above was treated with 0.5 N NaOH solution (80 mL) and extracted with three 50-mL portions of chloroform. The combined chloroform layer was washed with water (100 mL) and dried over Na_2SO_4. Evaporation of the solvent gave (*S*)-(−)-**5** (1.11 g, 36% based on the initially used (*S*)-(−)-**5**), mp 225–232 °C, $[\alpha]^{24}_D$ −107° (*c* 1.1, chloroform). (*S*)-(−)-**5**: ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 6 CH_3), 1.37 (s, 6 CH_3), 6.50 (d, 2 H, *J* = 7.9 Hz), 6.92 (t, 2 H, *J* = 7.0 Hz), 6.96–7.03 (m, 4 H), 7.06–7.14 (dd, 4 H, *J* = 7.6 and 12.5 Hz), 7.33–7.40 (m, 2 H), 7.44–7.53 (dd, 2 H, *J* = 8.6 and 13.1 Hz), 7.61–7.67 (m, 4 H), 7.75–7.84 (m, 6 H), 7.97 (d, 2 H, *J* = 7.0 Hz); ^{31}P NMR ($CDCl_3$) 29.5 ppm; IR (KBr) ν 3050 (m), 2950 (s), 2900 (m), 2870 (m), 1598 (m), 1553 (w), 1502 (m), 1462 (m), 1392 (m), 1363 (m), 1302 (w), 1265 (m), 1195 (s), 1133 (m), 1112 (w), 1018 (w), 869 (w), 815 (m), 810 (m), 751 (s), 740 (m), 693 (w), 683 (w), 650 (m), 607 (s), 581 (w), 568 (w), 557 (m), 522 (m), 489 (m) cm^{-1}; UV (ethanol) λ_{max} 233 (ε 130 000), 273 (sh, 12 000), 287 (12 000), 300 (sh, 10 000), 316 (sh, 3600), 332 (3500) nm.

The purification of the antipode (*R*)-(+)-**5**, which went to the mother liquor of recrystallization of the (*S*)-(−)-**5**–(−)-**7** complex was not carried out.

Reduction of (*S*)-(−)-5 into 2,2′-Bis[bis(*p*-*tert*-butylphenyl)phosphinyl]-1,1′-binaphthyl [*p*-*tert*-BuC$_6$H$_4$BINAP] [(*S*)-(−)-9]. To a mixture of (*S*)-(−)-**5** (1.50 g, 1.71 mmol) and triethylamine (1.65 mL, 1.20 g, 11.9 mmol) in xylene (25 mL) was added dropwise a solution of trichlorosilane (1.40 g, 10.3 mmol) in xylene (5 mL) at 20 °C. After the addition was completed, the mixture was heated with stirring at 100–110 °C for 3 h. Workup as described above gave 0.75 g (52%) of (*S*)-(−)-**9**, mp 263–265 °C, $[\alpha]^{24}_D$ −83° (*c* 1.0, benzene). (*S*)-(−)-**9**: ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 6 CH_3), 1.26 (s, 6 CH_3), 6.65 (d, 2 H, *J* = 8.5 Hz), 6.74 (t, with fine splitting, 2 H, *J* = 7.6 Hz), 6.92–6.98 (m, 4 H), 7.06 (d, 4 H, *J* = 7.9 Hz), 7.08–7.16 (m, 4 H), 7.20–7.32 (m, 6 H), 7.47 (d, with fine splitting, 2 H, *J* = 7.0 Hz), 7.78 (d, 2 H, *J* = 8.2 Hz), 7.87 (d, 2 H, *J* = 8.2 Hz); ^{31}P NMR ($CDCl_3$) −16.4 ppm; IR (KBr) ν 3050 (w), 2950 (s), 2895 (w), 2860 (w), 1596 (w), 1551 (w), 1495 (m), 1461 (m), 1392 (m), 1361 (m), 1307 (w), 1264 (s), 1200 (w), 1082 (s), 1015 (s), 946 (w), 865 (w), 825 (s), 815 (s), 776 (w), 745 (s), 697 (w), 645 (w), 581 (w), 556 (m), 515 (w), 456 (w), cm^{-1}; LRMS (70 eV), *m*/*z* (% intensity) 846 (M^+, 0.14), 552 (11), 551 (48), 550 (100), 549 (M^+ − (C_4H_9–C_6H_4)$_2$P, 1.3), 298 ((C_4H_9–C_6H_4)$_2$P, 2.3); HRMS (70 eV), *m*/*z* 846.4464, calcd for $C_{60}H_{64}P_2$ 846.4482. UV (ethanol) λ_{max} 221 (ε 125 000), 237 (sh, 100 000) nm. Anal. Calcd for $C_{60}H_{64}P_2$: C, 85.07; H, 7.62. Found: C, 84.95; H, 8.03.

X-ray Analysis of the Complex of (*S*)-(−)-3, (1*R*)-(−)-6, and Acetic Acid. Crystal data for the title complex are given in Table I. Single crystals were grown from a solution of the complex (0.25 g, 0.38 mmol) in a mixture of ethyl acetate (8.5 mL) and acetic acid (0.1 mL). A suitable crystal was sealed in a thin-walled glass capillary. Diffraction data were collected with graphite-monochromated Cu Kα radiation. Fifty accurately centered reflections in the range 40°<2θ<60° were used for determination and least-squares refinement of the unit cell parameters. A total of 8589 reflections were collected and 7842 reflections had $|F_o| > 3\sigma(F_o)$, in which 5062 are independent. Three standard reflections, measured after every 50 reflections, showed neither indication of any misalignment nor deterioration of the crystal. The intensities were empirically corrected for Lorents and polarization factors and used in the structure determination. The structure solution by the use of the direct method (MULTAN 78 program) for 5062 reflections revealed positions for 48 non-hydrogen atoms, containing two phosphorus atoms. Three cycles of blockdiagonal least-squares refinement converged to $R = 0.27$ and $R_w = 0.34$. The remaining non-hydrogen atoms and hydrogen atoms were located after carrying out a series of blockdiagonal least-squares refinement and Fourier and difference Fourier syntheses. Total 123 atoms were refined by use of anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms. Least-squares refinement based on 7842 observed reflections led to a final $R = 5.96\%$ and $R_w = 7.08\%$. The bond parameters in crystal solvent ethyl acetate have fairly large estimated standard deviations as is often observed for solvate molecules. Ten hydrogen atoms were not located from final difference Fourier maps. Selected bond lengths and angles appear in Table II. Coordinates and thermal parameters for 123 atoms, observed and calculated structure factor amplitudes, all bond lengths and angles, and best planes (14 pages) are included as supplementary material.

Acknowledgment. We thank Dr. C. Katayama, Nagoya University, for valuable contribution in X-ray crystal structure analysis. We gratefully acknowledge financial support from the Ministry of Education, Science, and Culture, Japan (No. 59540331 and 60219012).

Supplementary Material Available: Lists of atomic coordinates, thermal parameters, bond distances, bond angles, and best planes (14 pages). Ordering information is given on any current masthead page.

Approach to the Total Synthesis of Chlorothricolide: Synthesis of (±)-19,20-Dihydro-24-*O*-methylchlorothricolide, Methyl Ester, Ethyl Carbonate†[1]

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Received September 3, 1985

An approach to the total synthesis of the macrolide antibiotic aglycone chlorothricolide (**1b**) is presented. Herein is described the synthesis of the advanced intermediate (±)-19,20-dihydro-24-*O*-methylchlorothricolide, methyl ester, ethyl carbonate (**34**) from the "bottom half" acid **4** and the "top half" alcohol **3** by the sequence esterification, macrolactonization, ester enolate Claisen rearrangement, and decarboxylation.

Chlorothricin (**1a**), one of some 500 known macrolide antibiotics,[3] was isolated in 1969 by W. Keller-Schierlein.[4] Active against gram-positive bacteria, it functions as a noncompetitive inhibitor of pyruvate carboxylase.[5] The aglycone chlorothricolide methyl ester (**1b**) has been the subject of intense study by many synthetic chemists in recent years.[6] In previous reports[6a,b] from this group, a convergent synthetic strategy was presented for the construction of chlorothricolide (**1b**). Central to the proposal was the joining of two nearly equal halves along the C12–

† Contribution No. 7249.

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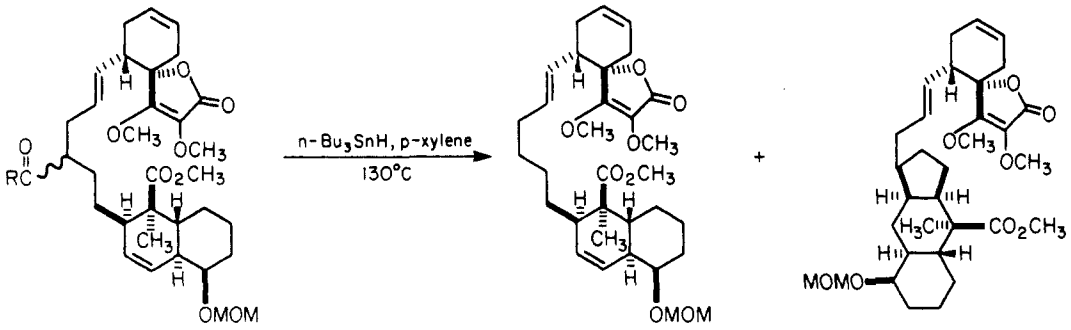
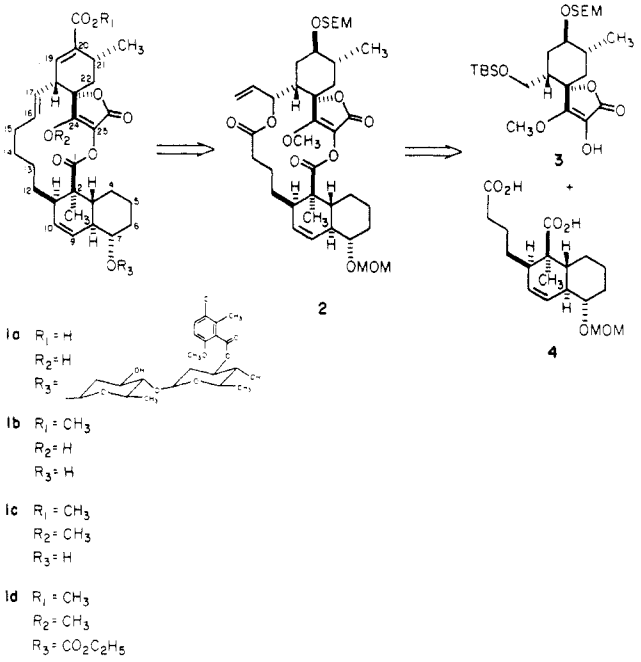
(2) Atlantic Richfield Foundation Research Fellow, 1984.

Chart I.[9] Attempted Decarboxylation of the Seleno Ester 5b



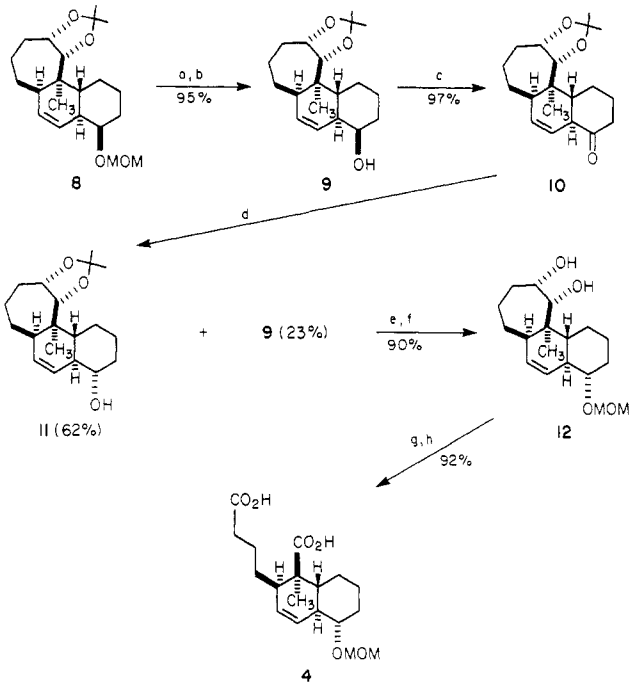
Scheme I



C17 side chain followed finally by lactone formation. An equally convergent, but alternate, approach to this macrocycle is presented herein (Scheme I). This plan hinges on the preparation of the dilactone **2** from the "top half" alcohol **3** and "bottom half" acid **4** by initial esterification across the C1 and C25 carbons followed by macrolactonization. Subsequent ester enolate Claisen rearrangement[7] and decarboxylation would then yield the intact monolactone.

Such a strategy change was deemed necessary as a result of two key experiments. The first, as reported previously,[6b]

Scheme II.[9] Inversion of the C-7 Alcohol and Synthesis of the Bottom Half 4[a]



[a] (a) *p*-TsOH, CH_3OH, H_2O, 85 °C; (b) $CH_3C(OCH_3)_2CH_3$, *p*-TsOH, CH_2Cl_2; (c) Me_2SO, ClCOCOCl, Et_3N, CH_2Cl_2; (d) $NaBH_4$, $CH_3CH(OH)CH_3$, 0 °C; (e) CH_3OCH_2Cl, $(i\text{-}C_3H_7)_2C_2H_5N$, CH_2Cl_2; (f) CH_3OH, H_2O, PyHOTs; (g) Me_2SO, PhH, $(i\text{-}C_3H_7N)_2C$, Cl_2CHCO_2H; (h) THF, H_2O, 10% aqueous KOH, 30% H_2O.

was attempted decarbonylation of the aldehyde **5a** with Wilkinson's catalyst. In this case, cyclopropane and isomerized olefin products were obtained (for details see ref 6b). The second, as shown in Chart I, was the radical decomposition[8] of the seleno ester **5b**. In this exploratory experiment, the pentacycle **7** and the aldehyde **5a** were obtained together with the desired decarboxylated product **6**. Modification of the reaction conditions never resulted in exclusive formation of compound **6**. It was felt that tying the side chain back, that is, making it part of a macrolactone, might restrict its motion enough to either reduce metal participation of the side-chain olefin to the point where no cyclopropanes were formed or, in the case of the seleno ester, allow for trapping of the intermediate radical before it could cyclize onto the C10 olefin. Results in this report bear this hypothesis as correct.

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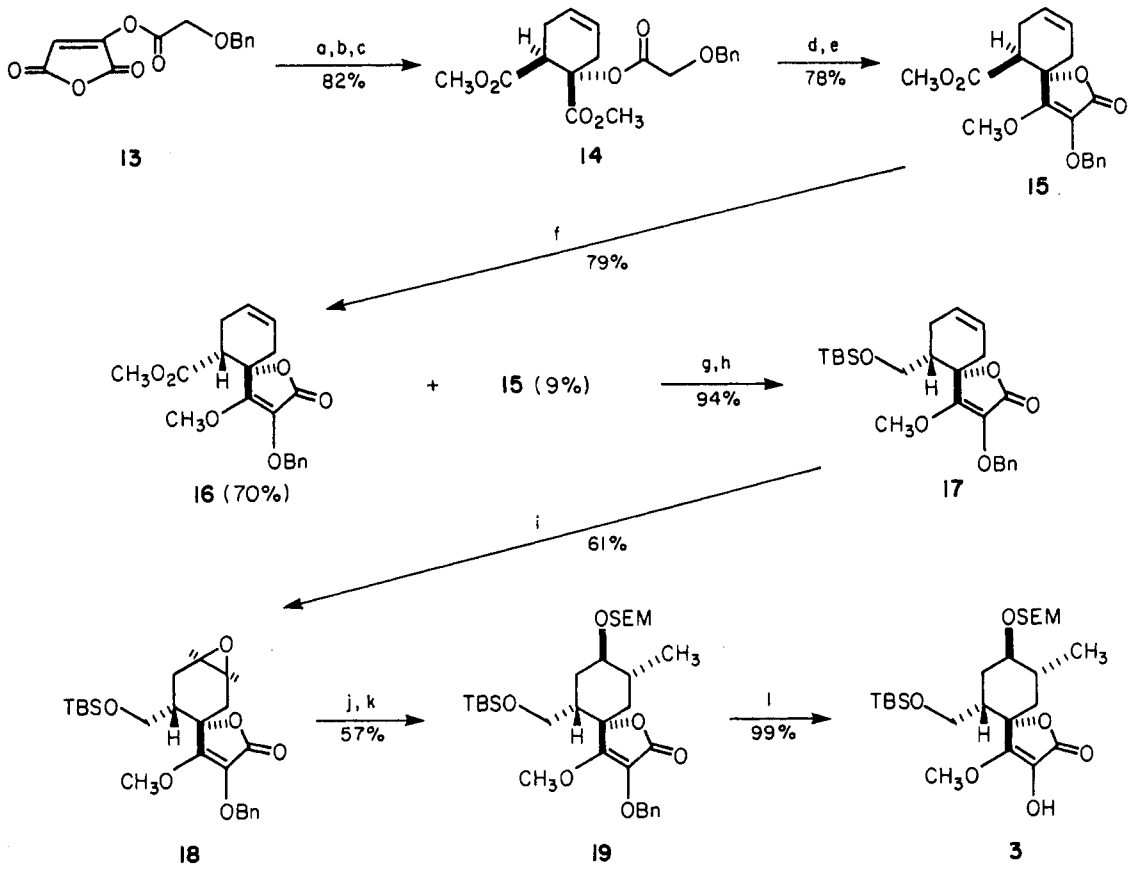
Scheme III.[9] Synthesis of the Top Half 3[a]



[a] (a) CH_2=CHCH=CH_2, PhH, pyrogallol, Δ; (b) CH_3OH, Δ; (c) ether, CH_2N_2; (d) LiHMDA, THF, −30 °C; (e) HMPA, CH_3OSO_2F; (f) catalytic $NaOCH_3$, CH_3OH, Δ; (g) $LiEt_3BH$, THF, 0 °C; (h) *t*-$BuMe_2SiCl$, pyridine, DMAP, CH_2Cl_2; (i) MCPBA, $LiClO_4$, Et_2O, 0 °C; (j) $LiMe_2Cu$, Et_2O, hexane, 0 °C; (k) SEMCl, $(i\text{-}C_3H_7)_2C_2H_5N$, CH_2Cl_2; (l) 10% Pd/C, H_2, C_2H_5OH.

The current effort can be divided into four distinct parts. First, a synthesis of the diacid **4** from the previously reported intermediate **8** was developed. Second, with some modifications, construction of the appropriately protected top half alcohol **3** was completed by a route similar to that developed earlier.[6a] Third, a successful scheme for the synthesis of the lactone **29** was realized through decarboxylation of the ester enolate Claisen rearrangement product **28**. Fourth, functionalization of the top portion of the ketone **32** is explored.

I. Inversion of the C-7 Alcohol and Synthesis of the Bottom Half Diacid 4. In a previous paper,[6a] the synthesis of "7-epi-bottom half" was outlined. Epimerization of the C-7 center was delayed because, at the time, its configuration had no effect on the outcome of the studies presented. For the sake of convergency, we felt that inversion of this center to the natural configuration would best be completed as early as possible. In Scheme II the inversion of the C-7 alcohol is presented together with a more efficient method of converting the 1,2-diol **12** to the diacid **4**.

Aqueous acid treatment of the tricyclic acetal **8**[6b] followed by reketalization with 1,2-dimethoxypropane provided the alcohol **9** in 95% yield. Swern[10] oxidation afforded the ketone **10** (97%) which when treated with sodium borohydride[11] in dry isopropyl alcohol yielded a separable mixture of the α- and β-alcohols **11** and **9** in a 2.6:1 ratio. Protection of the C7-hydroxy as a methoxymethyl ether[12] followed by selective hydrolysis (pyridinium tosylate, CH_3OH, H_2O, 80 °C) of the acetonide gave the 1,2-diol **12** in 90% yield. Oxidation of the 1,2-diol to the corresponding 1,2-dione[13] followed by treatment with basic hydrogen peroxide[14] (KOH, H_2O_2, THF, H_2O) afforded the diacid **4** in excellent yield. The ^1H NMR spectrum of the dimethyl ester of the synthetic diacid **4** and that of the one-carbon homologue obtained from natural chlorothricin[6b] were superimposable.

II. Synthesis of the Top Half Alcohol 3. After deciding upon the alcohol **3** as our key intermediate, we investigated two approaches for its construction. The first, shown in Scheme III, is an extension of earlier work reported from this group.[6a] A benzyl-protecting group was chosen in place of the previously used methyl group to insure selective deprotection. The starting material (α-(benzyloxy)acetoxy)maleic anhydride (**13**), was prepared by acylation of the pyridine salt of hydroxymaleic anhydride with (benzyloxy)acetyl chloride.[16] Diels–Alder reaction of the anhydride **13** with 1,3-butadiene (autoclave, 90 °C, 5 days) gave, after methanolysis and diazomethane treatment, the triester **14** in 82% yield.

After extensive experimentation, improved conditions for the cyclization of the triester **14** to the spirobutenolide **15** were found. In the case of lithium diisopropylamide (LDA), β-elimination was the major reaction pathway. The use of a weaker base, lithium hexamethyldisilazide

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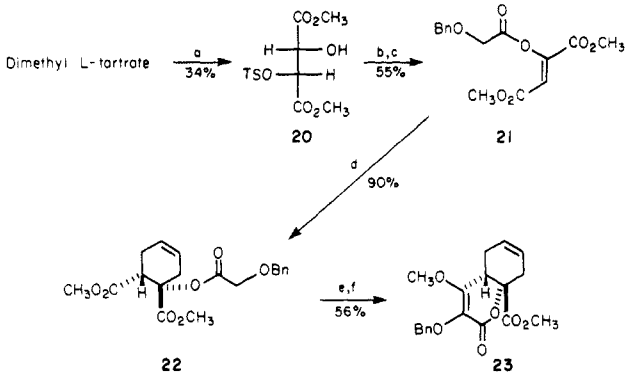
Scheme IV.[9] Tartrate Approach to the Top Half 3[a]



[a] (a) *p*-TsCl, pyridine, DMAP, CH_2Cl_2; (b) $BnOCH_2COCl$, pyridine, DMAP, CH_2Cl_2; (c) THF, $(C_2H_5)_3N$, DBU; (d) $CH_2{=}CHCH{=}CH_2$, PhH, pyrogallol, Δ; (e) LiHMDA, THF, 0 °C; (f) CH_2N_2.

(LiHMDA), along with low temperatures and long reaction times allowed for both improved yield and reproducibility. Thus, inverse addition of 2 equiv of LiHMDA in tetrahydrofuran (THF) at −78 °C to the triester **14** in THF at −78 °C and warming to −30 °C for 5 h afforded, after trapping with methyl fluorosulfonate, the desired spirobutenolide **15** in 78% yield. Equilibration of the pseudoaxial carbomethoxy group provided a 79% yield of **15** and **16** as an inseparable 1:7 mixture. Superhydride reduction (2 equiv of $LiEt_3BH$, THF, 0 °C) followed by protection with *tert*-butyldimethylsilyl chloride[18] (*t*-$BuMe_2SiCl$) afforded the protected alcohol **17** in 94% overall yield. Selective epoxidation of the cyclohexene double bond was accomplished in 61% yield with *m*-chloroperbenzoic acid (MCPBA) in ether containing 1 equiv of anhydrous lithium perchlorate.[6a] Treatment of the epoxide **18** with the higher order cuprates as described by Lipshutz[19] in various solvents failed to give any of the desired alcohol, giving instead starting material or decomposition products. Alternately, when the epoxide **18** was exposed to 10 equiv of lithium dimethylcuprate in hexane,[20] the alcohol was obtained in 62% yield, together with 17% of a ketonic product. Hexane was critical to the success of this reaction. Protection of the alcohol with β-(trimethylsilyl)ethoxymethyl chloride[21] (SEMCl) provided the ether **19** in 92% yield. Selective removal of the benzyl group (H_2 10% Pd/C, EtOH) gave the crystalline "top half" alcohol **3** in essentially quantitative yield.

Subsequent to the synthesis of the alcohol **3**, a shorter alternative route to the intermediate **16** was pursued (Scheme IV). This plan entailed the use of the relative stereochemistry of the hydroxy groups in natural tartaric acid to generate stereospecifically the trans dienophile **21**. Diels–Alder reaction and intramolecular Claisen condensation was to yield the spirolactone **16**. In the event, monotosylation[22] of dimethyl L-tartrate afforded the alcohol **20**. The moderate yield of this reaction was of no consequence since both starting materials were readily available. Treatment of this alcohol with (benzyoxy)acetyl chloride followed by elimination of the tosylate group provided the olefin **21** in 55% yield. The Diels–Alder reaction of olefin **21** with 1,3-butadiene gave adduct **22** in high yield (autoclave, 150 °C, 3 days). All that remained was the cyclization of the triester **22** to the spirobutenolide **16**. However, addition of the triester **22** to 2 equiv of LiHMDA in THF at −78 °C followed by warming afforded, after treatment with diazomethane, the δ-lactone **23** as the only cyclization product. The remainder of the material consisted of products resulting from β-elimination. Reversing the order of addition of the reagents and changing the trapping agent from diazomethane to methyl fluorosulfonate affected only the relative yields of **23** and β-eliminated products. This result, though unexpected, is not without precedent. In Dieckmann cyclizations of related triesters, small modifications in backbone structure resulted in drastic changes in product composition.[23] Inspection of molecule models of **14** and **22** was of little help, and it is possible that because of the kinetic nature of the reaction conditions, the proximity of the two reacting centers is the controlling factor. However, further studies are needed.

III. Formation of Macrolactone 29. With the two appropriately functionalized intermediates **3** and **4** in hand, the construction of the macrolactone **29** was pursued. The methyl ester acid chloride **24** was prepared in situ by selective esterification of the diacid chloride[24] of acid **4**. Connection of the two pieces was accomplished by adding a solution of the top half alcohol **3** and 4-(dimethylamino)pyridine[25] in CH_2Cl_2 to the bottom half acid chloride **24** in CH_2Cl_2 at 0 °C and then allowing the mixture to warm to room temperature (Scheme V). After aqueous workup, the ester **25** could be obtained in 77% overall yield.[26]

The methyl ester function of compound **25** was converted to the thiophenol ester by hydrolysis and reesterification.[27] This two-step sequence was necessary in light of the fact that selective esterification using the thiophenol of the diacid chloride of **4** was not successful.[28] Introduction of the vinyl group required removal of the *t*-$BuMe_2Si$ protecting group (HF_x·pyridine),[29] and it was at this stage that the two diastereomers, produced in the esterification step, became separable. A 1:1.26 ratio of the alcohols **26A,B** was obtained with the more mobile one (by chromatography) being the minor component **26A**. Since comparison with the natural product was impossible at this stage, all subsequent reactions were performed on both diastereomers individually. Oxidation of the alcohol **26** with pyridinium chlorochromate[30] (PCC) yielded the corresponding aldehyde which was immediately treated with vinyl-Grignard to provide the vinyl alcohol **27** in 65% overall yield.

The macrolactonization of the alcohol **27** and related compounds was studied in some detail. The "double

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(19) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305–2307.
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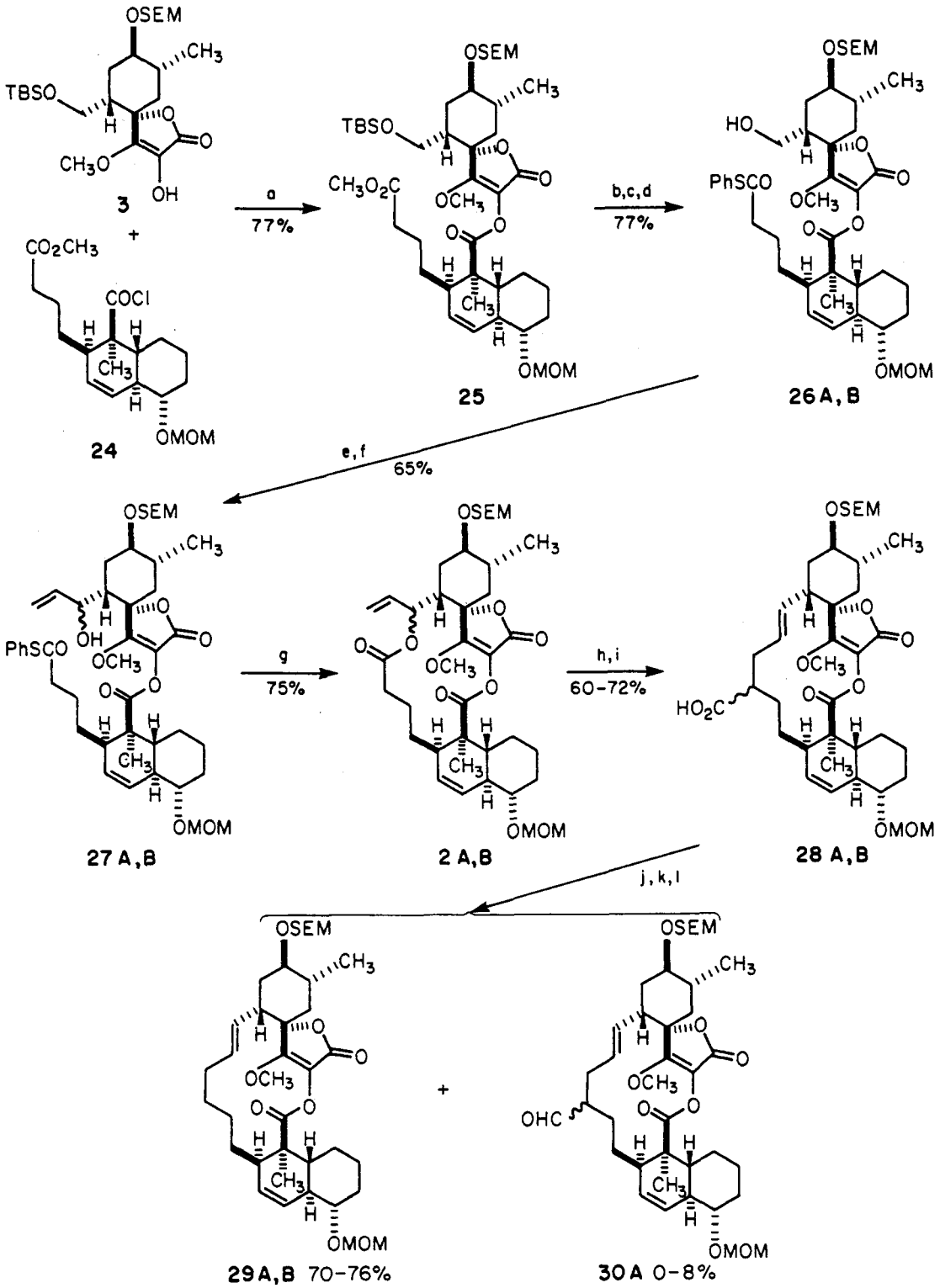
(25) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069–2076.
(26) Since the alcohol **3** and the diacid **4** are racemates, the connection of the two compounds produces a diastereomeric mixture. For the sake of clarity only one diastereomeric racemate is shown, but up to alcohol **26** the materials prepared were indeed inseparable mixtures of diastereoisomeric racemates.
(27) Neises, B.; Steglich, W. *Agnew. Chem., Int. Ed. Engl.* **1978**, *17*, 522–524.
(28) Attempted selective esterification of the diacid chloride of acid **4** with thiolphenol and pyridine at −90 °C gave only a 2:1 mixture of the side-chain thio ester over the ring thio ester.
(29) (a) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org.*

Scheme V.[9] Formation of Macrolactone 29[a]



[a] (a) DMAP, CH_2Cl_2; (b) LiOH, CH_3OH, H_2O; (c) PhSH, DCC, DMAP, CH_2Cl_2; (d) HF_x·pyridine, THF; (e) PCC, CH_2Cl_2; (f) CH_2=$CHMgBr$, THF, 0 °C; (g) $Ag(O_2CCF_3)$, Na_2HPO_4, PhH, 82 °C; (h) KHMDS, THF, HMPA, −78 °C; (i) HMPA, $(C_2H_5)_3SiCl$, $(C_2H_5)_3N$, THF; (j) Cl_2POOPh, $(C_2H_5)_3N$, THF, 0 °C; (k) PhSeH, $(C_2H_5)_3N$, THF, 0 °C; (l) $(n\text{-}C_4H_9)_3SnH$, AIBN, *p*-Xylene, 130 °C.

activation" methods of Corey[31] failed to produce any lactone as did Masamune's[32] mixed phosphate anhydride method. However, silver-promoted oxidation of the thiophenol ester **27**, as described by Masamune[33] under high dilution conditions, afforded the 14-membered macrodilactone **2** in 75% yield together with ~20% of the corresponding hydroxy acid hydrolysis product. This hydroxy acid could be recycled back to the thio ester **27** in 70–80% yield with diethyl chlorophosphate[34] and thiophenol.

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