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Heterocyclic ring scaffolds as small-molecule cholesterol absorption inhibitors

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Enantio- and diastereoselective syntheses of a substituted oxazolidinone, isoxazoline and pyrazoline as β-lactam surrogates are described. The substituted heterocycles were designed to incorporate side chains closely resembling those found in the β-lactam cholesterol absorption inhibitor ezetimibe (**1**). Additionally, the *in vitro* inhibitory efficacy of the novel compounds as cholesterol absorption inhibitors is reported using a brush border membrane vesicle assay.

Introduction

Enantio- and diastereoselective methods for the synthesis of substituted non-aromatic heterocycles are of prime importance. When incorporating multiple derivatization sites such methods facilitate diversity oriented synthesis. A recent example is the drug ezetimibe (**1**, Fig. 1),[1] which inhibits cholesterol absorption and contains a non-aromatic heterocycle in the form of a β-lactam ring. In the development of ezetimibe, the β-lactam was proposed to be essential for inhibitory activity,[2,3] with the corresponding ring-opened β-amino acid derivative being completely inactive.[3] In the course of an ongoing project aimed at the characterization and further study of intestinal cholesterol uptake, we became interested in the design of structurally well-defined, non-aromatic heterocycles which can mimic the β-lactam scaffold. The β-lactam ring is a rigid, almost planar heterocycle that defines out of plane vectors from a central core. Given our objectives of identifying structural congeners of β-lactams, we focused on generating structures in which the geometrical alignment of the three exit vectors of the substituents in the β-lactam are conserved (Fig. 1). Importantly, we additionally wished to identify β-lactam mimics that would not be prone to undergo hydrolysis as seen for β-lactams in general. In this report, we document the enantio- and diastereoselective syntheses of three β-lactam surrogates, namely an oxazolidinone, an isoxazoline, and a pyrazoline, which do not suffer from hydrolytic instability and display a set of exit vectors closely resembling those found in the β-lactam scaffold. We furthermore report their activities as cholesterol absorption inhibitors using our recently developed brush border membrane vesicle assay.[4]

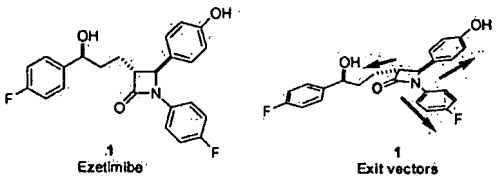

Fig. 1 Ezetimibe and the exit vectors of the β-lactam core.

Results and discussion

The oxazolidinone scaffold **2** has previously been suggested to serve as a structural mimic of the β-lactam of ezetimibe (**1**).[2] Our *ab initio* geometry optimizations[5] (Fig. 2) additionally suggested that the isoxazoline **3** and the pyrazoline **4** position three out of plane exit vectors in a manner that corresponds well to

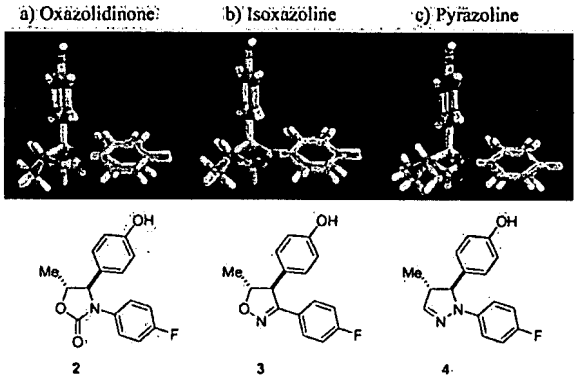

Fig. 2 Geometric overlap of oxazolidinone **2** (a), isoxazoline **3** (b), and pyrazoline **4** (c) with the β-lactam core structure of ezetimibe (**1**).

the β-lactam ring of ezetimibe. The excellent overlaps of the substituents are illustrated by superposition of each of the three heterocycles **2–4** with the β-lactam core found in ezetimibe. In order to focus on the exit vectors from the heterocyclic core, the flexible hydroxypropyl side chain in ezetimibe, which is not expected to strongly favor any single conformation, was replaced by a methyl group in the calculations.

The synthesis of the desired oxazolidinone **16** commenced with a Staudinger cycloaddition of imine **6**[6] and the ketene derived from acid **5**[7] (Scheme 1). The reaction proceeded in 75% yield (*cis*:*trans* = 95:5) to give a mixture of *cis*-diastereomers **7** and **8** (dr = 2:3 as determined by ^{1}H NMR spectroscopy).[8] These were separable by silica gel chromatography and afforded **8** as a single isomer. Acid-mediated cleavage of the ketal furnished α-hydroxy-β-lactam **9** in enantiomerically pure form and 51% yield. Although yield and diastereoselectivity were modest, the ready availability of the inexpensive starting materials as well as the straightforward and scalable reaction protocol were decisive in our synthetic plan. Cleavage of the β-lactam under alkaline conditions delivered amino alcohol **10** in 92% yield, which was converted to oxazolidinone **11** in 89% yield using triphosgene.

The methyl ester in **11** served as an appropriate handle to attach the 3′-aryl-3′-hydroxypropyl side chain found in ezetimibe (**1**). Initially, we envisaged reduction of the ester to the aldehyde and subsequent introduction of the side chain by an aldol condensation reaction. However, all attempts to isolate the aldehyde derived from **11** failed. Reduction of ester **11** or the corresponding Weinreb amide[9] with DIBAL-H resulted only in decomposition products, attributed to the presumed instability of the product aldehyde. In 1985 Ireland documented the manipulation

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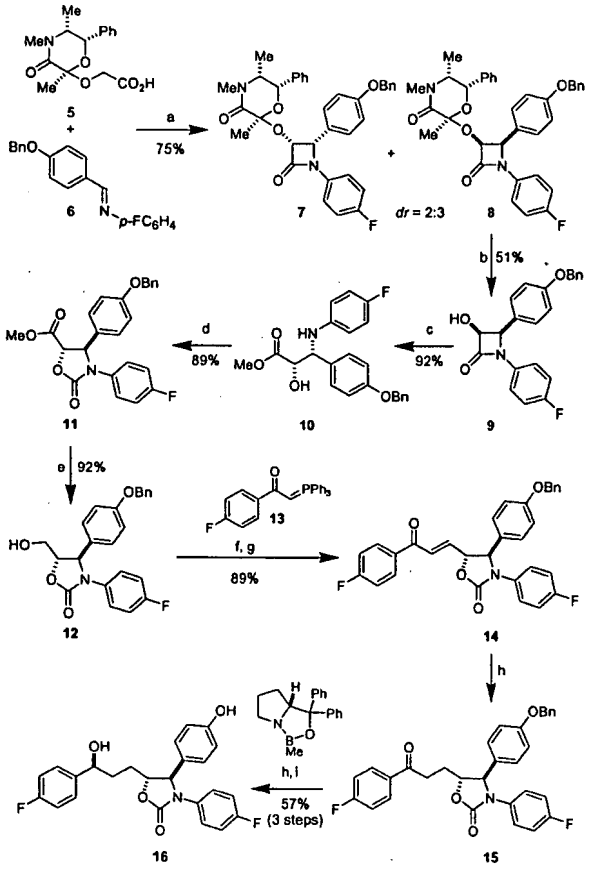
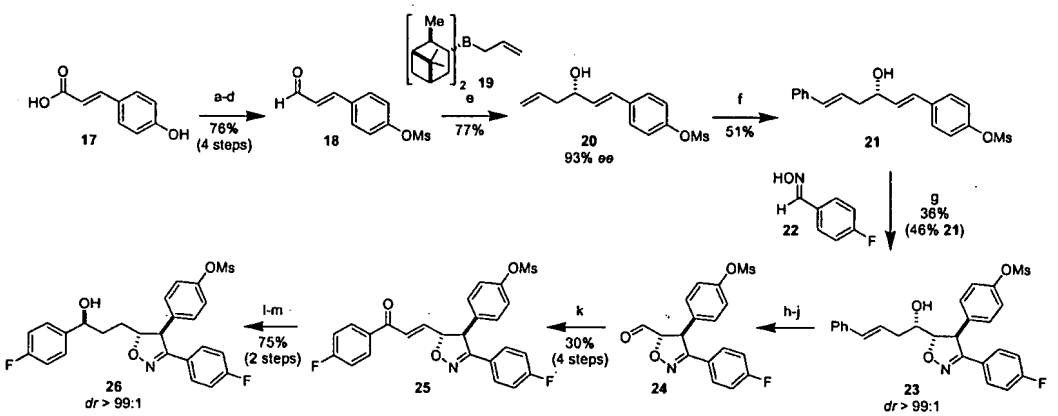


Scheme 1 *Reagents and conditions:* a) triphosgene, Et_3N, CH_2Cl_2, 0 °C to 23 °C. b) CSA, THF–H_2O, reflux. c) NaOMe, MeOH. d) Triphosgene, iPr_2NEt, DMAP, CH_2Cl_2, −78 °C to 23 °C. e) $NaBH_4$, EtOH. f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C. g) **13**. h) H_2, Pd/C, EtOH. i) (*R*)-CBS catalyst, $BH_3{\cdot}SMe_2$, CH_2Cl_2, −20 °C to 0 °C.

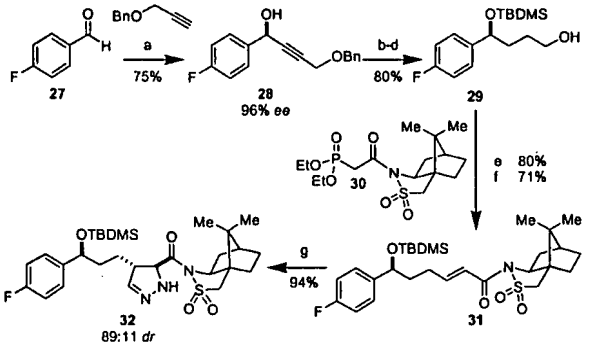
of unstable aldehydes through *in situ* Swern oxidation of the corresponding alcohols and subsequent Wittig reaction.[10] Consequently, ester **11** was reduced to the corresponding alcohol **12** by treatment with $NaBH_4$ in ethanol at 23 °C. Subsequent Swern oxidation[11] at −78 °C for 5 min furnished the intermediate aldehyde, which was subjected to *in situ* reaction with stabilized phosphorous ylide **13**.[12] The unusual low reaction temperature for this Wittig reaction (< −40 °C)[13] underscores the high electrophilicity of the intermediate aldehyde. Through this procedure *trans*-enone **14** could be conveniently prepared in 89% yield. Hydrogenation of the conjugated double bond afforded ketone **15**, which was diastereoselectively reduced using the (*R*)-CBS catalyst[14] (dr > 99:1 according to ^{19}F-NMR). Finally hydrogenolysis of the benzyl ether furnished the targeted oxazolidinone **16** in 57% yield over three steps. The above route thus furnished a rapid and straightforward access to the oxazolidinone scaffold with the desired side chains.

The stereoselective synthesis of the desired isoxazoline **26** was then pursued (Scheme 2) through a diastereoselective dipolar cycloaddition reaction of nitrile oxides and optically active allylic alcohols, which provides access to chiral optically active isoxazolines.[15] However, at the outset of our synthesis it was far from clear whether allylic alcohols wherein the olefin is conjugated to a functionalized aromatic ring could be used as dipolarophiles in this cycloaddition, since the vast majority of the described magnesium-mediated cycloadditions have been conducted with non-conjugated allylic alcohols. In order to test the strategy, the cinnamyl aldehyde **18** was prepared from commercially available 4-hydroxycinnamic acid (**17**) in 76% yield over 4 steps. Subsequent Brown allylation using (+)-β-allyldiisopinocampheyl borane (**19**)[16] afforded homoallylic alcohol **20** in 77% yield and 93% ee as determined by chiral HPLC. Cycloaddition of this allylic alcohol with the nitrile oxide derived from **22** delivered the product isoxazoline largely derived from cycloaddition to the terminal double bond. We speculated that this undesired regioselectivity could be circumvented by conversion of the terminal double bond to a corresponding di-substituted olefin, thereby reducing the rate of the cycloaddition reaction at this site. In this regard, **20** was subjected to Heck arylation[17] to give **21** in 51% yield. In initial investigations of the cycloaddition reaction we noted a major by-product resulting from dimerization of the nitrile oxide. In order to minimize the formation of this by-product, the reaction was conducted at low concentration of the nitrile oxide in the reaction mixture by slow addition of the hydroximinoyl chloride (generated from oxime oxidation with *tert*-butyl hypochloride) to the dipolarophile over a period of 30 h. Thus, cycloaddition of allylic alcohol **21** with the nitrile oxide derived from **22** proceeded completely regio- and diastereoselectively (dr > 99:1 as determined by NMR) to give isoxazoline **23** in 36% yield with 46% recovered starting material. Installation of the desired substituents commenced by conversion of **23** to aldehyde **24**. In analogy to the synthesis of the oxazolidinone **16** described earlier, aldehyde **24** was allowed to react with phosphorous ylide **13**[12] to afford enone **25** (30% over 4 steps). Hydrogenation of the double bond followed by diastereoselective ketone reduction (dr > 99:1 as determined by ^{1}H NMR) using the (*R*)-CBS catalyst[14] afforded the desired isoxazoline **26** in 75% yield over two steps.



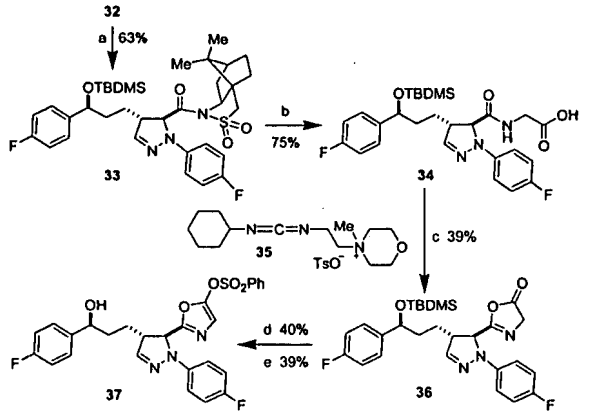
Scheme 2 *Reagents and conditions:* a) $SOCl_2$, MeOH. b) MsCl, Et_3N, THF. c) DIBAL-H, CH_2Cl_2, 0 °C. d) MnO_2, CH_2Cl_2. e) **19**, Et_2O, −78 °C. f) C_6H_5I, $Pd(OAc)_2$, PPh_3, Et_3N, MeCN. g) **22**, *t*BuOCl, *i*PrOH, EtMgBr, CH_2Cl_2. h) MsCl, pyr, CH_2Cl_2. i) DBU, CH_2Cl_2, reflux. j) $K_2OsO_4{\cdot}2H_2O$, $NaIO_4$, THF–H_2O. k) **13**. l) H_2, Pd/C, MeOH. m) (*R*)-CBS catalyst, $BH_3{\cdot}SMe_2$, CH_2Cl_2, −20 °C to 0 °C.

In the approach to the desired substituted pyrazolines, a diastereoselective 1,3-dipolar cycloaddition of TMS-diazomethane[18] was utilized to construct the heterocyclic core (Scheme 3). The synthesis commenced with a Zn-mediated enantioselective alkyne addition[19] to *p*-fluorobenzaldehyde **27** to give propargylic alcohol **28** in 75% yield (96% ee as determined by chiral HPLC). The yields were higher when the reaction was conducted slightly below room temperature (8–13 °C). Subsequent silylation was immediately followed by sequential reduction of the triple bond and removal of the benzyl group to give alcohol **29** in 80% overall yield. This was necessary because the intermediary propargylic silyl ether proved unstable and difficult to isolate. The propensity of the benzylic and propargylic C–OSi bond to undergo hydrogenolytic cleavage necessitated stepwise hydrogenation of the alkyne prior to removal of the benzyl group. Subsequent Dess–Martin oxidation[20] (80% yield) and Horner–Wadsworth–Emmons olefination using the camphorsultam derived phosphonate **30**[21,22] and LiCl–DBU[23] afforded the (*E*)-olefin **31** in 71% yield. The pyrazoline heterocyclic core was generated using a diastereoselective 1,3-dipolar cycloaddition of TMS-diazomethane,[18] which furnished the desired pyrazoline **32** in 94% combined yield (89:11 dr based on the yields of the isolated diastereomers). The diastereomeric products were readily separated by chromatography on silica gel to afford diastereomerically pure **32**.



Scheme 3 *Reagents and conditions:* a) $Zn(OTf)_2$, (+)-*N*-methylephedrine, Et_3N, toluene, 8–13 °C. b) TBDMSCl, imidazole, DMF. c) H_2, Pd/C, Na_2CO_3, EtOH. d) H_2, Pd/C, EtOH. e) Dess–Martin periodinane, CH_2Cl_2. f) **30**, DBU, LiCl, MeCN. g) $TMSCHN_2$, toluene–hexane; then TFA, CH_2Cl_2.

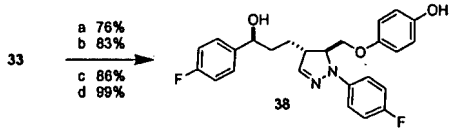
Typical conditions employed in Pd-mediated *N*-arylations[24] proved incompatible with the camphorsultam imide. However, a Cu-mediated *N*-arylation proceeded successfully employing either a boronic acid[25] or a triarylbismuth derivative[26] (Scheme 4).



Scheme 4 *Reagents and conditions:* a) $(p\text{-}FC_6H_4)_3Bi$, $Cu(OAc)_2$, Et_3N, CH_2Cl_2. b) Glycine, KCN, MeOH, 50 °C. c) **35**, CH_2Cl_2, reflux. d) $PhSO_2Cl$, Et_3N, CH_2Cl_2. e) HF·pyr, pyr, THF.

Optimal yields (63%) were obtained using the organobismuth reagent, $(p\text{-}FC_6H_4)_3Bi$, which was readily obtained by reaction of *p*-fluorophenylmagnesium bromide with $BiCl_3$. With this intermediate **33** in hand, we envisioned a rapid synthesis of various analogues by conversion of the carboxylic acid derivative into an oxazole as a substitute for the phenol substituent of ezetimibe. In this regard, substitution of the camphorsultam auxiliary with glycine catalyzed by KCN[27] (75%) and dehydration using the water-soluble DCC analogue **35**[28] afforded the desired, but rather unstable, oxazolone **36** in 39% isolated yield. Generation of the oxazole **37** was effected by benzene sulfonate ester formation and desilylation in 40% and 39% yields, respectively.

As an alternative pyrazoline derivatization, the chiral camphorsultam auxiliary of **33** was reductively removed ($LiAlH_4$, 76% yield) to give a primary alcohol which, following tosylation (83% yield), was subjected to nucleophilic displacement of the sulfonate by hydroquinone in 86% yield (Scheme 5). Subsequent desilylation afforded the pyrazoline **38** in 99% yield featuring an oxymethylene linker between the pyrazoline and the aromatic ring substituent.



Scheme 5 *Reagents and conditions*: a) $LiAlH_4$, THF, −78 °C. b) TsCl, DMAP. Et_3N, CH_2Cl_2. c) Hydroquinone, Cs_2CO_3, DMF, 80 °C. d) HF·pyr, pyr, THF.

The heterocyclic compounds **16**, **26**, and **37–38** were subsequently evaluated for inhibition of intestinal cholesterol uptake using our recent brush border membrane vesicle *in vitro* assay (Fig. 3).[4] We were pleased to observe that oxazolidinone **16** showed a similar *in vitro* activity (19% inhibition) to ezetimibe (**1**) (16% inhibition). Despite previous promising *in vitro* results for a wide range of sulfonate ester phenolic derivatives of ezetimibe,[4b] the sulfonate ester substituted isoxazoline (**26**) and pyrazoline (**37**) did not show any activity as cholesterol absorption inhibitors. The remaining pyrazoline **38** was likewise void of inhibitory activity. This attests that small changes of the

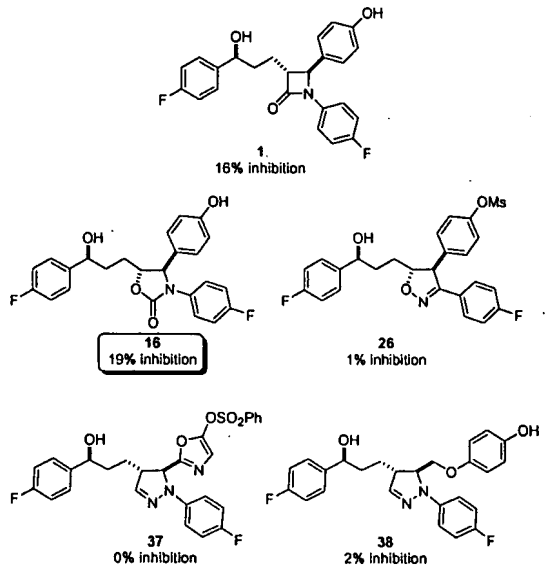


Fig. 3 Percentage inhibition in the brush border membrane vesicle assay using rabbit small intestine at nominal concentrations of 6 μM.[4] The average standard deviations were ±3% inhibition.

heterocyclic core can result in marked differences as cholesterol absorption inhibitors even though the geometric deviations of the exit vectors are only subtle (Fig. 2).

Conclusions

We have documented the enantio- and diastereoselective syntheses of three β-lactam surrogates with side chains resembling those found in the cholesterol absorption inhibitor ezetimibe (**1**). In the course of these investigations we expanded the substrate scope of the highly diastereoselective hydroxyl-directed nitrile oxide cycloadditions. The pyrazoline synthesis featured a diastereoselective dipolar cycloaddition of TMS-diazomethane and a copper-mediated *N*-arylation using an organobismuth reagent as the key steps. When evaluated in the brush border membrane vesicle assay, the oxazolidinone **16** showed similar activity as ezetimibe (**1**) as a cholesterol absorption inhibitor. This promising result suggests that an oxazolidinone ring scaffold could effectively replace the β-lactam of ezetimibe. Synthesis of additional analogues and their biological evaluation are underway and will be reported in due course.

Experimental

General experimental details

Reactions in anhydrous solvents were all performed using oven dried glassware under an atmosphere of argon. Reagent grade solvents were all purchased from chemical companies and used without prior purification. Anhydrous THF, ether, toluene, CH_3CN and CH_2Cl_2 were dried and purified through activated alumina columns as described.[29] Diisopropylamine, triethylamine and pyridine were distilled from KOH. For chromatographic purification, technical grade solvents were distilled prior to use. TLC was performed using Machery-Nagel Alugram Sil G/UV_{254} or Merck 0.25 mm silica gel 60 F_{254} TLC glass plates. Visualization of the developed chromatogram was performed by UV fluorescence at 254 nm and oxidative stain by either ceric ammonium molybdate solution, $KMnO_4$–$NaHCO_3$ water solution, phosphomolybdic acid or H_2SO_4–MeOH. Chromatographic purification of products was accomplished by dry column vacuum chromatography[30] on either Merck silica gel 60 (15–40 μm) or Brunschwig silica 18–32, 60 Å (18–32 μM) or by flash chromatography on silica gel 60 (230–400 mesh, 0.04–0.063 mm) from Merck at rt and 0.3–0.5 mbar air pressure. Concentration under reduced pressure was performed by rotary evaporation at 40 °C and the purified compounds were subsequently dried under high vacuum (<0.5 Torr). NMR spectra were recorded on a Varian Mercury 300 MHz apparatus operating at 300 MHz, 75 MHz and 282 MHz for ^1H, ^{13}C/DEPT and ^{19}F, respectively, and chemical shifts (δ) were referenced to the internal solvent signals for ^1H and ^{13}C. Multiplicities are reported as follows: ^1H: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet; ^{13}C: C, CH, CH_2, CH_3 (determined by DEPT); coupling constants are reported in Hz. Melting points were measured on a Büchi 510 apparatus in open capillaries and all melting points are uncorrected. IR-Spectra were recorded in $CHCl_3$ on a Perkin Elmer Spectrum RX I FT-IR apparatus (thin films on NaCl plates) and are reported as absorption maxima in cm^{-1}. Optical rotations are reported in 10^{-1}deg cm^2 g^{-1}. Elemental analysis was performed by the Mikroelementaranalytisches Laboratorium at the ETH, Zürich. High resolution matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) and electrospray ionization (ESI-MS) were performed by the mass spectrometry service of the LOC at the ETH, Zürich.

(2*S*,5*R*,6*S*)-2-[(1*S*,2*R*)-2-(4-Benzyloxyphenyl)-3-(4-fluorophenyl)-4-oxocyclobutoxy]-2,4,5-trimethyl-6-phenylmorpholin-3-one (8). To a solution of acid **5**[7] (30.0 g, 102 mmol, 1.11 eq.) in CH_2Cl_2 (600 ml) was added triethylamine (64.0 ml, 461 mmol, 5.00 eq.) followed by imine **6**[6] (28.1 g, 92.1 mmol, 1.00 eq.). The solution was cooled to −20 °C and triphosgene (16.4 g, 55.8 mmol, 0.600 eq.) was added in 50 ml CH_2Cl_2 over a period of 20 min. The solution was warmed to 23 °C over a period of 8 h and stirred for an additional 10 h at this temperature. The solution was poured onto 600 ml ice water and 200 ml CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with hexane–EtOAc (3:2 to 1:2 gradient) and then chromatography on silica gel eluting with EtOAc–CH_2Cl_2 (7:1 to 3:1 gradient) to afford β-lactam **8** as a colorless solid in 45% yield along with 30% yield of the undesired diastereomer **7**. Mp: 132 °C. R_f = 0.38 [hexane–EtOAc 1:1 (v/v)]. $\alpha_D^{30.5}$ = +77°, (*c* 1.075 in $CHCl_3$). ^1H-NMR (300 MHz, $CDCl_3$): δ 7.46–7.07 (16 H, m), 6.92–6.84 (2 H, m), 5.34 (1 H, d, *J* = 5.3 Hz), 5.06 (2 H, s), 4.95 (1 H, d, *J* = 5.3 Hz), 4.60 (1 H, d, *J* = 2.5 Hz), 3.23–3.14 (1 H, m), 2.90 (3 H, s), 1.70 (3 H, s), 0.83 (3 H, d, *J* = 6.2 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 165.4, 165.0, 159.3 (d, *J* = 244 Hz), 159.1, 137.1 (d, *J* = 5 Hz), 133.7, 129.9, 128.9, 128.6, 128.3, 128.0, 127.7, 125.7, 119.0 (d, *J* = 8 Hz), 116.0 (d, *J* = 23 Hz), 115.1, 100.1, 76.9, 71.2, 70.1, 62.2, 59.0, 33.8, 23.6, 12.4. IR (thin film): 2938, 1756, 1667, 1612, 1511, 1382, 1223, 1177, 1112, 1092, 834, 734. HRMS (EI): found, 580.2369. $C_{35}H_{33}FN_2O_5^+$ requires 580.2374.

(3*S*,4*R*)-4-(4-Benzyloxyphenyl)-1-(4-fluorophenyl)-3-hydroxyazetidin-2-one (9). To a solution of ketal **8** (17.0 g, 29.0 mmol, 1.00 eq.) in THF (242 ml) and water (48 ml) was added *p*-toluenesulfonic acid monohydrate (55.7 g, 293 mmol, 10.0 eq.). The solution was heated to reflux for 5 h. The solution was concentrated to an approximate volume of 60 ml and then poured onto EtOAc (150 ml) and water (250 ml). The aqueous phase was extracted with EtOAc (4 × 100 ml). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (3:2 to 2:3 gradient), to afford β-lactam **9** as a colorless solid in 51% yield. Mp: 168 °C. R_f = 0.26 [hexane–EtOAc 3:2 (v/v)]. $\alpha_D^{29.5}$ = −129°, (*c* 1.22 in acetone). ^1H-NMR (300 MHz, acetone-d_6): δ 7.50–7.47 (2 H, m), 7.42–7.29 (5 H, m), 7.10–7.01 (4 H, m), 5.33 (1 H, d, *J* = 5.3 Hz), 5.27 (1 H, dd, *J* = 7.2 Hz, 5.3 Hz), 5.11 (2 H, s), 5.07 (1 H, d, *J* = 7.2 Hz). ^{13}C-NMR (75 MHz, acetone-d_6): δ 166.5, 159.2, 159.0 (d, *J* = 241 Hz), 137.7, 134.7, 129.6, 128.6, 128.0, 127.8, 118.9 (d, *J* = 8 Hz), 115.8 (d, *J* = 23 Hz), 114.8, 78.0, 69.8, 62.3. IR (thin film): 3120, 1756, 1667, 1612, 1511, 1382, 1223, 1177, 1112, 1092, 834, 734. HRMS (EI): found, 363.1268. $C_{22}H_{18}FNO_3^+$ requires 363.1271. Anal.: found, C, 77.73; H, 5.20; N, 3.91. $C_{22}H_{18}FNO_3$ requires C, 72.72; H, 4.99; N, 3.85%.

(2*S*,3*R*)-3-(4-Benzyloxyphenyl)-3-(4-fluorophenylamino)-2-hydroxypropionic acid methyl ester (10). To a suspension of β-lactam **9** (2.00 g, 5.50 mmol, 1.00 eq.) in methanol (55.0 ml) was added sodium methoxide (1.49 g, 27.5 mmol, 5.00 eq.). The suspension was stirred at 23 °C for 2 h. To the forming solution was added $NH_4Cl_{(s)}$ and the suspension was concentrated *in vacuo*. To the solid was added EtOAc (50 ml) and water (50 ml). The aqueous phase was extracted with EtOAc (3 × 20 ml). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (3:2 to 1:1 gradient), to afford amino alcohol **10** as a colorless solid in 89% yield. Mp: 103 °C. R_f = 0.45 [hexane–EtOAc 3:2 (v/v)]. $\alpha_D^{25.3}$ = +13.9°, (*c* 1.10 in CH_2Cl_2). ^1H-NMR (300 MHz, $CDCl_3$): δ 7.44–7.24 (4 H, m), 6.97–6.91 (2 H, m), 6.84–6.76 (2 H, m), 6.53–6.46 (2 H, m), 5.02 (2 H, s), 4.81 (1 H, s), 4.60 (1 H, s), 4.46 (1 H, m), 3.79 (3 H, s), 3.07 (1 H, d, *J* = 3.7 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 158.2, 155.8 (d, *J* = 233 Hz), 142.5, 136.8, 131.0, 128.5, 127.9, 127.9, 127.4, 155.5 (d, *J* = 22 Hz), 114.9, 114.8, 74.6, 70.0, 59.1, 53.1, 114.8, 78.0, 69.8,

62.3. IR (thin film): 3390, 1737, 1610, 1510, 1221, 1113, 823. MS (EI): 306.1748 (2.54%), 186.2356 (18.8%), 91.0908 (100%). Anal.: found, C, 69.88; H, 5.78; N, 3.54. $C_{23}H_{22}FNO_4$ requires C, 69.86; H, 5.61; N, 3.54%.

(4*R*,5*S*)-4-(4-Benzyloxyphenyl)-3-(4-fluorophenyl)-2-oxooxazolidine-5-carboxylic acid methyl ester (11). To a solution of amino alcohol **10** (1.92 g, 4.86 mmol, 1.00 eq.) in CH_2Cl_2 (24.0 ml) was added diisopropylethylamine (2.54 ml, 14.6 mmol, 3.00 eq.) and 4-*N*,*N*-dimethylaminopyridine (59.0 mg, 0.486 mmol, 0.10 eq.). The solution was cooled to −78 °C and triphosgene (1.44 g, 4.86 mmol, 1.00 eq.) in CH_2Cl_2 (4.0 ml) was added over a period of 5 min. The solution was warmed to 23 °C over 8 h and stirred at this temperature for an additional 5 h. To this solution was added water (50 ml) and concentrated aqueous ammonium hydroxide solution (3 ml). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (2:1 to 1:1 gradient), to afford methyl ester **11** as a colourless solid in 82% yield. Mp: 118 °C. R_f = 0.54 [hexane–EtOAc 3:2 (v/v)]. $a_D^{29.3}$ = +18°, (*c* 1.10 in $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.40–7.32 (7 H, m), 7.29–7.22 (2 H, m), 6.98–6.93 (4 H, m), 5.33 (1 H, d, J = 4.4 Hz), 5.03 (2 H, s), 4.73 (1 H, d, J = 4.4 Hz), 3.89 (3 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.9, 160.1 (d, J = 244 Hz), 159.7, 154.3, 136.7, 132.7, 129.5, 128.9, 128.4, 127.8, 127.7, 123.2 (d, J = 8 Hz), 116.1 (d, J = 22 Hz), 116.0, 77.9, 70.3, 36.6, 53.5. IR (thin film): 1769, 1552, 1388, 1227, 1099, 834. HRMS (MALDI): found, 444.1224. $C_{24}H_{20}FNO_5Na^+$ requires 444.1224. Anal.: found, C, 68.18; H, 4.91; N, 3.38. $C_{24}H_{20}FNO_5$ requires C, 68.40; H, 4.78; N, 3.32%.

(4*R*,5*S*)-4-(4-Benzyloxyphenyl)-3-(4-fluorophenyl)-5-hydroxymethyloxazolidin-2-one (12). To a suspension of methyl ester **11** (1.68 g, 3.99 mmol, 1.00 eq.) in ethanol (27.0 ml) was added, at 23 °C, sodium borohydride (226 mg, 5.98 mmol, 1.50 eq.). The suspension was stirred for 2 h at this temperature after which point all solids had dissolved. To this solution was added $NH_4Cl_{(s)}$ and the volume was concentrated to 5 ml *in vacuo*. To this suspension was added water (50 ml) and EtOAc (50 ml). The aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (1:1 to 2:3 gradient), to afford alcohol **12** as a colorless solid in 92% yield. Mp: 143 °C. R_f = 0.40 [hexane–EtOAc 2:3 (v/v)]. $a_D^{32.4}$ = −16°, (*c* 1.54 in $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.42–7.19 (9 H, m), 6.97–6.90 (4 H, m), 5.26 (1 H, d, J = 6.5 Hz), 5.02 (2 H, s), 4.39 (1 H, m), 3.99 (1 H, d, J = 12.5 Hz), 3.74 (1 H, d, J = 12.5 Hz), 2.77 (1 H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 159.7 (d, J = 245 Hz), 159.0, 136.4, 132.7, 129.4, 128.5, 128.0, 127.9, 127.4, 123.6 (d, J = 8 Hz), 115.6 (d, J = 22 Hz), 115.6, 82.0, 70.1, 61.6, 61.2. IR (thin film): 3418, 2930, 2871, 1748, 1611, 1512, 1394, 1234. HRMS (EI): found, 393.1389. $C_{23}H_{20}FNO_4^+$ requires 393.1376. Anal.: found, C, 70.26; H, 5.21; N, 3.61. $C_{23}H_{20}FNO_4$ requires C, 70.22; H, 5.12; N, 3.56%.

(4*R*,5*R*)-4-(4-Benzyloxyphenyl)-3-(4-fluorophenyl)-5-[(*E*)-3-(4-fluorophenyl)-3-oxopropenyl]oxazolidin-2-one (14). To a solution of oxalyl chloride (508 mg, 4.00 mmol, 2.00 eq.) in CH_2Cl_2 (15.0 ml) was added, at −78 °C, dimethyl sulfoxide (0.355 ml, 5.00 mmol, 2.50 eq.). After 10 min at −78 °C, alcohol **12** (787 mg, 2.00 mmol, 1.00 eq.) in CH_2Cl_2 (15.0 ml) was added over a period of 5 min. After an additional 5 min at this temperature, triethylamine (1.14 ml, 8.00 mmol, 8.00 eq.) was added. After 5 min, 1-(4-fluorophenyl)-2-(triphenyl-λ^5-phosphanylidene)ethanone **13**[12] was added and the resulting suspension was warmed to 20 °C and stirred for an additional 30 min. To the solution was added saturated aqueous Na_2HCO_3 solution. The aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (2:1 to 1:1 gradient), to afford enone **14** as a colorless solid in 89% yield. Mp: 152 °C. R_f = 0.56 [hexane–EtOAc 3:2 (v/v)]. $a_D^{25.6}$ = +100°, (*c* 0.60 in $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.06–7.99 (2 H, m), 7.42–7.06 (14 H, m), 7.00–6.92 (4 H, m), 5.05–5.00 (4 H, m). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 187.1, 165.9 (d, J = 254 Hz), 159.8 (d, J = 243 Hz), 159.4, 154.8, 140.0, 136.2, 133.2, 132.3, 131.4 (d, J = 9 Hz), 128.6, 128.1, 128.1, 127.9, 127.4, 125.8, 123.5 (d, J = 9 Hz), 115.9 (d, J = 24 Hz), 115.8 (d, J = 24 Hz), 115.8, 80.5, 70.2, 66.0. IR (thin film): 1760, 1675, 1597, 1511, 1385, 1227. HRMS (MALDI): found, 534.1482. $C_{31}H_{23}F_2NO_4Na^+$ requires 534.1493. Anal.: found, C, 72.51; H, 4.78; N, 2.73. $C_{31}H_{23}F_2NO_4$ requires C, 72.79; H, 4.53; N, 2.74%.

(4*R*,5*R*)-3-(4-Fluorophenyl)-5-[(*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)oxazolidin-2-one (16). To enone **14** (910 mg, 1.78 mmol, 1.00 eq.) in ethanol (15.0 ml) was added, at 23 °C, Pd on carbon (10%) (100 mg). The suspension was vigorously stirred under 1 atm of hydrogen gas for 3 h. The suspension was filtered through a pad of celite, eluting with EtOAc, concentrated and the residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (2:1 to 1:1 gradient). A portion of the resulting benzyl ether **15** (310 mg, 0.604 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 and cooled to −20 °C. (*R*)-3,3-Diphenyl-1-methyltetrahydro-3*H*-pyrrolo-oxazaborole-2-methyl oxazaborolidine [solution in toluene (0.5 M) 0.600 ml, 0.302 mmol, 0.50 eq.] was added, followed by borane–dimethylsulfide complex (0.080 ml, 0.905 mmol, 1.50 eq.). The solution was stirred at −20 °C for 2 h, then warmed to 0 °C and quenched with methanol. To the solution was added saturated aqueous Na_2HCO_3 solution and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexane–EtOAc (3:2 to 1:1 gradient). A portion of the resulting alcohol (53 mg, 0.10 mmol, 1.0 eq.) was dissolved in ethanol and Pd on carbon (10 mg) was added. The suspension was vigorously stirred under an atmosphere of hydrogen for 2.5 h. The suspension was filtered through a plug of celite eluting with EtOAc. The residue was purified by chromatography on silica gel eluting with hexane–EtOAc (1:1 to 1:2 gradient) to afford oxazolidinone **16** as a colorless solid in 57% yield from enone **14**. Mp: 98 °C. R_f = 0.41 [hexane–EtOAc 2:3 (v/v)]. $a_D^{27.6}$ = −1°, (*c* 0.84 in $CHCl_3$). ^{1}H-NMR (300 MHz, acetone-d_6): δ 7.47–7.35 (4 H, m), 7.29–7.24 (2 H, m), 7.09–6.97 (4 H, m), 6.85–6.79 (2 H, m), 5.15 (1 H, d, J = 6.7 Hz), 4.76–4.68 (1 H, m), 4.43–4.34 (2 H, m), 2.02–1.76 (4 H, m). ^{13}C-NMR (75 MHz, acetone-d_6): δ 162.0 (d, J = 243 Hz), 159.5 (d, J = 242 Hz), 157.9, 155.3, 142.2 (d, J = 3 Hz), 134.3 (d, J = 2 Hz), 129.1, 128.7, 127.8 (d, J = 8 Hz), 123.8 (d, J = 9 Hz), 116.1, 115.2 (d, J = 23 Hz), 114.9 (d, J = 21 Hz), 82.4, 72.3, 65.6, 35.0, 30.3. IR (thin film): 3316, 2925, 1726, 1603, 1511, 1224, 835. HRMS (MALDI): found, 448.1326. $C_{24}H_{21}F_2NO_4Na^+$ requires 448.1337. The diastereoselectivity of the CBS reduction was established by integration of the fluorine signals in the ^{19}F-NMR spectrum by comparison to a mixture of **16** and *(4*R*,5*R*)-3-(4-fluorophenyl)-5-[(*R*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)oxazolidin-2-one*, obtained by $NaBH_4$ reduction of the corresponding ketone.

Methanesulfonic acid 4-[(*E*)-3-oxopropenyl]phenyl ester (18). To a suspension of 4-hydroxycinnamic acid **17** (8.85 g, 53.5 mmol, 1.00 eq.) in methanol (70 ml) at 0 °C was added dropwise thionyl chloride (6.40 g, 53.5 mmol, 1.00 eq.). The ice bath was removed and the solution was stirred at 23 °C for 16 h. A stream of air was bubbled through the solution

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