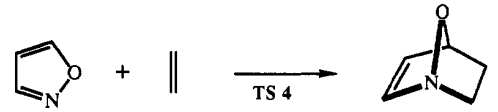
Summary: Ab initio calculations show why isoxazole Diels–Alder reactions have high activation energies and are generally not observed.

One of the most intriguing unsolved problems in heterocyclic chemistry is the different ability of oxazole and isoxazole rings to participate in Diels–Alder reactions. Diels–Alder reactions of oxazoles, **1**, have been widely exploited because of their synthetic versatility. Reactions with alkenes lead to pyridines, including Vitamin B_6, pyridoxine analogs, and condensed pyridines such as ellipticine,[1] while acetylenic dienophiles give furans.[1,2] Oxazoles also react readily with a variety of heterodienophiles.[3] Amazingly, however, there are no reports on Diels–Alder reactions of simple isoxazoles, **2**.[4]

We report here the results of a theoretical study of the Diels–Alder reactions of both oxazole and isoxazole, using ab initio molecular orbital theory. The geometries of the



1 **5**



2 **6**

reactants, oxazole, **1**, and isoxazole, **2**, the transition structures for the parent reactions of **1** and **2** with ethylene,

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[‡] Princeton University.
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EXHIBIT 22

J. Org. Chem. **1996**, *61*, 2713–2718

A Practical Titanium-Catalyzed Synthesis of Bicyclic Cyclopentenones and Allylic Amines

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Received September 26, 1995[⊗]

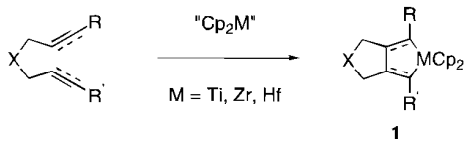
A practical titanium-catalyzed synthesis of bicyclic cyclopentenones and allylic amines is described. The process converts enyne substrates to iminocyclopentenes using 10 mol % of the air- and moisture-stable precatalyst Cp_2TiCl_2 in the presence of *n*-BuLi and triethylsilyl cyanide. The resulting iminocyclopentenes can be hydrolyzed to cyclopentenones in good yields or reduced to allylic silylamines with Red-Al or DIBALH. Treatment of the crude silylamines with acetyl chloride allows isolation of allylic amides in excellent yields.

In recent years, group IV metallocene-mediated reductive cyclizations of enynes,[1] diynes,[2] and dienes[3] have become an important methodology in organic synthesis (Scheme 1). The metallacycles formed (**1**) can be hydrolyzed, carbonylated, iminylated,[4] halogenated, and converted into a wide range of main group heterocycles[5] and highly substituted benzene derivatives.[6] These transformations have as a limitation their requirement for a stoichiometric quantity of metal.

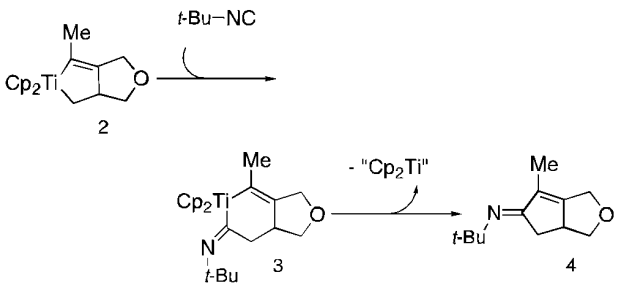
On the basis of the observation[4] that the product of the reaction of *tert*-butyl isocyanide with titanacycle **2** is converted to iminocyclopentene **4** with loss of "titanocene" (Scheme 2), the catalytic cycle in Scheme 3 was proposed. Initial efforts with *tert*-butyl isocyanide failed due to catalyst deactivation in the presence of excess isocyanide. This problem was overcome[7] by keeping the concentration of isocyanide low in solution with trialkylsilyl cyanides (R′ = Et_3Si, *t*-Bu$(Me)_2Si$),[8] which exist in equilibria with minor amounts of the isocyanides (99:1 for trimethylsilyl cyanide). Scheme 4 outlines the course of the catalytic procedure.[9]

Although this process, as the first early transition metal catalyzed cyclopentenone synthesis, represents an advance in methodology, there are a number of areas where improvements can be made. A major problem is

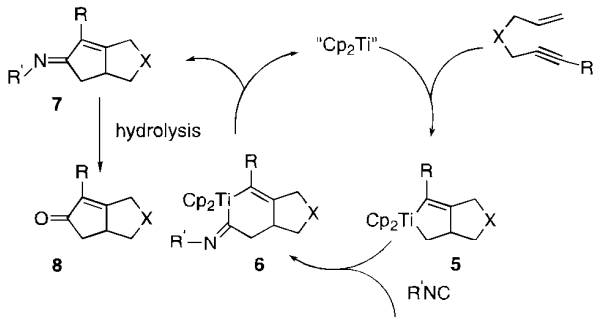
Scheme 1



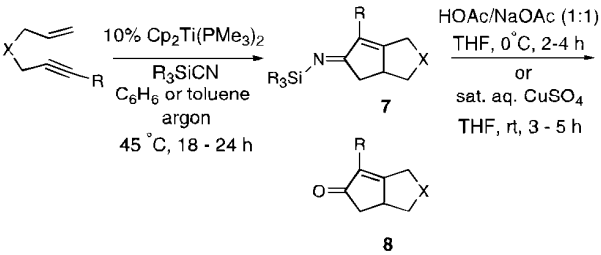
Scheme 2



Scheme 3



Scheme 4



that the precatalyst $Cp_2Ti(PMe_3)_2$[10] is extremely air- and moisture-sensitive and must be handled and stored in a

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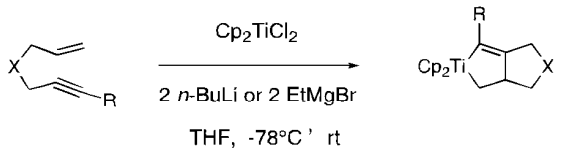
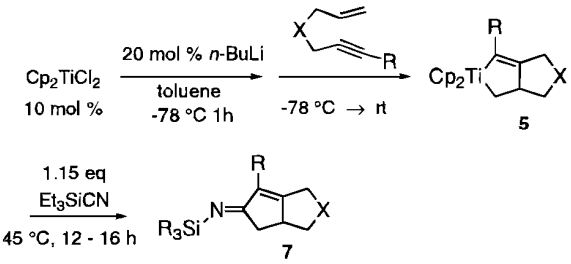
Scheme 5



Scheme 6



glovebox under argon. In addition, it would be advantageous to develop a catalyst system that did not require PMe_3 due to concerns about its stench and toxicity. A method to generate the catalytically active species *in situ* from Cp_2TiCl_2, which is air- and moisture-stable and inexpensive, would greatly increase the practicality of this methodology. The yields of cyclopentenones **8** (43–80%),[7] while comparable to related syntheses,[11] are disappointing considering that iminocyclopentene formation is quantitative (^{1}H NMR). This led to the search for alternative transformations that could give products in higher yields and exploit the silylimine functionality.

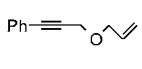
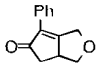
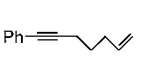
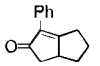
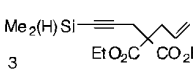
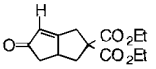
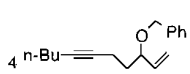
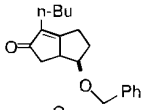
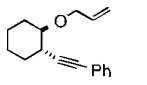
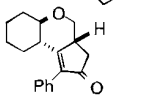
Titanacyclopentenes **5** are intermediates in the catalytic cycle depicted in Scheme 2. We have previously shown[4] that these metallacycles can be prepared from enynes by treatment with a mixture of Cp_2TiCl_2 and 2 equiv of EtMgBr or *n*-BuLi (Scheme 5). We decided, therefore, to see if the combination Cp_2TiCl_2/2 *n*-BuLi could serve as a catalyst in lieu of $Cp_2Ti(PMe_3)_2$.

Our initial attempts, employing THF as solvent, were unsuccessful. Although metallacycle formation was nearly quantitative (^{1}H NMR), the catalyst was rapidly decomposed under the reaction conditions. Attempts to run the reaction in the noncoordinating solvent toluene were hampered by the extremely low solubility of Cp_2TiCl_2. We found, however, that by using *n*-BuLi with finely ground Cp_2TiCl_2 in toluene (Scheme 6), the titanacycle **5** (X = O, R = Ph) was produced in 92% yield (^{1}H NMR) and was catalytically active at 10 mol %, the same level as with $Cp_2Ti(PMe_3)_2$.

To compare the two catalysts, a number of cyclopentenones were synthesized using the new system (Table 1). The yields indicate the processes employing Cp_2TiCl_2 and $Cp_2Ti(PMe_3)_2$ are equally effective. In addition, we found that a bicyclic enyne (Table 1, entry 5), using the new catalyst system, produces the tricyclic cyclopentenone in good yields.[12]

After developing the new *in situ* method of catalyst generation, we decided to explore other reactions of the silylimine intermediates. The chemistry of silylimines has developed rapidly in the past decade due in large part

Table 1. Comparison of Cyclopentenone Formation from Precatalysts $Cp_2Ti(PMe_3)_2$ and Cp_2TiCl_2

entry	starting material	product	$Cp_2Ti(PMe_3)_2$ yield (%)[a]	Cp_2TiCl_2 yield (%)
1			80	82
2			66	64
3			42	45
4			45 (12:1)	42 (12:1)
5			----	67[b]

[a] See Ref 7. [b] Only one diastereomer formed.

to the fact that the silyl group is easily removed from the products formed. Thus, silylimines serve as synthetic equivalents to unsubstituted imines. Hart initiated work in this area[13] by studying reductions of silylimines with $LiAlH_4$, addition reactions with alkyllithium and Grignard reagents, and condensations with ester enolates to form β-lactams.[14] The reactions of silylimines have since been expanded to include the synthesis of aziridines,[15] 1,2-amino alcohols,[16] and α-amino phosphonic acids.[17] Due to the importance of allylic amines[18] both as synthetic intermediates[19] and as biologically active compounds themselves,[20] we chose to explore hydride reductions of the silylimines produced by our methodology.[21]

After a range of reducing agents were surveyed, Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride) and DIBALH were found to give high yields of the corresponding silylamines **8** (Scheme 7). In the one reported example of silylimine reduction we are aware of, the amine which was isolated had been desilylated.[13] Since silyl groups can be utilized to protect amines, the development of reaction protocols which retain them is significant.[22] Although the crude silylamines could be utilized for further transformations, their isolation proved

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Scheme 7

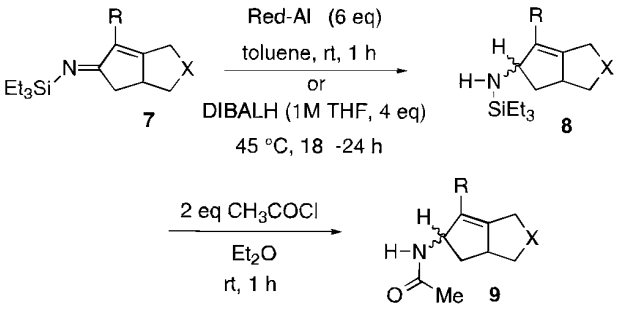
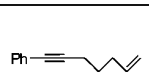
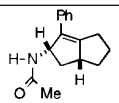
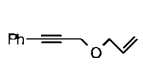
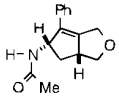
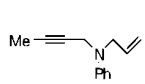
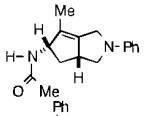
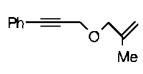
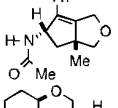
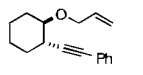
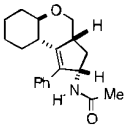
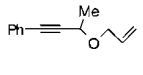
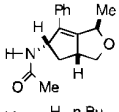
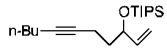
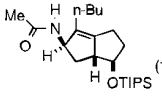
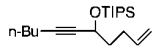
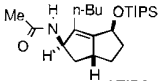
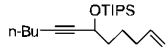
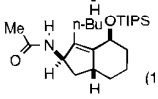


Table 2. Conversion of Enynes to Bicyclic Allylic Amides

entry	starting material	red. agent	product[a]	yield(%)	cyclopentenone yield (%)[d]
1		Red-Al		89	80
2		Red-Al		82	66
3		Red-Al		61	44
4		Red-Al		72[b]	58
5		Red-Al		72[c,e]	67
6		Red-Al		82	71 (5:1)
7		Red-Al		63[c] (1:1:3.5)	----
8		DIBAL		80[c] (4:1)	54 (1.6:1)
9		DIBAL		65[c] (16:16:2:1)	52

[a] Major diastereomer pictured. [b] Required 20 mol% catalyst for complete conversion. [c] Required 15 mol% catalyst for complete conversion. [d] See Ref 7. [e] Only diastereomer isolated.

difficult. Attempts to desilylate and isolate the free amines led to deamination and to complex mixtures of cyclopentadiene and allylic alcohol derivatives. For this reason, the silylamines were converted to amides **9** for their isolation.[23]

For most substrates (Table 2, entries 1−6), Red-Al reduction was completely diastereoselective. Reduction with DIBALH (substrate from Table 2, entry 1), however, produced a mixture of two diastereomers (3:2), with the same predominant product as from Red-Al reduction.[24]

The substrate with an allylic TIPS (triisopropylsilyl) ether (Table 2, entry 7) was reduced by Red-Al, but reaction occurred only slowly at elevated temperatures to give a mixture of three diastereomers.[25] With substrates containing propargylic TIPS ethers (Table 2, entries 8 and 9), reaction with Red-Al gave only low yields of products. However, DIBALH cleanly reduces the silylimines from entries 8 and 9 to give products in high yields with varying levels of diastereocontrol.

Acetylation of the reduction products with TIPS protecting groups required the addition of 4 equiv of NEt_3 to prevent decomposition. A substrate with an allylic benzyl ether (Table 1, entry 4) was cleanly reduced with Red-Al, but it decomposed upon attempted acetylation, even in the presence of NEt_3. Presumably, reaction of the benzyl group leads to decomposition, since the substrate with an allylic TIPS ether (Table 2, entry 8) was acetylated without problem. For all substrates, reduction and acetylation of the silylimines produces allylic amides in higher yields than hydrolysis to the corresponding cyclopentenones.

In conclusion, we have developed a practical, PMe_3-free catalytic system for synthesizing bicyclic iminocyclopentenes from the air- and moisture-stable precatalyst Cp_2TiCl_2. The yields of cyclopentenones from hydrolysis are the same as previously reported for the air- and moisture-sensitive precatalyst $Cp_2Ti(PMe_3)_2$. In addition, we have developed a reduction to give allylic amides in yields which are consistently higher than hydrolysis to the cyclopentenones. Future work will include the development both of intermolecular and asymmetric versions of these and related cyclizations.

Experimental Section

All reactions involving organometallic reagents were conducted under an atmosphere of purified argon using standard Schlenk techniques. All organic reactions were performed under an atmosphere of argon or nitrogen. Nuclear magnetic resonance (NMR) spectra were accumulated at 300 MHz. Toluene and tetrahydrofuran were dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl followed by distillation. Methylene chloride was dried by continuous refluxing over CaH_2 followed by distillation. Diethyl ether was used with no preparative drying. All enynes used for cyclization reactions, unless stated otherwise, were prepared as in Berk et al.[7] *trans*-1-(allyloxy)-2-(phenylethynyl)cyclohexane (Table 1, entry 5, and Table 2, entry 6) was prepared by ring opening of cyclohexene oxide with (phenylethynyl)lithium and $BF_3{\cdot}OEt_2$[26] followed by protection of the alcohol with allyl bromide.[27] Et_3SiCN was prepared by the procedure of Becu.[28] All other reagents were either prepared according to published procedures or were available from commercial sources and used without further purification. For all products, the stereochemistry at the ring carbon α to the acetamido group was assigned on the basis of the characteristic ^1H NMR shifts. For the *endo* acetamido groups, the amide NH peak occurs at around 7 ppm in $CDCl_3$. For the *exo* acetamido groups, the amide NH peak occurs at around 5.1 ppm in $CDCl_3$. NOE data

(23) Ojima, I.; Kogure, T.; Nagai, Y. *Tetrahedron Lett.* **1973**, 2475.

(24) The origins of the diastereoselectivites are unclear at the present time as the reduction of imines has received little mechanistic investigation.

(25) The cyclization reaction itself results in two diastereomers at the TIPS ether carbon (Table 2, entries 7−9). For diastereoselectivities of entries 8 and 9, see ref 7b (also contains discussion on origins of selectivities). NMR experiments have shown the selectivity for entry 7 to be 2.2:1 in favor of the *exo* TIPS ether.

(26) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

(27) Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1315.

(28) Becu, C.; Anteunis, M. J. O. *Bull. Soc. Chem. Belg.* **1987**, *96*, 115.

for one set of diastereomers from DIBALH reduction of an iminocyclopentene (Table 2, entry 5) were utilized to establish the relative stereochemistry. All other stereocenters on products were assigned by X-ray or NOE studies. Yields refer to isolated yields of compounds estimated to be >95% pure (unless otherwise noted) as determined by ^{1}H NMR and either capillary GC (known compounds) or combustion analysis (new compounds). Elemental analyses were performed by E + R Microanalytical Laboratory, Corona, NY.

General Procedure for the Conversion of Enynes to Iminocyclopentenes. A flame-dried Schlenk flask was attached to a Schlenk line and allowed to cool. Cp_2TiCl_2 (0.1 mmol, 26 mg) ground with a mortar and pestal and toluene (2−3 mL) were added to the flask, which was cooled to −78 °C. *n*-BuLi (80 μL of 2.5 M in hexanes) was added dropwise, with care to ensure that none of it touched the sides of the flask. After 1 h at −78 °C, the enyne (1.0 mmol) was added. The reaction mixture was stirred for another 1 h at −78 °C and was allowed to warm to rt over 1 h. After 3−5 h at rt, Et_3SiCN (1.15 mmol) was added. The flask was then heated overnight in an oil bath at 45−55 °C.

Conversion of Iminocyclopentenes to Allylic Silylamines. General Procedure A. The reaction was cooled to rt, and Red-Al (6 mmol equiv of "H", 840 μL) was added. After 1 h at rt, the reaction was quenched into 50 mL each of 5% NaOH and ether, and the aqueous layer was extracted with 2 × 50 mL of ether. The combined organic extracts were washed with brine and dried over $MgSO_4$, and the crude product mixture was concentrated to 15 mL.

General Procedure B. The reaction was cooled to rt, and DIBALH (4 mL of 1 M in THF) was added. After the reaction was heated to 50 °C overnight, it was quenched into 50 mL each of 5% NaOH and ether. The aqueous layer was extracted with 2 × 50 mL of ether, and the combined organic extracts were washed with brine and dried over $MgSO_4$. The crude product mixture was concentrated to 15 mL.

General Procedure for the Conversion of Silylamines to Amides. Acetyl chloride (2 mmol, 143 μL) was added to the crude silylamine. After 1 h at rt, the reaction was quenched with 50 mL each of 5% NaOH and ether. The aqueous layer was extracted with 2 × 50 mL of ether, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to produce the crude product.

3-((Triisopropylsilyl)oxy)-1-undecen-6-yne (Table 2, Entry 8). Undec-1-en-6-yn-3-ol[7] (30 mmol) was protected by the procedure of Corey.[29] The product was purified by flash chromatography (hexane) to yield 2.8 g (30%) of a pale yellow liquid. ^{1}H NMR (300MHz, $CDCl_3$): δ 5.76 (m, 1 H), 5.14 (m, 1 H), 5.03 (m, 1 H), 4.32 (quart, *J* = 3.0 Hz, 1 H), 2.15 (m, 4 H), 1.74 (m, 1 H), 1.64 (m, 1 H), 1.40 (m, 4 H), 1.04 (m, 21 H), 0.88 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1, 114.4, 80.4, 79.7, 73.0, 37.4, 31.2, 21.9, 18.4, 18.1, 14.3, 13.6, 12.4. IR (neat, cm^{-1}): 2943, 2866, 1464, 1382, 1093, 1067, 991, 922, 837, 681. Anal. Calcd for $C_{20}H_{38}OSi$: C, 74.46; H, 11.87. Found: C, 74.64; H, 12.03.

Tricyclic Cyclopentenone (Table 1, Entry 5). The silylimine from *trans*-1-(allyloxy)-2-(phenylethynyl)cyclohexane (240 mg, 1.0 mmol) was obtained using a modification of the general procedure with 0.15 mmol of Cp_2TiCl_2, 0.30 mmol of *n*-BuLi, and 5 mL of toluene. The toluene was removed from the Schlenk flask *in vacuo*, and the crude silylimine was cannula transferred with 30 mL of THF to a 250 mL Schlenk flask under argon. Three mL of saturated aqueous $CuSO_4$ was added dropwise followed by vigorous stirring of the mixture for 4 h at rt. The reaction mixture was extracted with 50 mL each of 0.5 N HCl and ether, and the aqueous layer was reextracted with 2 × 50 mL ether. The combined organic layers were washed with 0.5 N NaOH and brine and dried over $MgSO_4$ to afford the crude product. Purification by flash chromatography (ether:hexane = 4:1) afforded 180 mg (67%) of an off-white solid. Mp: 118−120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (m, 3 H), 7.01 (m, 2 H), 4.27 (dd, *J* = 6.2, 10.2 Hz, 1 H), 3.18 (t, *J* = 11.0 Hz, 1 H), 3.0 (m, 2 H), 2.50 (dd, *J* = 7.0, 18.6 Hz, 1 H), 2.31 (m, 1 H), 1.90 (m, 2 H), 1.62 (m, 1 H), 1.40 (m, 3 H), 1.06 (m, 2 H), 0.77 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 174.2, 138.7, 133.1, 129.9, 127.7, 127.6, 81.9, 73.6, 48.7, 41.0, 36.2, 33.2, 28.1, 25.6, 24.2. IR (KBr, cm^{-1}): 2920, 2858, 1692, 1643, 1443, 1108, 1092, 1003, 707. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.66; H, 7.72. The relative stereochemistry for the product was determined by X-ray crystallographic analysis.

3-Acetamido-2-phenylbicyclo[3.3.0]oct-1-ene (Table 2, Entry 1). 1-Phenyl-6-hepten-1-yne (170 mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure. The reduction was accomplished with procedure A. The crude amide was purified by filtering and washing several times with cold pentane to yield 195 mg (83%) of a white solid. Mp: 141−143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (t, *J* = 7.5 Hz, 3 H), 7.24 (d, *J* = 7.5 Hz, 2 H), 7.02 (s, 1 H), 3.46 (m, 1 H), 3.15 (dd, *J* = 9.6, 16.8 Hz, 1 H), 3.00 (m, 1 H), 2.72 (m, 1 H), 1.94 (s, 3 H), 1.78 (m, 1 H), 1.50 (m, 4 H), 1.33 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 136.4, 132.8, 128.9, 127.9, 126.8, 125.0, 50.6, 41.2, 38.2, 35.4, 31.5, 25.4, 24.1. IR (KBr, cm^{-1}): 3282, 2945, 2858, 1664, 1517, 1492, 1356, 1267, 764, 693. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.75; H, 8.15. If reduction was accomplished with procedure B, two diastereomers (3:2) were obtained. The two crude amides were separated and purified by flash chromatography (ethyl acetate:hexane = 1:1). The minor diastereomer was isolated as 70 mg (30%) of a white solid. Mp: 147−149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 3 H), 7.15 (m, 2 H), 5.80 (m, 1 H), 5.37 (m, 1 H), 3.20 (m, 3 H), 2.37 (m, 1 H), 2.13 (m, 1 H), 1.95 (m, 2 H), 1.86 (s, 3 H), 1.15 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 153.6, 135.8, 128.4, 128.3, 126.6, 126.1, 60.9, 50.8, 40.0, 32.3, 28.7, 25.5, 23.4. IR (KBr, cm^{-1}): 3307, 2956, 2859, 1644, 1538, 1497, 1443, 1372, 1303, 1152, 768, 693. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.50; H, 8.12.

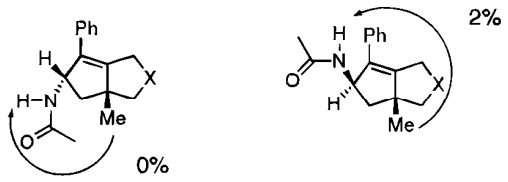
3-Acetamido-2-phenyl-7-oxabicyclo[3.3.0]oct-1-ene (Table 2, Entry 2). 3-(Allyloxy)-1-phenyl-1-propyne (170 mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure. The reduction was accomplished with procedure A. The crude amide was purified by filtration and washing several times with cold pentane to yield 215 mg (89%) of a white solid. Mp: 120−122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (t, *J* = 7.2 Hz, 3 H), 7.22 (d, *J* = 7.2 Hz, 2 H), 7.10 (s, 1 H), 3.87 (t, *J* = 8.1 Hz, 1 H), 3.64 (m, 3 H), 3.52 (m, 1 H), 3.18 (m, 2 H), 2.94 (m, 1 H), 1.94 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 135.6, 133.6, 129.1, 127.7, 127.1, 122.6, 75.7, 72.1, 51.8, 39.2, 39.0, 24.0. IR (KBr, cm^{-1}): 3292, 2963, 2833, 1665, 1515, 1490, 1366, 1268, 1088, 1044, 766, 693. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04. Found: C, 73.99; H, 7.05.

3-Acetamido-2-methyl-7-phenyl-7-azabicyclo[3.3.0]oct-1-ene (Table 2, Entry 3). *N*-(2-Butynyl)-*N*-allylaniline (247 mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure. The reduction was accomplished with procedure A. The product was purified by flash chromatography (ethyl acetate:hexane = 7:3) to afford 156 mg (61%) of a light orange solid. Mp: 174−176 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (t, *J* = 8.1 Hz, 2 H), 6.67 (t, *J* = 7.5 Hz, 1 H), 6.59 (d, *J* = 7.8 Hz, 2 H), 6.55 (s, 1 H), 3.46 (t, *J* = 9.0 Hz, 1 H), 3.28 (m, 3 H), 3.15 (m, 1 H), 3.00 (m, 2 H), 2.70 (d, *J* = 16.0 Hz, 1 H), 2.03 (s, 3 H), 1.60 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 148.4, 130.9, 129.1, 122.4, 116.5, 112.9, 55.7, 51.2, 50.8, 39.2, 37.9, 23.8, 11.8. IR (KBr, cm^{-1}): 3321, 2940, 1661, 1600, 1505, 1476, 1369, 1338, 1274, 1187, 746, 690. Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.76. Found: C, 74.79; H, 7.75.

3-Acetamido-5-methyl-2-phenyl-7-oxabicyclo[3.3.0]oct-1-ene (Table 2, Entry 4). 3-((2-Methyl-2-propenyl)oxy)-1-phenyl-1-propyne (372 mg, 2.0 mmol) was converted to the iminocyclopentene by the general procedure with the modification of 0.20 mmol of Cp_2TiCl_2, 0.40 mmol of *n*-BuLi, and 6 mL of toluene. The reduction was accomplished with procedure A. The product was purified by flash chromatography (ethyl acetate:hexane = 3:2) to give 370 mg (75%) of a white solid. Mp: 127−129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (t, *J* =

(29) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

7.3 Hz, 3 H), 7.21 (d, J = 7.0 Hz, 2 H), 7.11 (s, 1 H) 3.82 (dd, J = 7.2, 8.7 Hz, 1 H), 3.72 (d, J = 8.4 Hz, 1 H), 3.51 (d, J = 8.7 Hz, 2 H), 3.33 (d, J = 17.7 Hz, 1 H), 3.14 (m, 1 H), 2.93 (d, J = 17.7 Hz, 1 H), 1.96 (s, 3 H), 1.30 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 135.1, 132.1, 128.5, 127.2, 126.6, 121.9, 80.5, 72.0, 58.2, 46.6, 45.6, 24.8, 23.5. IR (KBr, cm^{-1}): 3233, 2959, 2846, 1662, 1638, 1520, 1496, 1352, 1274, 1062, 922, 768, 695. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 74.65; H, 7.44. To determine the relative stereochemistry at the ring carbon α to the acetamido group, the iminocyclopentene was also reduced by procedure B to yield a mixture of two diastereomers (3:2). The major diastereomer was the same one obtained exclusively with procedure A. A nuclear Overhauser enhancement study was undertaken to determine the relative configuration of each diastereomer. Irradiation of the C-5 methyl group at δ 1.4 (C_6D_6) of the major diastereomer gave no enhancement of the amide NH at δ 6.85, while the same experiment produced a 2% enhancement in the minor diastereomer. The stereochemistry for the two diastereomers was therefore assigned as shown:



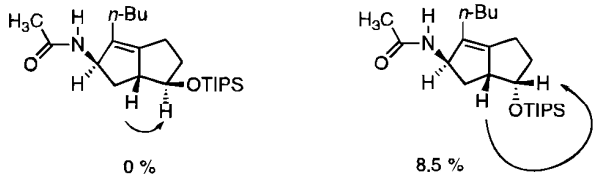
Red-Al product
major DIBALH product

minor DIBALH product

Table 2, Entry 5. *trans*-1-(Allyloxy)-2-(phenylethynyl)-cyclohexane (240 mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure with the modification of 0.15 mmol of Cp_2TiCl_2, 0.30 mmol of *n*- BuLi, and 5 mL of toluene. The reduction was effected by procedure A with the modification that the reaction was heated for 2 h at 50 °C. The product was purified by flash chromatography (ether:hexane = 9:1) to give 224 mg (72%) of a pale orange solid. The product exists as approximately a 3:2 mixture of amide rotamers by NMR. Although the product is unstable at room temperature for extended periods, it can be stored in the freezer with little decomposition. Mp: 50−53 °C. It proved difficult to assign ^{1}H peaks to the individual rotamers, so a list of peaks without assignments or integrations is given. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.26 (m), 7.12 (d), 6.64 (s), 6.18 (s), 5.92 (s), 4.00 (dd), 3.81 (m), 3.50 (t), 3.28 (m), 3.13 (m), 2.89 (m), 2.77 (m), 2.68 (m), 1.94 (m), 1.85 (s), 1.81 (s), 1.71−0.87 (m), 0.35 (m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 167.6, 141.7, 138.7, 137.7, 136.4, 129.2, 128.9, 128.5, 127.5, 127.2, 122.9, 112.8, 77.5, 77.1, 70.8, 68.0, 50.6, 48.3, 47.5, 44.0, 43.0, 42.5, 36.2, 34.6, 33.0, 32.6, 30.6, 26.6, 26.2, 24.9, 24.6, 24.2, 24.0. Ir (neat, cm^{-1}): 3288, 2932, 2857, 1682, 1514, 1450, 1367, 1260, 1100, 1012, 867, 751, 700. The relative stereochemistry of the tricyclic ring system was assigned based upon analogy to the related tricyclic ketone (Table 1, entry 5).

3-Acetamido-8-methyl-2-phenyl-7-oxabicyclo[3.3.0]oct-1-ene (Table 2, Entry 6). 3-(Allyloxy)-1-phenyl-1-butyne (186 mg, 1 mmol) was converted to the iminocyclopentene by the general procedure. The reduction was accomplished with procedure A. The product was purified by flash chromatography (ethyl acetate:hexane = 4:1) to give 210 mg (82%) of a 95:5 mixture of diastereomers as a white solid. Recrystallization from ether yields 185 mg (73%) of a single diastereomer as a white solid. Mp: 118−120 °C. ^{1}H NMR (300 MHz, $CDCL_3$): δ 7.40 (t, J = 7.2 Hz, 3 H), 7.25 (m, 2 H), 7.05 (s, 1 H), 4.18 (t, J = 7.8 Hz, 1 H), 3.60 (quin, J = 5.5 Hz, 1 H), 3.43 (t, J = 8.4 Hz, 1 H), 3.26 (m, 1 H), 3.06 (m, 3 H), 1.96 (s, 3 H), 1.11 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.9, 135.4, 132.8, 129.2, 127.8, 127.3, 122.4, 80.3, 74.2, 58.6, 39.9, 38.9, 24.2, 21.0. IR (KBr, cm^{-1}): 3296, 2966, 2849, 1665, 1516, 1493, 1355, 1254, 1056, 758, 696. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 74.51; H, 7.51.

3-Acetamido-2-butyl-6-((triisopropylsilyl)oxy)bicyclo[3.3.0]oct-1-ene (Table 2, Entry 7). 3-((Triisopropylsilyl)-oxy)-1-undecen-6-yne (324mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure with the modification of 0.15 mmol of Cp_2TiCl_2, 0.30 mmol of *n*-BuLi, and 5 mL of toluene. The reduction was accomplished by procedure A with the modification of heating the reaction overnight at 50 °C. To prevent product decomposition, the acetylation was carried out by the general procedure with the addition of 4 equiv of NEt_3. The product was purified by flash chromatography (ether:hexane = 3:2) to afford 236 mg (63%) of a mixture of three diastereomers (1:1:3.5) as a light yellow oil. A second chromatography allowed the first diastereomer to be isolated as a light yellow solid, but the other two diastereomers could not be separated. First diastereomer. Mp: 88−90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.23 (m, 2 H), 4.14 (t, J = 3.2 Hz, 1 H), 2.66 (m, 1 H), 2.25 (m, 2 H), 2.03 (m, 4 H), 1.95 (s, 3 H), 1.42 (m, 3 H), 1.28 (m, 3 H), 1.03 (m, 21 H), 0.85 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 146.0, 131.2, 71.1, 61.1, 54.8, 38.3, 30.2, 25.9, 23.6, 22.6, 20.9, 18.2, 18.1, 13.9, 12.4. IR (KBr, cm^{-1}): 3252, 3068, 2956, 2865, 1639, 1557, 1463, 1376, 1297, 1152, 1063, 1012, 882, 803, 682. Anal. Calcd for $C_{23}H_{43}NO_2Si$: C, 70.17; H, 11.01. Found: C, 70.32; H, 10.99. To determine the relative stereochemistry of the OTIPS group for the major diastereomeric product from Table 2, entry 7, an NOE study was undertaken. Irradiation of the C-5 proton at δ 3.83 (C_6D_6) of the major diastereomer gave no enhancement of the C-6 proton at δ 2.70, while the same experiment produced an 8.5% enhancement in the first minor diastereomer. The stereochemistry for the two diastereomers was therefore assigned as shown:



Major Diastereomer

Minor Diastereomer

3-Acetamido-2-butyl-8-((triisopropylsilyl)oxy)bicyclo[3.3.0]oct-1-ene (Table 2, Entry 8). 5-((Triisopropylsilyl)-oxy)-1-undecen-6-yne (324 mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure with the modification of 0.15 mmol of Cp_2TiCl_2, 0.30 mmol of *n*-BuLi, and 5 mL of toluene. The reduction was accomplished with procedure B, and acetylation was carried out by the general procedure with the addition of 4 equiv of NEt_3. The product was purified by flash chromatography (ether:hexane = 3:2) to afford 300 mg (80%) of a 4:1 mixture of diastereomers as a light yellow oil. A pure sample of the major diastereomer was obtained by a second chromatography. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 (quart, J = 9 Hz, 1 H), 4.8 (s, 1 H), 4.56 (d, J = 9 Hz, 1 H), 2.87 (m, 1 H), 2.43 (m, 1 H), 2.22 (m, 1 H), 1.97 (m, 4 H), 1.75 (m, 1 H), 1.57 (s, 3 H), 1.40 (m, 4 H), 1.14 (m, 21 H), 0.95 (t, J = 7.0 Hz, 3 H), 0.75 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.0, 148.8, 133.9, 68.2, 60.0, 44.4, 41.9, 38.8, 30.5, 29.8, 28.4, 23.4, 23.1, 18.1, 13.8, 12.5. IR (neat, cm^{-1}): 3275, 2956, 2865, 1650, 1556, 1464, 1373, 1296, 1052, 883, 681. Anal. Calcd for $C_{23}H_{43}NO_2Si$: C, 70.17; H, 11.01. Found: C, 70.29; H, 11.10. The stereochemistry of the TIPS ether was assigned on the basis of NOE studies on the corresponding cyclopentenone.[7]

3-Acetamido-2-butyl-9-((triisopropylsilyl)oxy)bicyclo[3.4.0]non-1-ene (Table 2, Entry 9). 6-((Triisopropylsilyl)-oxy)-1-dodecen-7-yne (336 mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure with the modification of 0.15 mmol of Cp_2TiCl_2, 0.30 mmol *n*-BuLi, and 5 mL of toluene. In addition, the reaction time at rt was increased to overnight. The reduction was affected by procedure B, while acetylation was carried out by the general procedure with the addition of 4 equiv of NEt_3. The product was purified by flash chromatography (ether:hexane = 7:3) to give 253 mg (65%) of a mixture of four diastereomers (16:16:2:1) as a yellow oil. The

first diastereomer was isolated by a second chromatography as a light yellow solid. First diastereomer. Mp: 74−76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.20 (d, J = 9 Hz, 1 H), 4.92 (m, 1 H), 4.62 (t, J = 2.8 Hz, 1 H), 2.8 (m, 1 H), 2.05 (m, 1 H), 1.9 (s, 3 H), 1.82 (m, 6H), 1.77 (m, 1 H), 1.39 (m, 1 H), 1.20 (m, 4 H), 0.99 (m, 21 H), 0.83 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.2, 144.6, 132.3, 64.8, 55.8, 40.4, 37.9, 36.3, 35.7, 30.0, 24.9, 23.5, 22.4, 19.9, 18.1, 13.8, 12.3. IR (neat, cm^{-1}): 3273, 2932, 2864, 1644, 1556, 1463, 1372, 1078, 1031, 883, 785, 680. Anal. Calcd for $C_{24}H_{45}NO_2Si$: C, 70.70; H, 11.13. Found: C, 70.98; H, 11.12. The stereochemistry of the TIPS ether was assigned on the basis of NOE studies on the corresponding cyclopentenone.[7]

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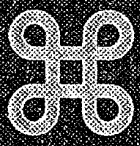

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alkyl. A paraffinic hydrocarbon group which may be derived from an alkane by dropping one hydrogen from the formula. Examples are methyl CH_3^+, ethyl $C_2H_5^+$, propyl $CH_3CH_2CH_2^+$, isopropyl $(CH_3)_2CH_3^+$. Such groups are often represented in formulas by the letter R and have the generic formula C_nH_{2n+1}.
See aryl.

alkylaryl polyethyleneglycol ether.
Use: In surface-active agents.
See isooctylphenoxypolyoxyethylene ethanol for a typical example of this class of compound.

alkylaryl sulfonate. An organic sulfonate of combined aliphatic and aromatic structure, e.g., alkylbenzene sulfonate.

alkylate. (1) A product of alkylation. (2) A term used in the petroleum industry to designate a branched-chain paraffin derived from an isoparaffin and an olefin, e.g., isobutane reacts with ethylene (with catalyst) to form 2,2-dimethylbutane (neohexane). The product is used as a high-octane blending component of aviation and civilian gasolines. (3) In the detergent industry, the term is applied to the reaction product of benzene or its homologs with a long-chain olefin to form an intermediate, e.g., dodecylbenzene, used in the manufacture of detergents. It also designates a product made from a long-chain normal paraffin that is chlorinated to permit combination with benzene to yield a biodegradable alkylate. The adjectives *hard* and *soft* applied to detergents refer to their ease of decomposition by microorganisms.
See biodegradability; detergent.

alkylation. (1) The introduction of an alkyl radical into an organic molecule. This was one of the early chemical processes used in Germany to furnish intermediates for improved dyes, e.g., dimethylaniline. Other alkylation products are cumene, dodecylbenzene, ethylbenzene, and nonylphenol. (2) A process whereby a high-octane blending component for gasolines is derived from catalytic combination of an isoparaffin and an olefin.
See alkylate (2); neohexane.

alkylbenzene sulfonate. (ABS). A branched-chain sulfonate type of synthetic detergent, usually a dodecylbenzene or tridecylbenzene sulfonate. Such compounds are known as "hard" detergents because of their resistance to breakdown by microorganisms. They are being replaced by linear sulfonates.
See alkyl sulfonate; linear molecule; detergent; sodium dodecylbenzene sulfonate.

alkyl diaryl phosphate ester. See "Santicizer 141" *[Solutia]*.

alkyldimethylbenzylammonium chloride. General name for a quaternary detergent.
See benzalkonium chloride.

alkylene. A phosphated long-chain alcohol.

alkyl fluorophosphate. See diisopropyl fluorophosphate.

alkylolamine. See alkanolamine.

alkyl sulfonate. (linear alkylate sulfonate; LAS). A straight-chain alkylbenzene sulfonate, a detergent specially tailored for biodegradability. The linear alkylates may be normal or iso (branched at the end only), but are C_{10} or longer.
See sodium dodecylbenzene sulfonate.

alkyne. See acetylene hydrocarbon.

Allan-Robinson reaction. Preparation of flavones or isoflavones by condensing *o*-hydroxyaryl ketones with anhydrides of aromatic acids and their sodium salts.

allantoin. (glyoxyldiureide; 5-ureidohydantoin). $C_4H_6N_4O_3$. The end product of purine metabolism in mammals other than humans and other primates; it results from the oxidation of uric acid.
Properties: White to colorless powder or crystals; odorless; tasteless. Mp 230C (decomposes). 1 g is soluble in 190 cc water or 500 cc alcohol; readily soluble in alkalies. Optically active forms are known.
Derivation: Produced by oxidation of uric acid. Also present in tobacco seeds, sugar beets, wheat sprouts.
Use: Biochemical research, medicine.

allele. One of two or more types of genes that may occur at a given position on a strand of DNA.

allelopathic chemical. Any of a wide range of natural herbicides of varying toxicity produced by many species of plants, as well as by soil microorganisms (bacteria, fungi). These compounds adversely affect other plants in the vicinity, either inhibiting germination and growth or killing them outright. They are extracted from the growing plant by leaching of its leaves, root exudates, and decomposition of dead tissue. Examples of plants found to be sources of these toxic compounds are sunflowers, oats, and soybeans. Among the products that have been identified are amygdalin, caffeine, gallic acid, and arbutin. Many types of chemical structure are represented. Research is directed toward breeding and cultivation of allelopathic plants to utilize their weed-killing ability.

allene. (propadiene; dimethylenemethane). $H_2C{:}C{:}CH_2$.
Properties: Colorless gas. Unstable. Fp −136.5C, bp 34.5C. Can be readily liquefied.

ability of a catalyst to discriminate among molecules on the basis of their shapes is of great value in the cracking of straight-chain hydrocarbons and has attractive possibilities in other types of catalytic reactions.
See zeolite; cage zeolite.

catalyst, stereospecific. An organometallic catalyst that permits control of the molecular geometry of polymeric molecules. Examples are Ziegler and Natta catalysts derived from a transition metal halide and a metal alkyl or similar substances. There are many patented catalysts of this general type, most of them developed in connection with the production of polypropylene, polyethylene, or other polyolefins.
See polymer, stereospecific; Natta catalyst; Ziegler catalyst.

catalyst, thermonuclear. See carbon cycle (2).

cataphoresis. The migration of colloidal particles toward an electrode under the influence of an electric current.

catechol. See pyrocatechol.

catecholborane. (1,3,2-benzodioxaborole). A monofunctional hydroborating agent.
Properties: A liquid. Mw 119.92, mp 12C, bp 50C (50 mm Hg), optical rotation 1.5070 degrees (20C).
Use: Preparation of alkaneboronic acid and esters from olefins.

catenane. A compound with interlocking rings that are not chemically bonded but that cannot be separated without breaking at least one valence bond. The model would resemble the links of a chain.

catenyl. An ester that has been reacted with an alkylene oxide or its polymer.

"Cat-Floc" *[Nalco].* (diallyldimethylammonium chloride). TM for a quaternary ammonium polymer.
Derivation: Monomer in water solution is mixed with a catalytic amount of butylhydroperoxide and kept at 50–75C for 48 h. The solid formed is taken up in water, precipitated, and washed with acetone.
Use: Flocculating agent, textile spinning aid, antistatic agent, wet-strength improvers in paper, rubber accelerators, curing epoxy resins, surfactants, bacteriostatic and fungistatic agents.

catharometer. Device for determining rate of flow or change in composition of gases.

cathetometer. A device for exact measurement or observation of short vertical distances, which consists of a horizontal-reading telescope or microscope movable along a vertical scale.

cathode. The negative electrode of an electrolytic cell, to which positively charged ions migrate when a current is passed as in electroplating baths. The cathode is the source of free electrons (cathode rays) in a vacuum tube. In a primary cell (battery), the cathode is the positive electrode.
See anode; electrode.

cathode sputtering. See sputtered coating.

cathodic protection. The reduction or prevention of corrosion of a metallic surface by making it cathodic, e.g. by the use of sacrificial anodes for impressed currents bringing a metal, by an external current, to a potential where it is thermodynamically stable.

catholyte. The solution surrounding the cathode in an electrolytic cell.

cation. An ion having a positive charge. Cations in a liquid subjected to electric potential collect at the negative pole, or cathode.

cation exchange. See ion exchange.

cationic reagent. One of several surface-active substances in which the active constituent is the positive ion. Used to flocculate and collect minerals that are not flocculated by oleic acid or soaps (in which the surface-active ingredient is the negative ion). Reagents used are chiefly quaternary ammonium compounds, e.g., cetyltrimethylammonium bromide.

catlinite. (pipestone). A fine-grained silicate mineral related to pyrophyllite, which is easily compressible, has high surface friction, and is used for gaskets in very high-pressure equipment.

caulking compound. See sealant.

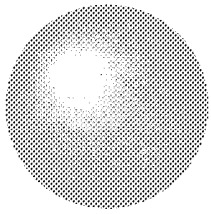
caustic. (1) Unqualified, this term usually refers to caustic soda (NaOH). (2) As an adjective, it refers to any compound chemically similar to NaOH, e.g., caustic alcohol (C_2H_5ONa). (3) Any strongly alkaline material that has a corrosive or irritating effect on living tissue.

caustic baryta. See barium hydroxide.

caustic embrittlement. The corrosion resulting in cracking of steel stressed beyond its yield point, due to localized concentration of hydroxide ions breaking down the cohesion between the ferrite grains.

causticized ash. Combinations of soda ash and caustic soda in definite proportions and marketed for

EXHIBIT 24



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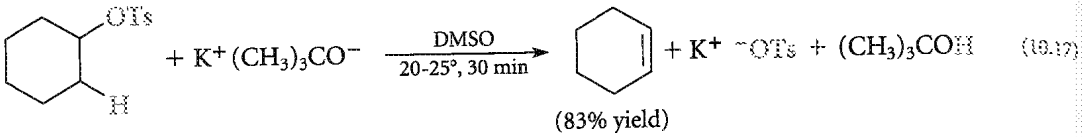
The E2 reactions of sulfonate esters, like the analogous reactions of alkyl halides, can be used to prepare alkenes:

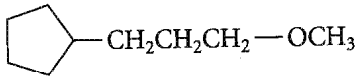


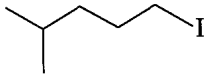
This reaction is especially useful for cases in which the acidic conditions of alcohol dehydration lead to rearrangements or other side reactions, or for primary alcohols in which dehydration is not an option.

To summarize: An alcohol can be made to undergo substitution and elimination reactions typical of the corresponding alkyl halides by converting it into a sulfonate ester.

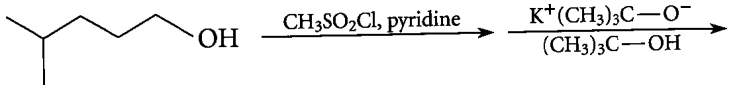
Problems

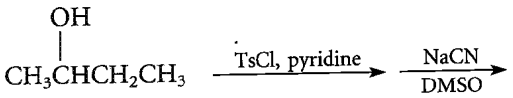
10.10 Design a preparation of each of the following compounds from an alcohol using sulfonate ester methodology.

*(a) 

(b) 

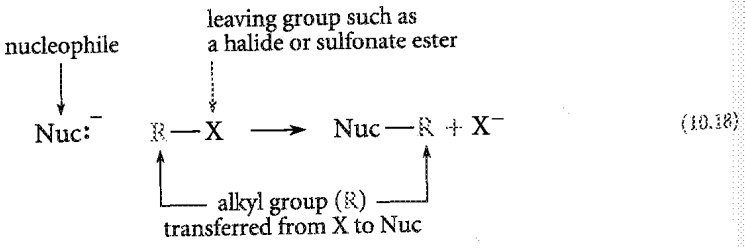
10.11 Give the product of each of the following sequences of reactions.

*(a) 

(b) 

B. Alkylating Agents

As you've learned, alkyl halides, alkyl tosylates, and other sulfonate esters are reactive in nucleophilic substitution reactions. In a nucleophilic substitution, an alkyl group is transferred from the leaving group to the nucleophile.

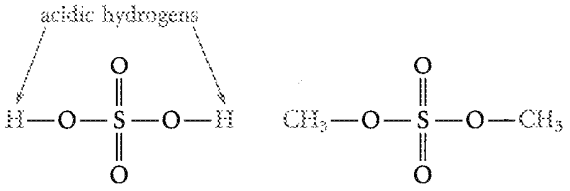


The nucleophile is said to be **alkylated** by the alkyl halide or the sulfonate ester in the same sense that a Brønsted base is *protonated* by a strong acid. For this reason, alkyl

halides, sulfonate esters, and related compounds are sometimes referred to as **alkylating agents.** To say that a compound is a *good alkylating agent* usually means that it reacts rapidly with nucleophiles in substitution reactions—that is, in S_N2 and S_N1 reactions.

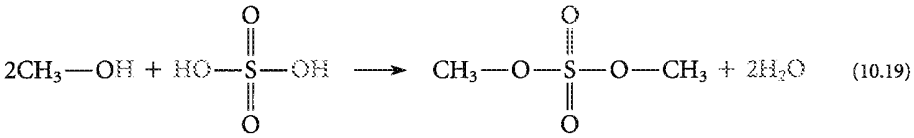
C. Ester Derivatives of Strong Inorganic Acids

Esters of strong inorganic acids are well known compounds. The structure of such an ester is derived conceptually by replacing the acidic hydrogen(s) of a strong acid with alkyl or aryl group(s). For example, dimethyl sulfate is an ester in which the acidic hydrogens of sulfuric acid are replaced by methyl groups.



sulfuric acid dimethyl sulfate

Because dimethyl sulfate can be prepared from methanol, it can also be viewed as a methanol derivative.



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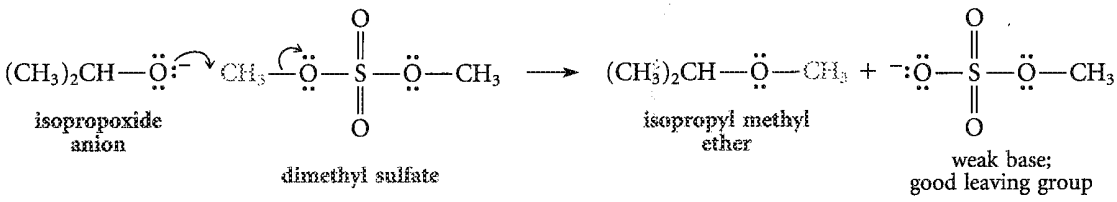
Alkyl esters of strong inorganic acids are typically very potent alkylating agents, because they contain leaving groups that are very weak bases. For example, dimethyl sulfate is a very effective methylating agent, as shown in the following example.



(10.20)

Dimethyl sulfate and diethyl sulfate are available commercially. These reagents, like other reactive alkylating agents, are toxic because they react with nucleophilic functional groups on proteins and nucleic acids.

Certain monoalkyl esters of phosphoric acid are utilized in nature as alkylating agents (Sec. 17.6B). DNA and RNA themselves are polymerized dialkyl esters of phosphoric acid (Sec. 27.11B).

Along the same line, alkyl halides can be thought of as alkyl esters of the halogen acids. Methyl bromide, for example, is conceptually derived by replacing the acidic hydrogen of HBr with a methyl group. As you have learned, this "ester" is an effective alkylating agent.