Assignment of Stereochemistry in the Oligomycin/Rutamycin/Cytovaricin Family of Antibiotics. Asymmetric Synthesis of the Rutamycin Spiroketal Synthon

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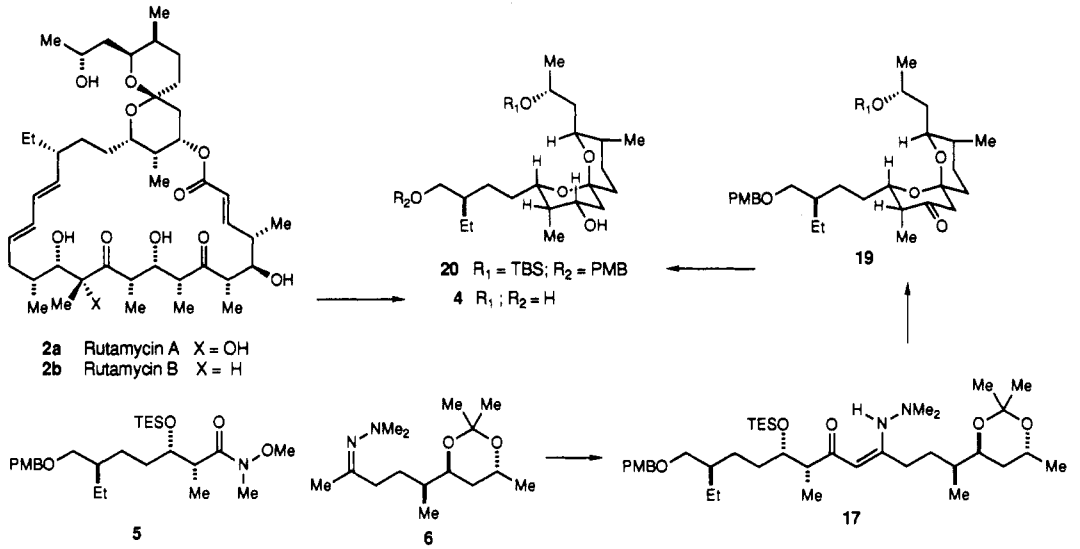
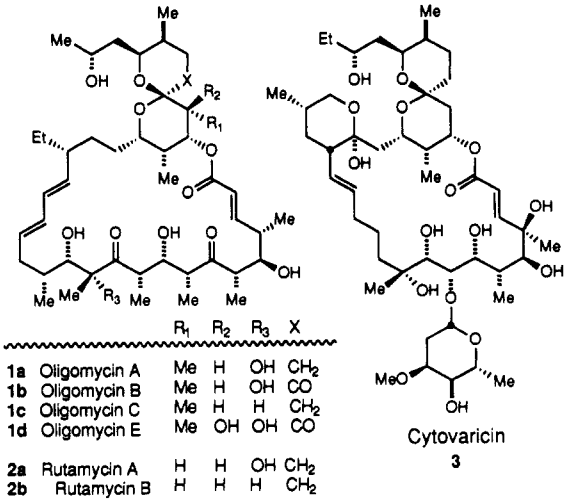
The absolute stereochemistry of the rutamycin antibiotics **2a,b** has been established through asymmetric synthesis of the known degradation product **4**. One of the key steps in the assemblage process involves acylation of the metalated hydrazone **6** with the *N*-methoxy-*N*-methyl amide **5**. Both of these enantiomerically pure intermediates have been prepared in good overall yield and high diastereoselectivity (de > 94%). All absolute stereochemical relationships were established through alkylation and aldol bond constructions using *N*-acyloxazolidinone chiral auxiliaries. Subjection of **17** to acid hydrolysis/deprotection resulted in loss of protecting groups and subsequent spiroketalization to **19** (80%). Silylation of the secondary alcohol in **19** was followed by a samarium-catalyzed Meerwein–Ponndorf–Verley reduction to provide the equatorial alcohol **20** in excellent yield and stereoselectivity (de = 97%). Control experiments indicate that this surprisingly stereoselective reaction operates under kinetic control and that the observed stereochemical outcome may be the result of coordination of the reactive reducing agent to the axial spiroketal oxygen. Conversion of **20** to triol **4** afforded material that is identical with the rutamycin degradation product in all respects. These results establish that the absolute stereochemistry of the rutamycins is as shown (**2a,b**).



The oligomycin/rutamycin/cytovaricin family of antibiotics **1–3** consists of highly functionalized spiroketals bridged by a polypropionate-derived macrolactone chain.[1] These macrolides have been of considerable value in biochemical research as specific inhibitors of mitochondrial ATPase. These studies have provided important contributions to our understanding of the mechanism of oxidative phosphorylation.[2,3] To date, the structures of oligomycin B, rutamycin A, and cytovaricin have been elucidated by single-crystal X-ray analysis;[1b,c,4] however, cytovaricin is the only member of the class for which the absolute stereochemistry has been unequivocally determined. This was achieved by degradation and characterization of the deoxy sugar β-D-cymarose[5] and was recently confirmed by total synthesis.[6]



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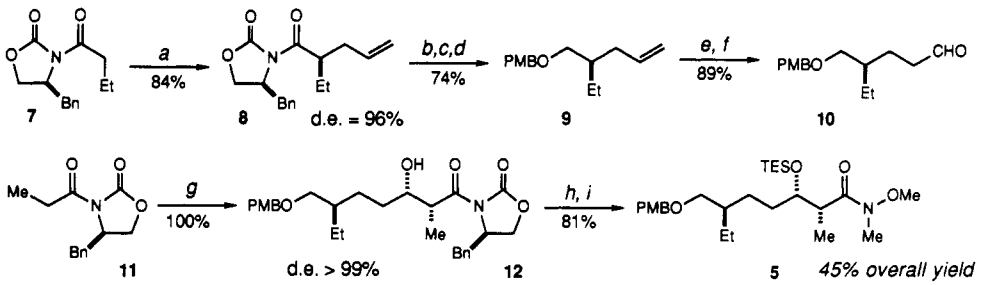
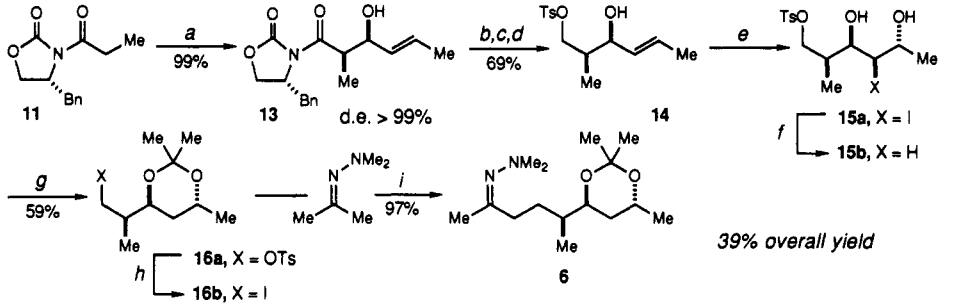
Scheme I[a]



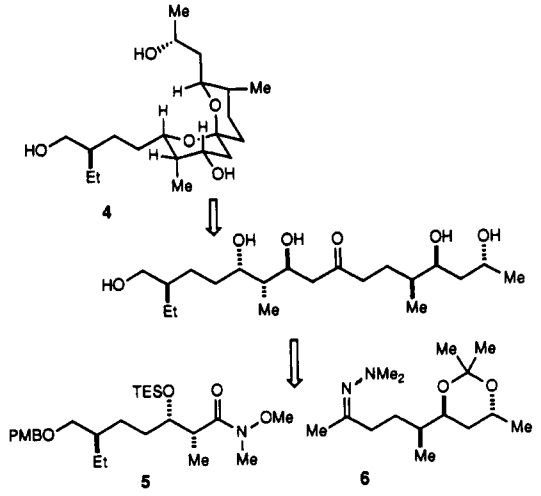
[a] (a) $NaNTMS_2$, allyl iodide; (b) LiOOH, $THF-H_2O$; (c) $LiAlH_4$; (d) PMB-Br, NaH; (e) 9-BBN, NaOOH; (f) Swern oxidation; (g) **10**, n-Bu_2BOTf, Et_3N; (h) $AlMe_3$, MeONHMe·HCl; (i) TES-Cl, imidazole.

Scheme II[a]



[a] (a) n-Bu_2BOTf, Et_3N, crotonaldehyde; (b) LiOOH, $THF-H_2O$; (c) $LiAlH_4$; (d) Ts-Cl, Et_3N; (e) I_2, $THF-H_2O$, KH_2PO_4; (f) n-Bu_3SnH, AIBN; (g) $Me_2C(OMe)_2$, H^+; (h) NaI, acetone; (i) n-BuLi, THF.

We wish to report that, in conjunction with efforts directed toward the development of a total synthesis of rutamycins A and B, the absolute stereochemistry of the rutamycins has now been determined. This has been accomplished through an independent asymmetric synthesis of spiroketal **4**, a known degradation product of rutamycins A and B,[1e] via the amide and hydrazone subunits **5** and **6** illustrated below.



Synthesis of amide **5** (Scheme I) began with the acyloxazolidinone **7**, which was prepared in analogy with our published procedure.[7] Alkylation[8] of the sodium enolate derived from **7** ($NaNTMS_2$, THF) with allyl iodide (3 equiv, −78 °C, 3 h) afforded **8** (84%, de = 96%), which was subjected to saponification (LiOOH, 3:1 THF/H_2O, 0 °C, 1 h)[9] and reduction ($LiAlH_4$, Et_2O, 25 °C, 4 h). Protection of the resulting alcohol (PMBBr, NaH, 1:1 DMF/THF, 25 °C, 24 h) gave the p-methoxybenzyl ether **9** (74% overall from **8**). Hydroboration (9-BBN, THF; NaOOH, 97%) and Swern oxidation (92%)[10] provided aldehyde **10**, which was subsequently employed in a boron-mediated aldol reaction[11] with the N-propionyloxazolidinone **11**[12] to afford the β-hydroxy imide **12** (100%, de >99%). Transamination of **12** ($AlMe_3$ (3 equiv), MeONHMe·HCl (3 equiv), THF, 0 °C, 2.5 h)[13] and silylation of the resulting β-hydroxy amide (TESCl, imidazole, DMF) gave the desired amide **5** in 81% overall yield from **11**. As executed, this route is efficient enough to readily deliver 20-g quantities of **5** without difficulty.

Synthesis of fragment **6** (Scheme II) was initiated with an asymmetric aldol addition[11] of the boron enolate derived from N-propionyloxazolidinone **11** to crotonaldehyde to provide imide **13** (99%) with excellent stereoselectivity (de > 99%). Subsequent saponification,[9] reduction ($LiAlH_4$, Et_2O, 77% from **13**), and monotosylation (TsCl, Et_3N, CH_2Cl_2, 90%) afforded allylic alcohol **14**. At this point, a method for the stereoselective hydration of **14** to produce the requisite anti 1,3-diol was needed. After initial attempts employing mercuric trifluoroacetate on related systems had been proven to be unsuccessful,[14] it was found

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(12) For a detailed procedure for the synthesis of the enantiomeric chiral propionimide, see ref 7.
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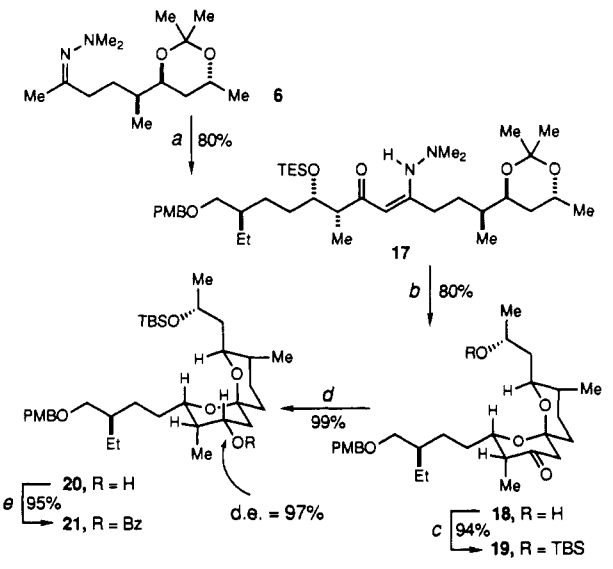
Scheme III[a]



[a] (a) LDA, 5; (b) HF, MeCN–H_2O; (c) TBSCl, Et_3N; (d) SmI_2, Me_2CHOH; (e) BzCl, Et_3N.

that the iodohydroxylation procedure of Chamberlin (I_2, 1:1 THF/pH 5 0.25 M aqueous phosphate buffer, 5–10 °C, 3 h)[15] proceeded with excellent stereoselectivity to afford a 97:3 ratio of iodo diol diastereomers wherein the anti 1,3-diol **15a** was presumed to be the major product in analogy to the Chamberlin precedent. Removal of the iodide by treatment of the unpurified iodo diol mixture with tri-*n*-butylstannane (cat. AIBN, C_6H_6, reflux, 1 h), chromatographic separation of the minor diol diastereomer, and ketalization (2,2-dimethoxypropane, cat. *p*-TsOH, 25 °C, 17 h) afforded the diastereomerically pure acetonide **16a** in 59% overall yield from **14**. At this juncture, the stereochemistry of the iodo hydration reaction (**14** → **15a**) was confirmed by ^{13}C NMR spectroscopy on acetonide **16a**. The chemical shifts of the two acetonide methyl groups were observed to be 24.9 and 24.8 ppm, in excellent agreement with the values commonly observed for an anti 1,3-diol acetonide (25.0 ppm); no resonances were observed in the regions expected for a syn 1,3-diol acetonide (ca. 19 and 30 ppm).[16]

The synthesis of **6** was completed by conversion of tosylate **16a** to the corresponding iodide (NaI, acetone, 25 °C, 40 h), which was treated with (–35 °C, 19 h) 2 equiv of the lithiated (*n*-BuLi, THF, –78 °C, 30 min) acetone dimethylhydrazone[17] to provide the desired hydrazone **6** in excellent yield (97% from **16b**). In the development of this route, the iodo hydration step (**14** → **15a**) was viewed to be one of the most problematic steps. We were concerned that, without adequate deactivation of the primary alcohol function, this heteroatom was ideally positioned to intervene during the olefin iodination. The successful incorporation of the requisite primary tosylate ester into the synthesis *prior* to olefin derivatization provided a convenient solution to the problem of controlling this undesired reaction.

The two spiroketal subunits were assembled according to the acylation procedure outlined in Scheme III.[18] Hydrazone **6** was metalated (LDA, THF, Et_2O, 0 °C, 30 min), cooled to –78 °C, and then transfered by cannula to a THF solution containing amide **5** (–55 → –45 °C, 21 h). Under these conditions, a good yield (80%) of the unstable vinylogous amide **17** was obtained. The choice of solvent and base was found to be critical to the success of this reaction; the LDA in this experiment was prepared by the addition of a solution of MeLi in Et_2O to a solution of diisopropylamine in THF (–30 °C → 0 °C). In contrast, the use of LDA prepared from *n*-BuLi in hexane in closely related systems resulted in incomplete deprotonation. Additives such as hexamethylphosphoramide (HMPA) facilitated proton abstraction but adversely affected the desired acylation reaction. Similar results were obtained when the lithium counterion was varied (KDA vs LDA). Such effects have been independently observed in other hydrazone deprotonation studies.[19] *It appears that a hexane-free medium is essential for complete metalation.* The use of an ethereal solvent mixture (THF with either 2,6-dimethyltetrahydrofuran[19] or Et_2O as cosolvent) is a key component in achieving synthetically useful amounts of hydrazone anions. Utilization of neat Et_2O or THF/hexane (1.6:1) solvent mixtures led to incomplete deprotonation. In our example, the reaction also displayed a concentration dependence; under optimal conditions, the reaction was performed at a substrate concentration of >0.35 M.

Multiple deprotection of **17** and spiroketalization to **18** (80%) was carried out under carefully defined conditions (MeCN/HF/H_2O (84:4:10), 25 °C, 18 h). The selection of the appropriately labile secondary alcohol protecting group (TES) in **17** proved to be important for this transformation. In related studies, an analogous spiroketalization executed with the TBS-protected secondary alcohol resulted in some epimerization at the methyl-bearing stereocenter adjacent to the ketone functionality. Control experiments indicate that epimerization occurs in this system at an intermediate stage in the spiroketalization process.[20]

After silylation of ketone **18** (TBSCl, Et_3N, CH_2Cl_2, 25 °C, 94%), a number of reducing agents that might normally be expected to provide the desired equatorial alcohol **20** proved to be unsatisfactory. For example, $LiAlH_4$ reduction of **19** afforded an ~1:1 mixture of carbinol diastereomers. Similar difficulties in related reductions in the milbemycin area have been previously documented.[21] A welcome solution to this stereochemical issue was found in the application of the samarium(II)-catalyzed Meerwein–Ponndorf–Verley reduction[22] to **19** (0.15 equiv of

(14) These experiments were carried out on the allylic alcohol i. Reaction of i (R_1 = R_2 = acetonide or TBS; R_1 = H, R_2 = TBS, TBDPS, Pv) with $Hg(OTFA)_2$ followed by demercuration with *n*-Bu_3SnH resulted in formation of ii in 40–62% yield and 34–80% de.

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(20) For a more detailed discussion of related cyclizations, see ref 6b.

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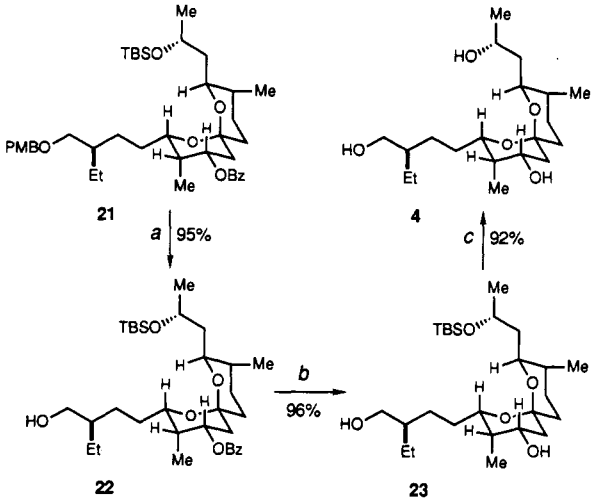
Scheme IV[a]



[a] (a) DDQ, CH_2Cl_2–H_2O; (b) LiOH, THF–MeOH–H_2O; (c) HF, MeCN–CH_2Cl_2.

SmI_2, 10 equiv of Me_2CHOH, THF, 25 °C, 18 h), which produced the desired equatorial alcohol **20** (98%), along with the readily separable axial alcohol contaminant (1%). *Control experiments indicate that this surprisingly stereoselective reaction operates under kinetic control and that the observed stereochemical outcome may be the result of coordination of the reactive reducing agent to the axial spiroketal oxygen.*[23] Benzoylation of equatorial alcohol **20** (BzCl, Et_3N, CH_2Cl_2, 25 °C) gave the differentially protected triol **21** in excellent yield. The choice of protecting groups in this intermediate reflects our intention to utilize this compound in the synthesis of the rutamycins.

Comparison of the absolute stereochemical relationships in the spiroketal degradation product **4** with the protected synthetic analogue **21** was accomplished as described in Scheme IV. Removal of the PMB ether [DDQ, CH_2Cl_2/H_2O (18:1), 95%][24] afforded the primary alcohol **22**, a key intermediate in our projected synthesis of rutamycin. Further deprotection to the triol was performed as shown [(1) LiOH, THF/MeOH/H_2O (2:2:1), 25 °C, 96%; (2) 47% aqueous HF/CH_2Cl_2/CH_3CN (1:5:5), 25 °C, 92%]. The resulting synthetic **4** exhibits chromatographic and spectral characteristics (IR, 500-MHz ^1H NMR, 100-MHz ^{13}C NMR, MS) identical with material derived from rutamycins A and B (**2a,b**). Additionally, the observed optical rotation of the synthetic triol, $[\alpha]^{24}_D$ −95.1° (*c* 0.225, $CHCl_3$), is in good agreement with the value reported for **4**, $[\alpha]_D$ −88.6° (*c* 1.10, $CHCl_3$).[1e] This comparison establishes that the absolute configuration of the rutamycins is as shown (**2a,b**) and that there is a stereochemical homology between the rutamycins and cytovaricin in the spiroketal region. Further work in this area pertaining to total syntheses of rutamycins A and B will be reported in due course.

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(23) Attempts to oxidize the axial alcohol to ketone **19** (excess acetone, THF, 25 °C) or to equilibrate the axial alcohol to equatorial alcohol **20** (1 equiv of acetone, 10 equiv of Me_2CHOH, THF, 25 °C) under samarium catalysis were unsuccessful. Since the samarium-catalyzed Meerwein–Ponndorf–Verley reduction of 4-*tert*-butylcyclohexanone has been reported to give a 3:1 ratio of axial:equatorial alcohols,[22b] we believe the axial spiroketal oxygen in our system must be playing a key role in reduction of **19**.

(24) For a review, see: Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021–3028.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer 781 infrared spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Bruker AM300, AM400, or AM500 spectrometers. Chemical shifts are reported in ppm downfield from a tetramethylsilane internal standard. Optical rotations were measured on a JASCO DIP-181 digital polarimeter. Ethereal solvents were distilled from sodium benzophenone ketyl under N_2. Dichloromethane, acetonitrile, 2-propanol, triethylamine, diisopropylamine, crotonaldehyde, benzene, and diisopropylethylamine were distilled from CaH_2 under N_2. Butyryl chloride and oxalyl chloride were distilled under N_2 prior to use. Dimethylformamide and dimethyl sulfoxide were used as received and stored over 4-Å molecular sieves. Di-*n*-butylboryl trifluoromethanesulfonate[25] and samarium diiodide (SmI_2)[26] were prepared according to the literature procedures. The (*S*)- and (*R*)-4-(phenylmethyl)-1,3-oxazolidin-2-one chiral auxiliaries were prepared as described.[7] All other reagents were used as received. Flash chromatography[27] was performed on silica gel 60 (230–400 mesh, E.M. Science). Analytical HPLC analyses were performed on a Hewlett-Packard HP1090 liquid chromatograph (DuPont Zorbax column, 4.6 mm × 25 cm, 5 μm silica gel, 2 mL/min, 254 nm).

(*S*)-3-(1-Oxobut-1-yl)-4-(phenylmethyl)-1,3-oxazolidin-2-one (7). The following acylation reaction was carried out in analogy to the published procedure.[7] (*S*)-4-(Phenylmethyl)-1,3-oxazolidin-2-one (17.7 g, 0.100 mol) and 5 mg of triphenylmethane were dissolved in 300 mL of THF and cooled to −78 °C under N_2. *n*-BuLi (41.4 mL of a 2.44 M hexane solution, 0.101 mol) was added dropwise until a deep-orange color developed. Butyryl chloride (11.7 g, 11.4 mL, 0.110 mol) was added in one portion, and the light yellow solution was stirred at −78 °C for 30 min and then warmed to ambient temperature. Saturated aqueous NH_4Cl (60 mL) was added, and the THF was removed in vacuo. The residue was extracted twice with 80 mL of CH_2Cl_2; the combined organic extracts were washed successively with 75 mL of 1 N aqueous NaOH and 75 mL of brine, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by flash chromatography (27.5% EtOAc in hexane) to give 24.35 g (99%) of **7** as a light-yellow oil: $[\alpha]^{28}_D$ +58.9° (*c* 1.68, $CHCl_3$); IR (neat) 2965, 1780, 1700, 1385, 1350, 1210, 1095, 760, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (m, 5 H, Ar*H*), 4.68 (m, 1 H, C*H*N), 4.18 (m, 2 H, CH_2O), 3.03 (AB of ABX, J_{AB} = 13.3 Hz, J_{AX} = 9.6 Hz, J_{BX} = 3.3 Hz, $\Delta\nu_{AB}$ = 160.6 Hz, 2 H, ArCH_2), 2.92 (m, 2 H, CH_2CO), 1.73 (m, 2 H, CH_2CH_3), 1.02 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.9, 153.2, 135.3, 129.2, 128.6, 127.0, 65.9, 54.8, 37.7, 37.1, 17.5, 13.4. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. Found: C, 67.88; H, 6.91.

(*S*)-3-[(*R*)-2-Ethyl-1-oxo-4-penten-1-yl]-4-(phenylmethyl)-1,3-oxazolidin-2-one (8). Sodium hexamethyldisilazide (46.0 mL of a 0.97 M THF solution, 0.0445 mol) was cooled to −78 °C under N_2, resulting in a thick suspension. A solution of 10.0 g (0.0405 mol) of the imide **7** in 35 mL of THF was added dropwise at such a rate as to maintain the internal temperature below −70 °C. After 30 min, 20.5 g (11.1 mL, 0.122 mol) of allyl iodide (freshly filtered through neutral alumina into a dry, N_2-flushed flask) was added at such a rate as to maintain the internal temperature below −70 °C. The resulting yellow solution was stirred at −78 °C for 3 h. Saturated aqueous NH_4Cl (20 mL) was added and the THF was removed in vacuo. The residue was diluted with 100 mL of Et_2O and washed successively with 30 mL of H_2O, 30 mL of 1 N aqueous $NaHSO_4$, 30 mL of H_2O, 30 mL of saturated aqueous $NaHCO_3$, and 30 mL of brine. The organic phase was dried ($MgSO_4$) and purified by flash chromatography (20% EtOAc in hexane) to give 9.81 g (84%) of **8** as a very pale yellow oil (diastereomer ratio 98:2 by analytical HPLC): $[\alpha]^{28}_D$ +55.0° (*c* 1.04, $CHCl_3$); IR (neat) 2975, 1785, 1700, 1390, 1350, 1235, 1210, 760, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5 H, Ar*H*), 5.83 (ddt, *J* = 17.1 Hz, *J* = 10.0 Hz, *J* = 7.1 Hz, 1 H, C*H*=CH_2), 5.08 (m, 2 H, CH=CH_2), 4.70 (m, 1 H, C*H*N), 4.15

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(m, 2 H, CH_2O), 3.86 (tt, J = 7.9 Hz, J = 5.8 Hz, 1 H, CHCO), 2.98 (AB of ABX, J_{AB} = 13.3 Hz, J_{AX} = 10.0 Hz, J_{BX} = 3.3 Hz, $\Delta\nu_{AB}$ = 189.5 Hz, 2 H, $ArCH_2$), 2.40 (m, 2 H, $CH_2CH{=}CH_2$), 1.66 (m, 2 H, CH_2CH_3), 0.92 (t, J = 7.4 Hz, 3 H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.7 153.0, 135.4, 135.3, 129.2, 128.7, 127.1, 116.7, 65.8, 55.2, 43.7, 38.0, 36.0, 24.4, 11.3. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37. Found: C, 71.03; H, 7.46. This isomeric mixture was carried forward and the minor isomer was separated from compound **12**.

(*R*)-4-[[(4-Methoxyphenyl)methoxy]methyl]-1-hexene (9). A 30% aqueous hydrogen peroxide solution (16.8 mL, 148 mmol) and a solution of 1.78 g (74.0 mmol) of LiOH in 23 mL of H_2O were added to a solution of 10.61 g (37.0 mmol) of imide **8** in 185 mL of THF/H_2O (3:1) at 0 °C under N_2. After 1 h, 108 mL (163 mmol) of 1.5 N aqueous Na_2SO_3 was added to quench the excess H_2O_2, and the THF was removed in vacuo. The residue (pH = 13) was extracted with three 100-mL portions of CH_2Cl_2. The aqueous phase was acidified (1 N HCl, pH = 1) and extracted with three 100-mL portions of Et_2O. The combined ethereal extracts were dried ($MgSO_4$) and evaporated in vacuo to give the unpurified acid as a clear, colorless oil: IR (CCl_4) 3600–2500, 2960, 1710, 1640, 1280, 1225, 915 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (ddt, J = 17.0 Hz, J = 10.2 Hz, J = 6.7 Hz, 1 H, $CH{=}CH_2$), 5.06 (m, 2 H, $CH{=}CH_2$), 2.40 (m, 2 H, $CH_2CH{=}CH_2$), 2.27 (m, 1 H, CHCO), 1.63, (m, 2 H, CH_2CH_3), 0.95 (t, J = 7.4 Hz, 3 H, CH_2CH_3).

A solution of $LiAlH_4$ (47.8 mL, 1 M in Et_2O, 47.8 mmol) was added dropwise to a solution of the unpurified acid in 160 mL of Et_2O at 0 °C under N_2. The resulting milky mixture was stirred at ambient temperature for 4 h and cooled to 0 °C, and 1.8 mL of H_2O, 1.8 mL of 15% aqueous NaOH, and 5.4 mL of H_2O were added sequentially to quench the excess hydride. Anhydrous Na_2SO_4 was added, and the mixture was stirred at ambient temperature for 10 h to remove residual water. This mixture was filtered through Celite (Et_2O wash), and the solvent was removed from the filtrate by distillation at atmospheric pressure (Vigreaux column) to give the unpurified alcohol as a clear liquid: IR (neat) 3330, 2960, 1640, 1460, 1440, 1035, 995, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddt, J = 17.1 Hz, J = 10.1 Hz, J = 7.2 Hz, 1 H, $CH{=}CH_2$), 5.05 (m, 2 H, $CH{=}CH_2$), 3.57 (AB of ABX, J_{AB} = 10.8 Hz, J_{AX} = 6.0 Hz, J_{BX} = 5.3 Hz, $\Delta\nu_{AB}$ = 5.6 Hz, 2 H, CH_2OH), 2.12 (m, 2 H, $CH_2CH{=}CH_2$), 1.54 (m, 1 H, CH), 1.36 (m, 2 H, CH_2CH_3), 0.92 (t, J = 7.4 Hz, 3 H, CH_2CH_3).

Sodium hydride dispersion (60% in oil), 2.6 g (63.8 mmol), was added in portions to a solution of the unpurified alcohol in 64 mL of THF/DMF (1:1) at 0 °C under N_2. After 15 min, 12.8 g (7.4 mL, 63.8 mmol) of 4-methoxybenzyl bromide was added dropwise, and the resulting mixture was stirred at ambient temperature for 20 h. After cooling to 0 °C, 12.8 mL of H_2O was added dropwise to quench the excess hydride. Diethylamine (4.7 g, 6.6 mL, 63.8 mmol) was added to destroy the excess 4-methoxybenzyl bromide, and the mixture was stirred at 0 °C for 1 h. This mixture was diluted with 250 mL of Et_2O and washed successively with 125 mL of H_2O, two 125-mL portions of saturated aqueous $CuSO_4$, and 125 mL of H_2O. The aqueous layers were extracted twice with 125 mL of Et_2O. The combined organic extracts were dried ($MgSO_4$) and purified by flash chromatography (5% EtOAc in hexane) to give 6.39 g (74%) of ether **9** as a clear, colorless oil: $[\alpha]^{28}_D$ +1.9° (*c* 2.01, $CHCl_3$); IR (neat) 2965, 1615, 1515, 1245, 1170, 1090, 1035, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 2 H, ArH), 6.88 (m, 2 H, ArH), 5.77 (ddt, J = 17.1 Hz, J = 10.0 Hz, J = 7.2 Hz, 1 H, $CH{=}CH_2$), 5.00 (m, 2 H, $CH{=}CH_2$), 4.42 (s, 2 H, $ArCH_2$), 3.81 (s, 3 H, OCH_3), 3.32 (d, J = 5.9 Hz, 2 H, CH_2O), 2.11 (m, 2 H, $CH_2CH{=}CH_2$), 1.64 (m, 1 H, CH), 1.36 (m, 2 H, CH_2CH_3), 0.88 (t, J = 7.4 Hz, 3 H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.2, 137.1, 131.1, 128.9, 115.6, 113.8, 72.7, 72.5, 55.2, 40.0, 35.5, 23.7, 11.1. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.91; H, 9.59.

(*R*)-4-[[(4-Methoxyphenyl)methoxy]methyl]-1-hexanol. A solution of 4.41 g (18.8 mmol) of the alkene **9** in 19 mL of THF was added dropwise to a solution of 4.59 g (37.6 mmol) of 9-borabicyclo[3.3.1]nonane in 75 mL of THF at ambient temperature under N_2. After 30 min, the solution was cooled to 0 °C, and 30 mL (113 mmol) of a 15% aqueous NaOH solution was added dropwise to quench the excess 9-BBN. A 30% aqueous hydrogen peroxide solution (30 mL) was added dropwise (exothermic!). After 15 min, the ice bath was removed and the mixture was stirred at ambient temperature for 3 h. This mixture was diluted with 95 mL of H_2O and 190 mL of Et_2O. The aqueous layer was separated and the organic layer was washed with 95 mL of H_2O and 45 mL of brine. The combined aqueous layers were extracted twice with 50 mL of Et_2O. The combined organic extracts were dried ($MgSO_4$) and purified by flash chromatography (55% EtOAc in hexane) to give 4.58 g (97%) of the title compound as a colorless oil: $[\alpha]^{28}_D$ +1.5° (*c* 1.42, $CHCl_3$); IR (neat) 3390, 2940, 1615, 1465, 1250, 1175, 1090, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 2 H, ArH), 6.88 (m, 2 H, ArH), 4.42 (s, 2 H, $ArCH_2$), 3.81 (s, 3 H, OCH_3), 3.63 (m, 2 H, CH_2OH), 3.34 (AB of ABX, J_{AB} = 9.3 Hz, J_{AX} = 6.2 Hz, J_{BX} = 5.7 Hz, $\Delta\nu_{AB}$ = 12.0 Hz, 2 H, CH_2O), 1.55 (m, 3 H, CH + CH_2CH_2OH), 1.38 (m, 4 H, CH_2CH_3 + $CHCH_2$), 0.87 (t, J = 7.4 Hz, 3 CH_2CH_3); CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.0, 130.7, 129.0, 113.6, 72.7, 72.6, 63.0, 55.1, 39.4, 29.9, 27.0, 23.9, 11.0. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.11; H, 9.57.

(*R*)-4-[[(4-Methoxyphenyl)methoxy]methyl]hexanal (10). Dimethyl sulfoxide (10.8 g, 9.8 mL, 138 mmol) was added to a solution of 8.8 g (6.0 mL, 69 mmol) of oxalyl chloride in 120 mL of CH_2Cl_2 at −78 °C under N_2. After 20 min, 4.5 g (57.5 mmol) of the precursor alcohol was added as a solution in 115 mL of CH_2Cl_2, giving a white precipitate. After 15 min, 13.9 g (19.2 mL, 138 mmol) of triethylamine was added and the thick mixture was warmed slowly to ambient temperature. Ether (250 mL) was added and the mixture was washed twice with 100 mL of half-saturated brine and once with 100 mL of brine. The combined aqueous layers were extracted with 100 mL of Et_2O. The combined organic extracts were dried ($MgSO_4$) and purified by flash chromatography (25% EtOAc in hexane) to give 13.2 g (92%) of aldehyde **10** as a clear colorless oil: $[\alpha]^{28}_D$ +2.1° (*c* 1.82, $CHCl_3$); IR (neat) 2940, 1725, 1615, 1510, 1245, 1090, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, J = 1.8 Hz, 1 H, CHO), 7.25 (m, 2 H, ArH), 6.88 (m, 2 H, ArH), 4.40 (s, 2 H, $ArCH_2$), 3.81 (s, 3 H, OCH_3), 3.32 (AB of ABX, J_{AB} = 9.4 Hz, J_{AX} = 6.2 Hz, J_{BX} = 4.9 Hz, $\Delta\nu_{AB}$ = 22.4 Hz, 2 H, CH_2O), 2.43 (m, 2 H, CH_2CHO), 1.69 (m, 2 H, CH_2CH_2CHO), 1.57 (m, 1 H, CH), 1.35 (m, 2 H, CH_2CH_3), 0.88 (t, J = 7.4 Hz, 3 H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.5, 159.1, 130.9, 129.0, 113.7, 72.7, 72.3, 55.2, 41.4, 39.4, 23.9, 23.6, 11.1. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.90; H, 8.73.

(*R*)-3-{(2*R*,3*S*,6*R*)-3-Hydroxy-6-[[(4-methoxyphenyl)-methoxy]methyl]-2-methyl-1-oxo-1-octyl}-4-(phenylmethyl)-1,3-oxazolidin-2-one (12). Di-*n*-butylboryl trifluoromethanesulfonate (17.4 g, 16.0 mL, 63.5 mmol) was added to a 0 °C solution of 13.4 g (57.7 mmol) of (*R*)-3-(1-oxoprop-1-yl)-4-(phenylmethyl)-1,3-oxazolidin-2-one (**11**) in 105 mL of CH_2Cl_2 under N_2 at such a rate to maintain the internal temperature below +5 °C (thermocouple thermometer). Diisopropylethylamine (8.9 g, 12.0 mL, 69.1 mmol) was then added (internal temperature below +5 °C), giving a light yellow solution. This solution was cooled to −78 °C, giving a yellow mixture, and 13.1 g (52.4 mmol) of the aldehyde **10** was added as a solution in 26 mL of CH_2Cl_2 dropwise by cannula (internal temperature below −70 °C). After 20 min, the solution was warmed to 0 °C and stirred at that temperature for 1 h. This solution was cooled to −10 °C (ice–acetone bath) and the reaction was quenched by dropwise addition of 50 mL of pH 7 phosphate buffer, 150 mL of MeOH, and 150 mL of MeOH/30% aqueous H_2O_2 (2:1) (internal temperature below +10 °C). The resulting mixture was stirred at 0 °C for 1 h and the volatiles were removed in vacuo. The residue was extracted with three 150-mL portions of Et_2O. The combined organic extracts were washed with 100 mL of saturated aqueous $NaHCO_3$ and 100 mL of brine. The combined aqueous layers were extracted with 50 mL of Et_2O. The combined organic extracts were dried ($MgSO_4$) and purified by flash chromatography (55% EtOAc in hexane) to give 25.30 g (100%) of the aldol **12** as a colorless oil (de > 99% by analytical HPLC): $[\alpha]^{28}_D$ −40.9° (*c* 0.350, $CHCl_3$); IR (neat) 3530, 2940, 1785, 1700, 1515, 1385, 1245, 1210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 7 H, ArH), 6.87 (m, 2 H, ArH), 4.69 (m, 1 H, CHN), 4.42 (s, 2 H, $ArCH_2$), 4.20 (m, 2 H, $NCHCH_2O$), 3.91 (m, 1 H, CHOH), 3.80 (s, 3 H, OCH_3), 3.74 (qd, J = 7.1 Hz, J = 2.6 Hz, 1 H, $CHCH_3$), 3.33 (d, J = 5.5 Hz, 2 H, CH_2O), 3.01 (AB of ABX, J_{AB} = 13.4 Hz, J_{AX} = 9.5 Hz, J_{BX} = 3.3 Hz, $\Delta\nu_{AB}$ = 138.7 Hz, 2 H, CH_2Ph), 2.89 (d, J = 3.0 Hz,

1 H, OH), 1.66–1.29 (m, 7 H, $CH_2CHCH_2CH_2$), 1.25 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 0.87 (t, J = 7.4 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.4, 158.9, 152.9, 135.0, 130.8, 129.3, 129.0, 128.9, 127.3, 113.6, 72.6, 71.7, 66.0, 55.2, 55.1, 55.0, 42.0, 39.5, 37.7, 31.0, 27.2, 23.9, 11.0, 10.4. Anal. Calcd for $C_{28}H_{37}NO_6$: C, 69.54; H, 7.71. Found: C, 69.51; H, 7.75.

(2*R*,3*S*,6*R*)-*N*,2-Dimethyl-*N*-methoxy-6-[[(4-methoxyphenyl)methoxy]methyl]-3-[(triethylsilyl)oxy]octanamide (5). $AlMe_3$ (78.8 mL of a 2.0 M toluene solution, 158 mmol) was added to a suspension of 15.2 g (156 mmol) of MeHNOMe·HCl in 80 mL of THF at 0 °C under N_2 (gas evolution). The ice bath was removed and the solution was stirred at ambient temperature for 30 min. This solution was cooled to −15 °C and a solution of 25.1 g (52.0 mmol) of the imide **12** in 80 mL of THF was added by cannula. The resulting mixture was allowed to warm to 0 °C and stirred at that temperature for 2.5 h. The resulting clear solution was transferred by cannula to a well-stirred mixture of 400 mL of CH_2Cl_2 and 800 mL of 0.5 N aqueous HCl at 0 °C. This mixture was stirred at 0 °C for 1 h and the organic layer was separated. The aqueous layer was extracted with three 250-mL portions of CH_2Cl_2. The combined organic extracts were washed with 250 mL of brine, dried (Na_2SO_4), and evaporated in vacuo to give a mixture of the oxazolidinone and the hydroxy amide as a pale yellow oil.

Chlorotriethylsilane (8.6 g, 9.6 mL, 57.3 mmol) and 7.1 g (104 mmol) of imidazole were added to a solution of the unpurified hydroxy amide in 104 mL of DMF at ambient temperature under N_2. A mild exotherm developed. After 30 min, 200 mL of H_2O was added, and the mixture was extracted with three 200-mL portions of Et_2O. The combined organic extracts were washed twice with 100 mL of saturated aqueous $CuSO_4$ and once each with 100 mL of H_2O and brine. The organic layer was dried ($MgSO_4$) and purified by flash chromatography (25% EtOAc in hexane) to give 20.14 g (81%) of **5** as a very pale yellow oil: $[\alpha]^{28}_D$ −1.3° (*c* 1.10, $CHCl_3$); IR (neat) 2965, 1665, 1515, 1460, 1245, 1110, 1100, 1055, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 2 H, ArH), 6.86 (m, 2 H, ArH), 4.39 (s, 2 H, $ArCH_2$), 3.93 (m, 1 H, CHOTES), 3.80 (s, 3 H, OCH_3), 3.62 (s, 3 H, $NOCH_3$), 3.29 (d, J = 5.4 Hz, 2 H, CH_2O), 3.13 (s, 3 H, NCH_3), 2.95 (m, 1 H, $CHCH_3$), 1.42 (m, 7 H, $CH_2CHCH_2CH_2$), 1.16 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 0.96 (t, J = 7.6 Hz, 9 H, $SiCH_2CH_3$), 0.85 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.62 (q, J = 7.6 Hz, 6 H, $SiCH_2CH_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 176.5, 158.9, 130.9, 128.9, 113.5, 73.9, 72.7, 72.6, 61.2, 55.1, 55.1, 40.6, 40.1, 33.1, 25.5, 24.0, 14.4, 11.0, 6.9, 5.1. Anal. Calcd for $C_{26}H_{47}NO_5Si$: C, 64.82; H, 9.83. Found: C, 64.99; H, 9.95.

(4*R*)-3-[(*E*)-(2*R*,3*R*)-3-Hydroxy-2-methyl-1-oxo-4-hexen-1-yl]-4-(phenylmethyl)-1,3-oxazolidin-2-one (13). Di-*n*-butylboryl trifluoromethanesulfonate (25.9 g, 23.8 mL, 94.4 mmol) was added dropwise to a 0 °C solution of 20.0 g (85.8 mmol) of (*R*)-3-(1-oxoprop-1-yl)-4-(phenylmethyl-1,3-oxazolidin-2-one (**11**) in 172 mL of CH_2Cl_2 under N_2 at such a rate to maintain the internal temperature below 3 °C. To the resulting copper-colored solution was added 10.4 g (14.3 mL, 103 mmol) of Et_3N (internal temperature below 3 °C). The resulting yellow solution was cooled to −78 °C, and 6.6 g (7.9 mL, 94.4 mmol) of crotonaldehyde was added dropwise (internal temperature below −70 °C). After 20 min at −78 °C, the solution was warmed to 0 °C and stirred at 0 °C for 1 h. This tan solution was cooled to −10 °C and the reaction was quenched by addition of 86 mL of pH 7 aqueous phosphate buffer solution and 258 mL of MeOH (internal temperature below 10 °C). A solution of MeOH/30% aqueous H_2O_2 (2:1, 259 mL) was added dropwise (internal temperature below 10 °C), and the pale yellow solution was stirred at 0 °C for 1 h. The resulting colorless solution was concentrated on a rotary evaporator, and the residue was extracted with three 500-mL portions of Et_2O. The combined organic extracts were washed with 500 mL of saturated aqueous $NaHCO_3$ and 500 mL of brine and then dried over $MgSO_4$. Purification by flash chromatography (40% EtOAc in hexane) gave 25.74 g (99%) of **13** as a colorless oil (de = >99% by analytical HPLC): $[\alpha]^{28}_D$ −58.1° (*c* 0.645, $CHCl_3$); IR (neat) 3520, 1780, 1700, 1455, 1380, 1210, 1110, 965, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.18 (m, 5 H, ArH), 5.77 (dq, J = 15.3 Hz, J = 6.4 Hz, 1 H, $CHCHCH_3$), 5.52 (ddq, J = 15.3 Hz, J = 6.4 Hz, J = 1.5 Hz, 1 H, $CHCHCH_3$), 4.71 (m, 1 H, NCH), 4.43 (m, 1 H, CHOH), 4.20 (m, 2 H, CH_2O), 3.86 (qd, J = 7.0 Hz, J = 3.7 Hz, 1 H, $CHCH_3$), 3.02 (AB of ABX, J_{AB} = 13.4 Hz, J_{AX} = 9.5 Hz, J_{BX} = 3.3 Hz, $\Delta\nu_{AB}$ = 140.7 Hz, 2 H, CH_2Ar), 1.72 (br d, J = 6.5 Hz, 3 H, $CH{=}CHCH_3$), 1.25 (d, J = 7.0 Hz, 3 H, $CHCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.2, 153.0, 135.0, 130.4, 129.2, 128.7, 127.8, 127.2, 72.7, 66.0, 55.0, 42.8, 37.6, 17.5, 11.3. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98. Found: C, 67.30; H, 7.04.

(*E*)-(2*S*,3*R*)-2-Methyl-4-hexene-1,3-diol. A 30% aqueous H_2O_2 solution (38.8 mL, 380 mmol) and a solution of 4.56 g (190 mmol) of LiOH in 51 mL of H_2O were added to a solution of 28.78 g (95.0 mmol) of the imide **13** in 475 mL of THF/H_2O (3:1) at 0 °C under N_2. The resulting solution was stirred at 0 °C for 1 h, and then 279 mL (418 mmol) of 1.5 N aqueous Na_2SO_3 was added to quench the excess H_2O_2. The solvent was removed in vacuo and the residue (pH = 12) was extracted with three 100-mL portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were extracted with 100 mL of 3:1 H_2O/saturated aqueous $NaHCO_3$. The combined aqueous layers were acidified with 6 N aqueous HCl (pH = 1), saturated with NaCl, and extracted with five 100-mL portions of EtOAc. The combined EtOAc extracts were dried (Na_2SO_4) and evaporated in vacuo to give 13.24 g (97%) of the unpurified acid as a clear oil: IR (neat) 3700–2300, 1720, 1460, 1380, 1240, 1010, 965 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (dqd, J = 15.3 Hz, J = 6.5 Hz, J = 0.9 Hz, 1 H, $CHCHCH_3$), 5.51 (ddq, J = 15.3 Hz, J = 7.0 Hz, J = 1.7 Hz, 1 H, $CHCHCH_3$), 4.37 (m, 1 H, CHOH), 2.69 (qd, J = 7.1 Hz, J = 4.2 Hz, 1 H, $CHCH_3$), 1.73 (dd, J = 6.5 Hz, J = 1.7 Hz, 3 H, $CH{=}CHCH_3$), 1.19 (d, J = 7.1 Hz, 3 H, $CHCH_3$).

A solution of $LiAlH_4$ (184 mL, 1 M in Et_2O, 184 mmol) was added dropwise to a solution of the unpurified hydroxy acid in 194 mL of Et_2O at 0 °C under N_2. The resulting mixture was stirred at ambient temperature for 4 h. After recooling to 0 °C, 184 mL of saturated aqueous sodium potassium tartrate was added dropwise to quench the excess hydride. This mixture was diluted with 184 mL of H_2O and stirred vigorously for 21 h. The organic layer was separated and the aqueous layer was extracted with five 100-mL portions of EtOAc. The combined organic extracts were dried (Na_2SO_4) and purified by flash chromatography (90% EtOAc in hexane) to give 9.19 g (77%) of the title compound as a colorless oil: $[\alpha]^{28}_D$ −0.35° (*c* 0.865, $CHCl_3$); IR (neat) 3360, 2920, 1450, 1380, 1100, 1030, 965, 925 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (dq, J = 15.3 Hz, J = 6.2 Hz, 1 H, $CHCHCH_3$), 5.58 (ddq, J = 15.3 Hz, J = 6.8 Hz, J = 1.3 Hz, 1 H, $CHCHCH_3$), 4.23 (dd, J = 6.8 Hz, J = 3.9 Hz, 1 H, CHOH), 3.67 (AB of ABX, J_{AB} = 10.8 Hz, J_{AX} = 7.6 Hz, J_{BX} = 4.2 Hz, $\Delta\nu_{AB}$ = 17.0 Hz, 2 H, CH_2OH), 2.33 (s, 2 H, OH), 1.95 (m, 1 H, $CHCH_3$), 1.74 (br d, J = 6.2 Hz, 3 H, $CH{=}CHCH_3$), 0.87 (d, J = 7.1 Hz, 3 H, $CHCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 131.1, 127.0, 75.1, 65.4, 39.8, 17.5, 11.3. Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.35; H, 10.69.

(*E*)-(2*S*,3*R*)-2-Methyl-1-[[(4-methylphenyl)sulfonyl]oxy]-4-hexen-3-ol (14). Triethylamine (14.3 g, 19.7 mL, 141 mmol), 20.2 g (106 mmol) of 4-(methylphenyl)sulfonyl chloride, and a catalytic amount of 4-(dimethylamino)pyridine were added to a solution of 9.19 g (70.7 mmol) of the precursor diol in 141 mL of CH_2Cl_2 at ambient temperature under N_2. After being stirred for 16 h, the mixture was diluted with 300 mL of Et_2O and washed twice with 150 mL of H_2O and once with 150 mL of brine. The combined aqueous layers were extracted with 150 mL of Et_2O. The combined organic extracts were dried ($MgSO_4$) and purified by flash chromatography (30% EtOAc in hexane) to give 18.01 g (90%) of **14** as a colorless oil: $[\alpha]^{28}_D$ −6.2° (*c* 1.36, $CHCl_3$); IR (neat) 3550, 1365, 1190, 1175, 1100, 965, 835, 815, 665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 2 H, ArH), 7.35 (m, 2 H, ArH), 5.64 (dqd, J = 15.3 Hz, J = 6.3 Hz, J = 0.9 Hz, 1 H, $CHCHCH_3$), 5.40 (ddq, J = 15.3 Hz, J = 6.8 Hz, J = 1.5 Hz, 1 H, $CHCHCH_3$), 4.08 (m, 1 H, CHOH), 3.98 (AB of ABX, J_{AB} = 9.6 Hz, J_{AX} = 6.7 Hz, J_{BX} = 6.1 Hz, $\Delta\nu_{AB}$ = 55.4 Hz, 2 H, CH_2O), 2.45 (s, 3 H, $ArCH_3$), 1.93 (m, 1 H, $CHCH_3$), 1.67 (dd, J = 6.3 Hz, J = 1.5 Hz, 3 H, $CH{=}CHCH_3$), 0.90 (d, J = 6.9 Hz, 3 H, $CHCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.6, 133.1, 131.3, 129.7, 127.8, 127.7, 74.0, 72.4, 38.5, 21.4, 17.4, 10.9. Anal. Calcd for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.09. Found: C, 59.25; H, 7.21.

(4*S*,6*R*)-2,2-Dimethyl-6-methyl-4-[(*S*)-1-[[(4-methylphenyl)sulfonyl]oxy]-2-propanyl]-1,3-dioxane (16a). A solution of 48.3 g (190 mmol) of I_2 in 297 mL of THF was added dropwise to a rapidly stirred mixture of 18.01 g (63.4 mmol) of

the allylic alcohol **14** in 99 mL of THF and 396 mL of 0.25 M aqueous KH_2PO_4 at 5 °C. The mixture was maintained between 5 °C and 10 °C for 3 h and then at ambient temperature for 1 h. Saturated aqueous Na_2SO_3 was added to quench the excess I_2, and the mixture was extracted with four 400-mL portions of EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give a mixture of iodo diols **15a** as a yellow, highly viscous oil.

Benzene (127 mL), AIBN (cat.), and tri-*n*-butylstannane (22.1 g, 20.5 mL, 76.1 mmol) were added to the unpurified iodo diols **15a**, and the resulting mixture was heated under reflux for 1 h. After cooling to ambient temperature, the solvent was removed in vacuo. The residue was diluted with 600 mL of hexane and extracted with three 150-mL portions of CH_3CN. The combined CH_3CN extracts were dried (Na_2SO_4) and the minor syn diol was separated by flash chromatography (50% EtOAc in hexane) to give the pure anti diol **15b** containing some tri-*n*-butyliodostannane (approximately 10%).

A catalytic amount of *p*-toluenesulfonic acid was added to a solution of the unpurified diol **15b** in 158 mL of 2,2-dimethoxypropane at ambient temperature under N_2. After 17 h, the solution was diluted with 450 mL of Et_2O and washed with 150 mL of saturated aqueous $NaHCO_3$ and 150 mL of brine. The combined aqueous layers were extracted with 150 mL of Et_2O. The combined organic extracts were dried ($MgSO_4$) and purified by flash chromatography (25% EtOAc in hexane) to give 12.83 g (59%) of **16a** as a colorless oil: $[\alpha]^{28}_D$ −18.9° (*c* 1.205, CH_2Cl_2); IR (neat) 2990, 1365, 1225, 1190, 1175, 970, 945, 835, 815, 665 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.71 (m, 2 H, Ar*H*), 6.85 (m, 2 H, Ar*H*), 3.96 (AB of ABX, J_{AB} = 8.5 Hz, J_{AX} = 6.5 Hz, J_{BX} = 5.9 Hz, $\Delta\nu_{AB}$ = 69.8 Hz, 2 H, CH_2O), 3.72 (m, 1 H, one of CHO), 3.65 (m, 1 H, one of CHO), 1.80 (s, 3 H, $ArCH_3$), 1.63 (m, 1 H, $CHCH_3$), 1.32 (m, 1 H, one of $CHCH_2CH$), 1.23 (s, 6 H, $C(CH_3)_2$), 1.02 (m, 1 H, one of $CHCH_2CH$), 1.02 (d, *J* = 6.2 Hz, 3 H, $OCHCH_3$), 0.80 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$); ^{13}C NMR (75.5 MHz, C_6H_6) δ 144.5, 134.2, 129.9, 128.1, 100.1, 71.9, 66.0, 62.9, 37.5, 37.0, 24.9, 24.8, 21.8, 21.2, 11.3. Anal. Calcd for $C_{17}H_{26}O_5S$: C, 59.63; H, 7.65. Found: C, 59.47; H, 7.57.

(5*S*)-5-[(4*S*,6*R*)-2,2-Dimethyl-6-methyl-1,3-dioxan-4-yl]-2-hexanone Dimethylhydrazone (6). Sodium iodide (27.4 g, 183 mmol) was added to a solution of 12.5 g (36.5 mmol) of the tosylate **16a** in 73 mL of acetone at ambient temperature under N_2. After being stirred for 40 h, the mixture was diluted with 140 mL of Et_2O and washed with three 140-mL portions of H_2O. The combined aqueous layers were extracted twice with 140 mL of Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give the iodide **16b** as a brown oil.

A solution of *n*-BuLi (22 mL, 2.40 M in hexane, 52.8 mmol) was added dropwise to a solution of 7.0 g (8.9 mL, 70.4 mmol) of acetone dimethylhydrazone in 70 mL of THF at −78 °C under N_2. After 30 min, a solution of the unpurified iodide **16b** in 140 mL of THF was added by cannula, and the resulting mixture was stirred at −35 °C overnight (22 h). Saturated aqueous NH_4Cl (140 mL) was added to quench and the mixture was warmed to ambient temperature. This mixture was diluted with 280 mL of Et_2O and washed with three 100-mL portions of H_2O and once with 100 mL of brine. The combined aqueous layers were extracted twice with 100 mL of Et_2O. The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give 9.57 g (97%) of **6** as a very pale yellow oil (*E*:*Z* = 4.2:1.0 by ^1H NMR): bp 87–91 °C (16 mTorr); $[\alpha]^{28}_D$ −45.4° (*c* 0.815, CH_2Cl_2); IR (neat) 2990, 1380, 1225, 1180, 1150, 1135, 1010 cm^{-1}; ^1H NMR (major isomer, 300 MHz, C_6D_6) δ 3.81 (m, 1 H, $CH_3CH(O)CH_2$), 3.60 (dt, *J* = 9.5 Hz, *J* = 6.1 Hz, 1 H, $CH_2CH(O)CH$), 2.42 (s, 6 H, $N(CH_3)_2$), 2.17 (m, 2 H, CH_2CN), 1.80 (s, 3 H, CH_3CN), 1.74 (m, 1 H, $CHCH_3$), 1.52 (m, 2 H, CH_2CH_2CN), 1.36 (s, 6 H, $C(CH_3)_2$), 1.29 (m, 2 H, CH_2CH_2CH), 1.10 (d, *J* = 6.3 Hz, 3 H, $OCHCH_3$), 0.97 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$); minor isomer shows δ 2.43 (s, $N(CH_3)_2$), 1.82 (s, CH_3CN), 1.37 (s, $C(CH_3)_2$), 0.98 (d, *J* = 6.6 Hz, $CHCH_3$); ^{13}C NMR (major isomer, 75.5 MHz, C_6D_6) δ 166.2, 100.0, 69.8, 63.0, 47.7, 47.2, 38.0, 37.6, 36.6, 29.2, 25.2, 24.9, 22.0, 16.5, 15.0; minor isomer shows δ 168.2, 69.4, 63.1, 48.2, 37.9, 37.5, 29.1, 22.4, 14.8. Anal. Calcd for $C_{15}H_{30}N_2O_2$: C, 66.63; H, 11.18. Found: C, 66.56; H, 10.97.

(*Z*)-(2*S*,8*R*,9*S*,12*R*)-5-(2,2-Dimethylhydrazino)-12-[[(4-methoxyphenyl)methoxy]methyl]-8-methyl-9-[(triethylsilyl)oxy]-2-[(4*R*,6*S*)-2,2,4-trimethyl-1,3-dioxan-6-yl]-5-tetradecen-7-one (17). A solution of methyllithium (35.4 mL, 1.4 M in Et_2O, 49.6 mmol) was added to a solution of 5.6 g (7.8 mL, 55.8 mmol) of diisopropylamine in 22 mL of THF at −30 °C under N_2. The solution was stirred at 0 °C for 10 min and then cooled to −10 °C. A solution of 11.96 g (44.3 mmol) of hydrazone **6** in 11 mL of THF was added by cannula, and the resulting yellow solution was stirred at 0 °C for 30 min and then cooled to −78 °C. This solution was then added by cannula to a cold (−55 °C) solution of 20.0 g (41.6 mmol) of amide **5** in 29 mL of THF. The resulting yellow-orange solution was stirred at −45 °C for 18 h. This solution was cooled to −78 °C and transferred by cannula to a cool (0 °C), rapidly stirred mixture of 120 mL of Et_2O and 120 mL of saturated aqueous NH_4Cl. After 10 min, the organic layer was separated and the aqueous layer was extracted with three 120-mL portions of EtOAc. The combined organic extracts were dried (Na_2SO_4) and purified by flash chromatography (20% EtOAc in hexane) to give 22.95 g (80%) of the unstable vinylogous amide **17** as a colorless oil: ^1H NMR (500 MHz, C_6D_6) δ 11.73 (s, 1 H, N*H*), 7.27 (m, 2 H, Ar*H*), 6.83 (m, 2 H, Ar*H*), 5.15 (s, 1 H, $CHCO$), 4.36 (s, 2 H, $ArCH_2$), 4.32 (m, 1 H, $CHOTES$), 3.85 (m, 1 H, $CH_3CH(O)CH_2$), 3.67 (dt, *J* = 9.6 Hz, *J* = 6.0 Hz, 1 H, $CH_2CH(O)CH$), 3.35 (d, *J* = 5.4 Hz, 2 H, CH_2O), 3.31 (s, 3 H, OCH_3), 2.72 (m, 1 H, CH_3CHCO), 2.37 (AB of ABXY, 2 H, CH_2CN), 2.10 (s, 6 H, $N(CH_3)_2$), 1.87–1.32 (m, 12 H), 1.43 (d, *J* = 7.0 Hz, 3 H, CH_3CHCO), 1.38 (s, 3 H, one of $C(CH_3)_2$), 1.37 (s, 3 H, one of $C(CH_3)_2$), 1.14 (d, *J* = 6.2 Hz, 3 H, $OCHCH_3$), 1.09 (t, *J* = 8.0 Hz, 9 H, $SiCH_2CH_3$), 1.00 (d, *J* = 6.7 Hz, 3 H, $CHCH_3$), 0.92 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 0.73 (q, *J* = 8.0 Hz, 6 H, $SiCH_2CH_3$).

(2*S*,3*R*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-hydroxy-1-propyl]-2-{(*R*)-3-[[(4-methoxyphenyl)methoxy]methyl]-1-pentyl}-1,7-dioxaspiro[5.5]undecan-4-one (18). The vinylogous amide **17** (223.3 mg, 0.324 mmol) was dissolved in 2 mL of 9:1 [95:5 CH_3CN/47% aqueous HF]/H_2O, and the solution was stirred at ambient temperature for 18 h. Saturated aqueous $NaHCO_3$ (2 mL) and 10 mL of H_2O were added, and the mixture was extracted with one 10-mL portion of EtOAc and three 10-mL portions of Et_2O. The combined organic extracts were washed with 10 mL of brine, dried ($MgSO_4$), and purified by flash chromatography (35% EtOAc in hexane) to give 123.5 mg (80%) of **18** as a colorless oil: $[\alpha]^{20}_D$ −79.7° (*c* 1.25, $CHCl_3$); IR (neat) 3480, 2960, 1720, 1305, 1245, 1095, 1055, 1040, 975 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.26 (m, 2 H, Ar*H*), 6.88 (m, 2 H, Ar*H*), 4.42 (s, 2 H, $ArCH_2$), 4.00 (m, 2 H, two of CHO), 3.85 (m, 1 H, $CHOH$), 3.81 (s, 3 H, OCH_3), 3.33 (AB of ABX, J_{AB} = 9.1 Hz, J_{AX} = 6.3 Hz, J_{BX} = 5.8 Hz, $\Delta\nu_{AB}$ = 57.3 Hz, 2 H, CH_2O), 2.41 (AB, J_{AB} = 14.4 Hz, $\Delta\nu_{AB}$ = 107.4 Hz, 2 H, CH_2CO), 2.32 (m, 1 H, $CHCO$), 2.14 (m, 1 H, $O_2CCH_2CH_{ax}$), 1.67–1.14 (m, 14 H), 1.09 (d, *J* = 6.2 Hz, 3 H, CH_3CHOH), 1.08 (d, *J* = 7.0 Hz, 3 H, $CH_2CHC{=}O$), 0.90 (d, *J* = 6.9 Hz, 3 H, $CH_3CHCH_2CH_2$), 0.87 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 210.8, 159.0, 130.6, 129.1, 113.6, 98.9, 72.6, 72.6, 70.6, 67.9, 63.9, 55.1, 48.3, 48.0, 42.2, 39.7, 30.1, 29.4, 28.3, 26.8, 26.5, 24.6, 23.7, 11.1, 10.5, 0.7. Anal. Calcd for $C_{28}H_{44}O_6$: C, 70.56; H, 9.30. Found: C, 70.65; H, 9.28.

(2*S*,3*R*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl]-2-{(*R*)-3-[[(4-methoxyphenyl)methoxy]methyl]-1-pentyl}-1,7-dioxaspiro[5.5]undecan-4-one (19). Imidazole (2.2 g, 32.1 mmol) and 4.0 g (26.9 mmol) of *tert*-butylchlorodimethylsilane were added to a solution of 10.2 g (21.4 mmol) of alcohol **18** in 40 mL of CH_2Cl_2 at ambient temperature under N_2. After 5 h, the mixture was diluted with 40 mL of H_2O and 80 mL of Et_2O. The aqueous layer was separated and the organic layer was washed with 40 mL of H_2O and 40 mL of brine. The combined aqueous layers were extracted twice with 40 mL of Et_2O. The combined organic extracts were dried ($MgSO_4$) and purified by flash chromatography (15% EtOAc in hexane) to give 11.89 g (94%) of **19** as a colorless oil: $[\alpha]^{20}_D$ −55.0° (*c* 1.05, $CHCl_3$); IR (neat) 2950, 1725, 1515, 1245, 1090, 1040, 980, 835, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 2 H, Ar*H*), 6.86 (m, 2 H, Ar*H*), 4.42 (s, 2 H, $ArCH_2$), 3.82 (m, 1 H, $CHOTBS$), 3.80 (s, 3 H, OCH_3), 3.74 (m, 2 H, two of CHO), 3.33 (AB of ABX, J_{AB} = 9.2 Hz, J_{AX} = 5.8 Hz, J_{BX} = 5.5 Hz, $\Delta\nu_{AB}$ = 15.8 Hz, 2 H, CH_2O), 2.40 (AB, J_{AB} = 14.5 Hz, $\Delta\nu_{AB}$ = 114.9 Hz, 2 H, CH_2CO), 2.30 (m, 1 H, $CHCO$), 2.10 (m, 1 H, $O_2CCH_2CH_{ax}$), 1.68–1.25 (m, 13 H), 1.11 (d, *J* = 6.0 Hz, 3 H, $CH_3CHOTBS$), 1.07

(d, J = 7.1 Hz, 3 H, $CH_3CHC{=}O$), 0.92 (d, J = 6.9 Hz, 3 H, $CH_3CHCH_2CH_2$), 0.87 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.02 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 159.0, 130.7, 129.0, 113.6, 99.0, 72.6, 72.4, 70.6, 70.0, 67.1, 55.1, 48.2, 48.0, 42.9, 39.8, 29.4, 29.1, 28.7, 27.5, 26.4, 25.8, 24.3, 23.5, 18.0, 11.0, 10.9, 10.6, -4.4, -4.6. Anal. Calcd for $C_{34}H_{58}O_6Si$: C, 69.11; H, 9.89. Found: C, 69.19; H, 9.93.

(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl]-2-{(*R*)-3-[[(4-methoxyphenyl)methoxy]methyl]-1-pentyl}-1,7-dioxaspiro[5.5]undecan-4-ol (20) and (2*S*,3*S*,4*R*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl]-2-{(*R*)-3-[[(4-methoxyphenyl)methoxy]methyl]-1-pentyl}-1,7-dioxaspiro[5.5]undecan-4-ol. Method A. A solution of $LiAlH_4$ (1.01 mL, 1.0 M in THF, 1.01 mmol) was added to a solution of 596 mg (1.01 mmol) of the ketone **19** in 6.0 mL of THF at -78 °C under N_2. After 1 h, 6 mL of saturated aqueous sodium potassium tartrate was added carefully, and the mixture was stirred rapidly at ambient temperature for 1 h. The resulting mixture was diluted with 6 mL of H_2O and extracted with three 25-mL portions of Et_2O. The combined organic extracts were dried ($MgSO_4$) and purified by flash chromatography (20% EtOAc in hexane, then 50% EtOAc in hexane) to give 330.5 mg (55%) of the equatorial alcohol **20** and 266.1 mg (45%) of the axial alcohol as colorless oils.

Method B. To a solution of 10.73 g (18.2 mmol) of the ketone **19** in 62 mL of THF at ambient temperature under N_2 were added 10.9 g (13.9 mL, 182 mmol) of degassed 2-propanol and 27.3 mL (2.73 mmol) of a 0.1 M solution of SmI_2 in THF. The resulting deep blue-green solution was stirred at ambient temperature for 18 h. Saturated aqueous $NaHCO_3$ (60 mL) was added to quench. This mixture was diluted with 120 mL of Et_2O and the layers were separated. The organic layer was washed with 60 mL of saturated aqueous $NaHCO_3$. The combined aqueous layers were extracted twice with 60 mL of Et_2O. The combined organic extracts were washed with 60 mL of 1.5 N aqueous Na_2SO_3 and 60 mL of brine. After drying over $MgSO_4$, the organic layer was purified by flash chromatography (18% EtOAc in hexane, then 50% EtOAc in hexane) to give 10.56 g (98%) of the equatorial alcohol **20** and 0.14 g (1%) of the axial alcohol as colorless oils. The equatorial:axial ratio was 98.5:1.5.

Data for the equatorial alcohol 20: $[\alpha]^{18}_D$ -42.2° (*c* 0.495, $CHCl_3$); IR (neat) 3420, 2940, 1515, 1245, 1090, 1040, 1180, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 2 H, Ar*H*), 6.86 (m, 2 H, Ar*H*), 4.42 (s, 2 H, $ArCH_2$), 4.18 (dt, J = 11.8 Hz, J = 4.8 Hz, 1 H, C*H*OH), 3.80 (s, 3 H, OCH_3), 3.78 (m, 1 H, one of C*H*O), 3.74 (m, 1 H, one of C*H*O), 3.54 (m, 1 H, C*H*OTBS), 3.33 (d, J = 5.7 Hz, 2 H, CH_2O), 2.07 (tt, J = 13.5 Hz, J = 4.3 Hz, 1 H, $O_2CCH_2CH_{ax}$), 1.84-1.23 (m, 16 H), 1.16 (d, J = 6.0 Hz, 3 H, $CH_3CHOTBS$), 0.93 (d, J = 7.0 Hz, 3 H, $CH_3CHCH_2CH_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.87 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.82 (d, J = 6.9 Hz, 3 H, $CH_3CHCHOH$), 0.04 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.0, 130.9, 129.0, 113.6, 97.4, 72.7, 72.6, 71.2, 69.2, 67.3, 67.2, 55.2, 43.2, 39.8, 39.0, 37.9, 29.8, 29.7, 29.6, 27.8, 26.4, 25.8, 24.4, 23.6, 18.0, 11.0, 10.9, 4.0, -4.4, -4.6. Anal. Calcd for $C_{34}H_{60}O_6Si$: C, 68.87; H, 10.20. Found: C, 68.97; H, 10.39.

Data for the axial alcohol: $[\alpha]^{18}_D$ -31.0° (*c* 0.345, $CHCl_3$); IR (neat) 3520, 2940, 1515, 1245, 1120, 1090, 1045, 975, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 2 H, Ar*H*), 6.86 (m, 2 H, Ar*H*), 4.42 (s, 2 H, $ArCH_2$), 3.91 (m, 1 H, C*H*OH), 3.84 (m, 1 H, one of C*H*O), 3.80 (m, 1 H, one of C*H*O), 3.80 (s, 3 H, OCH_3), 3.71 (m, 1 H, C*H*OTBS), 3.33 (d, J = 5.6 Hz, 2 H, CH_2O), 2.05 (m, 1 H, $O_2CCH_2CH_{ax}$), 1.76-1.24 (m, 16 H), 1.68 (d, J = 3.0 Hz, 1 H, O*H*), 1.13 (d, J = 6.1 Hz, 3 H, $CH_3CHOTBS$), 0.94 (d, J = 7.0 Hz, 3 H, $CH_3CHCH_2CH_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.87 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.83 (d, J = 7.2 Hz, 3 H, $CH_3CHCHOH$), 0.04 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.0, 130.9, 128.9, 113.6, 98.3, 72.7, 72.6, 71.3, 69.6, 66.4, 66.2, 55.1, 43.1, 39.9, 37.6, 35.8, 29.7, 29.7, 29.1, 27.6, 25.8, 24.0, 23.5, 17.9, 10.9, 10.8, 10.6, -4.4, -4.6. Anal. Calcd for $C_{34}H_{60}O_6Si$: C, 68.87; H, 10.20. Found: C, 68.82; H, 10.35.

(2*S*,3*R*,4*S*,6*R*,8*S*,9*S*)-4-(Benzoyloxy)-3,9-dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl]-2-{(*R*)-3-[[(4-methoxyphenyl)methoxy]methyl]-1-pentyl}-1,7-dioxaspiro[5.5]undecane (21). Triethylamine (7.2 g, 10.0 mL, 71.2 mmol), 7.5 g (6.2 mL, 53.4 mmol) of benzoyl chloride, and a catalytic amount of 4-(dimethylamino)pyridine were added to a solution of 10.56 g (17.8 mmol) of the equatorial alcohol **20** in 45 mL of CH_2Cl_2 at ambient temperature under N_2. After being stirred for 36 h, the mixture was diluted with 45 mL of Et_2O and 75 mL of saturated aqueous Na_2CO_3. This mixture was vigorously stirred for 13 h to hydrolyze the excess benzoyl chloride. Water (75 mL) was added and the mixture was extracted with four 100-mL portions of Et_2O. The combined organic extracts were dried ($MgSO_4$) and purified by flash chromatography (10% EtOAc in hexane) to give 11.71 g (95%) of **21** as a colorless oil: $[\alpha]^{20}_D$ -56.2° (*c* 0.240, $CHCl_3$); IR (neat) 2950, 1720, 1515, 1270, 1245, 1110, 1095, 830, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 7.6 Hz, 2 H, Ar*H*), 7.55 (t, J = 7.3 Hz, 1 H, Ar*H*), 7.43 (t, J = 7.7 Hz, 2 H, Ar*H*), 7.25 (m, 2 H, Ar*H*), 6.86 (m, 2 H, Ar*H*), 5.50 (dt, J = 12.2 Hz, J = 5.0 Hz, 1 H, C*H*OBz), 4.42 (s, 2 H, $ArCH_2$), 3.83 (m, 1 H, one of C*H*O), 3.79 (s, 3 H, OCH_3), 3.78 (m, 1 H, one of C*H*O), 3.72 (m, 1 H, C*H*OTBS), 3.32 (d, J = 4.4 Hz, 2 H, CH_2O), 2.19 (m, 1 H, C*H*CHOBz), 2.09 (m, 1 H, $O_2CCH_2CH_{ax}$), 1.89 (dd, J = 12.6 Hz, J = 5.0 Hz, 1 H, $BzOCHCH_{eq}$), 1.74 (t, J = 12.4 Hz, 1 H, $BzOCHCH_{ax}$), 1.69-1.24 (m, 13 H), 1.20 (d, J = 5.9 Hz, 3 H, $CH_3CHOTBS$), 0.94 (d, J = 7.0 Hz, 3 H, $CH_3CHCH_2CH_2$), 0.91 (d, J = 6.9 Hz, 3 H, $CH_3CHCHOBz$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.87 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 0.05 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 165.4, 158.9, 132.6, 130.8, 130.6, 129.3, 128.9, 128.1, 113.5, 97.3, 72.5, 71.2, 70.6, 69.3, 69.3, 67.2, 55.0, 54.9, 43.2, 39.8, 35.7, 35.1, 29.6, 29.6, 27.7, 26.3, 25.8, 24.4, 23.5, 17.9, 10.9, 10.9, 5.0, -4.4, -4.6. Anal. Calcd for $C_{41}H_{64}O_7Si$: C, 70.65; H, 9.25. Found: C, 70.49; H, 9.30.

(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-4-(Benzoyloxy)-3,9-dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl]-2-[(*R*)-3-(hydroxymethyl)-1-pentyl]-1,7-dioxaspiro[5.5]undecane (22). DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (53 mg, 0.234 mmol) was added to a mixture of 125 mg (0.180 mmol) of the PMB ether **21** in 1.5 mL of CH_2Cl_2/H_2O (18:1) at 5 °C with vigorous stirring. The initially green mixture became brown with orange water droplets after 5 min. After stirring for 1.5 h, 5 mL of saturated aqueous $NaHCO_3$ and 10 mL of H_2O were added, and the mixture was extracted with three 15-mL portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and purified by flash chromatography (1% Et_2O in CH_2Cl_2, then 10% Et_2O in CH_2Cl_2) to give 98.2 mg (95%) of **22** as a colorless oil: $[\alpha]^{20}_D$ -60.3° (*c* 0.310, $CHCl_3$); IR (neat) 3460, 2960, 1725, 1275, 1115, 1095, 1070, 965, 835, 755, 715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (m, 2 H, Ar*H*), 7.55 (m, 1 H, Ar*H*), 7.43 (m, 2 H, Ar*H*), 5.50 (dt, J = 12.1 Hz, J = 4.9 Hz, 1 H, BzOC*H*), 3.85 (m, 1 H, one of C*H*O), 3.79 (m, 1 H, one of C*H*O), 3.75 (m, 1 H, C*H*OTBS), 3.57 (AB of ABX, J_{AB} = 10.7 Hz, J_{AX} = 5.5 Hz, J_{BX} = 5.0 Hz, $\Delta\nu_{AB}$ = 11.8 Hz, 2 H, CH_2OH), 2.21 (m, 1 H, BzOC*H*), 2.08 (m, 1 H, $O_2CCH_2CH_{ax}$), 1.90 (dd, J = 12.6 Hz, J = 5.0 Hz, 1 H, $BzOCHCH_{eq}$), 1.75, (t, J = 12.3 Hz, 1 H, $BzOCHCH_{ax}$), 1.69-1.28 (m, 13 H), 1.22 (d, J = 6.0 Hz, 3 H, $CH_3CHOTBS$), 0.94 (d, J = 6.9 Hz, 3 H, $CH_3CHCH_2CH_2$), 0.93 (d, J = 6.7 Hz, 3 H, $CH_3CHCHOBz$), 0.91 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.06 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 165.6, 132.7, 130.5, 129.4, 128.2, 97.4, 71.2, 70.7, 69.4, 67.2, 64.9, 43.2, 42.1, 35.7, 35.2, 29.7, 29.6, 29.5, 27.2, 26.3, 25.8, 24.4, 23.2, 18.0, 10.9, 10.9, 5.0, -4.4, -4.6. Anal. Calcd for $C_{33}H_{56}O_6Si$: C, 68.75; H, 9.79. Found: C, 68.90; H, 9.63.

(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-propyl]-2-[(*R*)-3-(hydroxymethyl)-1-pentyl]-1,7-dioxaspiro[5.5]undecan-4-ol (23). Lithium hydroxide (8 mg, 0.334 mmol) was added to a solution of 96 mg (0.167 mmol) of benzoate **22** in 900 μL of THF/MeOH/H_2O (2:2:1) at ambient temperature. The resulting yellow solution was stirred at ambient temperature for 17 h. This solution was diluted with 20 mL of Et_2O and washed with 10 mL of saturated aqueous $NaHCO_3$ and 10 mL of brine. The combined aqueous layers were extracted with 10 mL of Et_2O. The combined organic extracts were dried ($MgSO_4$) and purified by flash chromatography (65% EtOAc in hexane) to give 75.5 mg (96%) of **23** as a colorless oil: $[\alpha]^{20}_D$ -59.4° (*c* 2.59, $CHCl_3$); IR (neat) 3390, 2950, 2920, 1090, 1035, 1005, 970, 830, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.19 (dt, J = 11.9 Hz, J = 4.8 Hz, 1 H, C*H*OH), 3.80 (m, 1 H, one of C*H*O), 3.75 (td, J = 7.0 Hz, J = 2.4 Hz, 1 H, one of C*H*O), 3.57 (AB of ABX, J_{AB} = 10.8 Hz, J_{AX} =

5.3 Hz, J_{BX} = 5.3 Hz, $\Delta\nu_{AB}$ = 14.2 Hz, 2 H, CH_2OH), 3.57 (m, 1 H, CHOTBS), 2.05 (m, 1 H, $O_2CCH_2CH_{ax}$), 1.85-1.25 (m, 16 H), 1.18 (d, J = 6.0 Hz, 3 H, $CH_3CHOTBS$), 0.93 (d, J = 7.2 Hz, 3 H, $CH_3CHCH_2CH_2$), 0.91 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.84 (d, J = 6.9 Hz, 3 H, $CH_3CHCHOH$), 0.05 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 97.5, 71.2, 69.2, 67.1, 67.1, 64.7, 43.2, 42.1, 38.9, 38.0, 29.8, 29.7, 29.5, 27.4, 26.3, 25.8, 24.3, 23.3, 18.0, 11.0, 10.9, 4.0, -4.5, -4.6. Anal. Calcd for $C_{26}H_{52}O_5Si$: C, 66.05; H, 11.09. Found: C, 66.04; H, 10.95.

(2*S*,3*S*,4*S*,6*R*,8*S*,9*S*)-3,9-Dimethyl-8-[(*R*)-2-hydroxy-1-propyl]-2-[(*R*)-3-(hydroxymethyl)-1-pentyl]-1,7-dioxaspiro[5.5]undecan-4-ol (4). A 48% aqueous solution of hydrofluoric acid (157 μL) was added to a solution of 74 mg (0.157 mmol) of silyl ether **23** in 1.57 mL of CH_2Cl_2/CH_3CN (1:1) at ambient temperature. After stirring for 7 h, 2 mL of saturated aqueous $NaHCO_3$ was added. The resulting mixture was diluted with 10 mL of H_2O and extracted with three 15-mL portions of EtOAc. The combined organic extracts were dried (Na_2SO_4) and purified by flash chromatography (19:1 $CHCl_3$/MeOH) to give 51.6 mg (92%) of **4** as a white foam: $[\alpha]^{24}_D$ -95.1° (*c* 0.225, $CHCl_3$) {lit.[1e] $[\alpha]_D$ -88.6° (*c* 1.10, $CHCl_3$)}; IR (neat) 3360, 2970, 1460, 1385, 1100, 1080, 1055, 1030, 970 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.17 (dt, J = 11.8 Hz, J = 4.8 Hz, 1 H, CHCHOH), 4.07 (br d, J = 10.8 Hz, 1 H, one of CHO), 4.00 (m, 1 H, one of CHO), 3.71 (m, 1 H, one of CHO), 3.55 (AB of ABX, J_{AB} = 10.8 Hz, J_{AX} = 5.8 Hz, J_{BX} = 4.7 Hz, $\Delta\nu_{AB}$ = 46.7 Hz, 2 H, CH_2OH), 2.25 (br s, 3 H, OH), 2.13 (m, 1 H, $O_2CCH_2CH_{ax}$), 1.84-1.21 (m, 16 H), 1.21 (d, J = 6.2 Hz, 3 H, CH_3CHOH), 0.92 (d, J = 7.0 Hz, 3 H, $CH_3CHCH_2CH_2$), 0.91 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.84 (d, J = 6.9 Hz, 3 H, $CH_3CHCHOH$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 97.5, 71.3, 67.4, 67.4, 64.7, 64.7, 42.5, 42.1, 39.1, 37.8, 30.8, 29.8, 29.2, 26.8, 26.6, 24.5, 23.5, 11.3, 11.2, 3.9. Anal. Calcd for $C_{20}H_{38}O_5$: C, 67.00; H, 10.68. Found: C, 66.83; H, 10.57.

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Potent Inhibition of Pepsin and Penicillopepsin by Phosphorus-Containing Peptide Analogues

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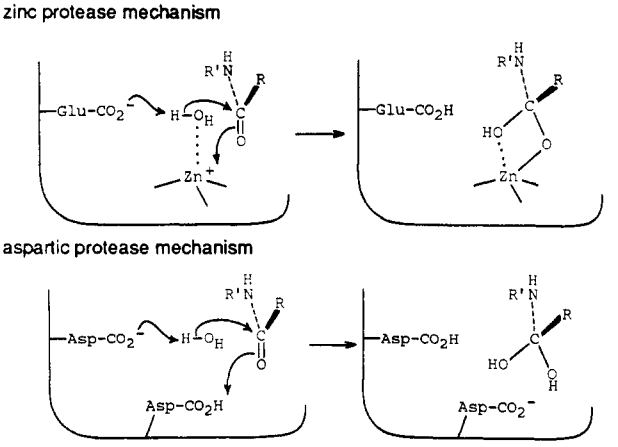
Phosphinic and phosphonic acid peptide derivatives have been evaluated as inhibitors of the aspartic proteases pepsin and penicillopepsin. The most potent of those studied is isovaleryl-Val-Val-Leu^P-(O)Phe-Ala-Ala-OMe (**4**) (Leu^P represents the phosphonic acid analogue of leucine; (O)Phe represents L-β-phenyllactic acid, the alcohol analogue of phenylalanine), for which the K_i values for pepsin and penicillopepsin are 0.26 and 0.19 nM, respectively. While this compound binds to penicillopepsin with an association rate constant, k_{on}, of $(6.5 \pm 1.5) \times 10^5$ M^{-1} s^{-1}, it does not show slow- or two-step binding with pepsin. The binding of Cbz-Ala-Ala-Leu^P-(O)Phe-OMe (**1**) to penicillopepsin is strongly dependent on pH: in comparison to pH 4.5, the affinity at pH 3.5 is increased 10-fold and at pH 5.5 it is decreased 40-fold. The two diastereomers of a nonionic phosphinamide analogue (**10A, 10B**) of a statine-containing inhibitor were prepared; however, both are significantly weaker inhibitors of pepsin than the phosphinic acid itself (**7**).

Introduction

Although the zinc proteases and the aspartic proteases differ in many respects, they are related by mechanism: both catalyze the direct addition of water to the amide linkage, with formation of tetrahedral intermediate as the critical step in hydrolysis of an oligopeptide substrate (Scheme I).

Both mechanisms involve basic catalysis from a carboxylate side chain and acidic or Lewis acidic catalysis from another functional group in the active site. Moreover, both types of enzymes are inhibited by electrophilic keto analogues of substrates[1,2] because of the ability of these compounds to undergo hydration to form a mimic of the tetrahedral intermediate.[3,4] X-ray crystallographic analysis of representative enzymes from both classes provides support for these mechanistic interpretations, as well as detailed pictures of the configurations of the active sites and the orientation of substrates and analogues when

Scheme I



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