Synthesis of the Lipophilic Side Chain of the Cyclic Hexadepsipeptide Antibiotic L-156,602

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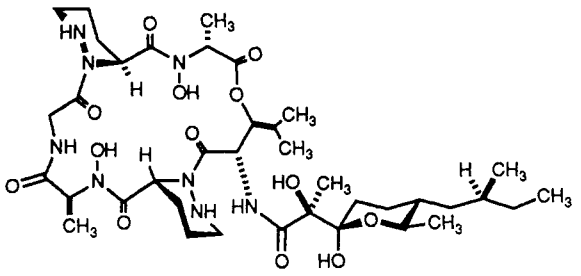
The 14-carbon tetrahydropyranylpropionic acid side chain of the cyclic hexadepsipeptide antibiotic L-156,602 (1) has been prepared as the methyl ester derivative 5. Asymmetric synthesis of the key intermediate 11-carbon lactone 7 was accomplished using diastereoselective alkylation of the alkoxide enolate of methyl (*R*)-3-hydroxybutanoate. A second route to lactone 7 utilized sequential organometallic reactions of the pinanediol boronic ester 17 to control two chiral centers. The enolate of the chiral dioxolanone 6 condensed with lactone 7 to produce the complete 14-carbon skeleton as a single diastereomer.

Introduction

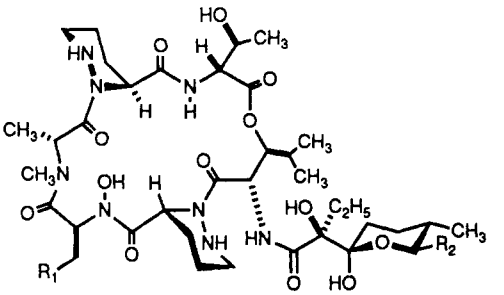
The natural hexadepsipeptide antibiotic L-156,602 (1) has recently been isolated from cultures of *Streptomyces* spp. MA6348.[1] A single-crystal X-ray diffraction study carried out on L-156,602 determined that the structure consists of a cyclic peptide unit attached at its N-terminus to a tetrahydropyranylpropionic acid side chain containing five asymmetric centers.[2] The absolute configuration indicated for L-156,602 was established by comparison of the 3-hydroxyleucine obtained from its acid hydrolysis with authentic samples of (2*R*,3*R*)- and (2*S*,3*S*)-3-hydroxyleucine.[2,3] L-156,602 appears to be identical to PD 124,966, for which spectral data, but no structure, have been published.[4,5]



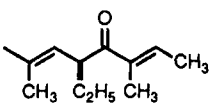
1, L-156,602

The structure of L-156,602 is related to the antibiotics azinothricin[6] (2) and A83586C[7] (3). All three compounds possess a 19-membered cyclic hexadepsipeptide moiety containing a residue of (2*S*,3*S*)-3-hydroxyleucine as well as two enantiomeric residues of piperazic acid. Substitutions for the glycine and (*R*)- and (*S*)-*N*-hydroxyalanine residues of L-156,602 are found in azinothricin and A83586C. The monamycins comprise a related class of cyclic hexapeptide antibiotics containing residues of piperazic acid.[8]

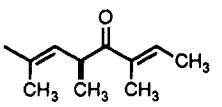
While the side chain of L-156,602 is similar to the side chains of azinothricin and A83586C, notable differences



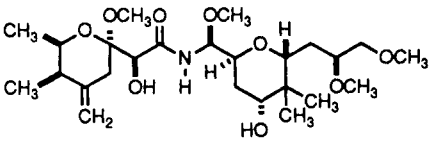
2, Azinothricin: $R_1 = OCH_3$, R_2 =



3, A83586C: $R_1 = H$, R_2 =



are found in the structures of the alkyl substituents on the tetrahydropyran ring. The potent protein biosynthesis inhibitor pederin (4) contains a tetrahydropyranylacetic acid amide substructure resembling the side chain of L-156,602.[9] Recently the structures of onnamide A and mycalamide A and B, marine natural products isolated from sponges, have been described. These natural products, having cytotoxic and antitumor activity, have been shown to contain a tetrahydropyranylacetic acid unit identical with that found in pederin.[10–12]



4, Pederin

Results and Discussion

As part of our effort toward the total synthesis of L-156,602, we undertook the asymmetric synthesis of the

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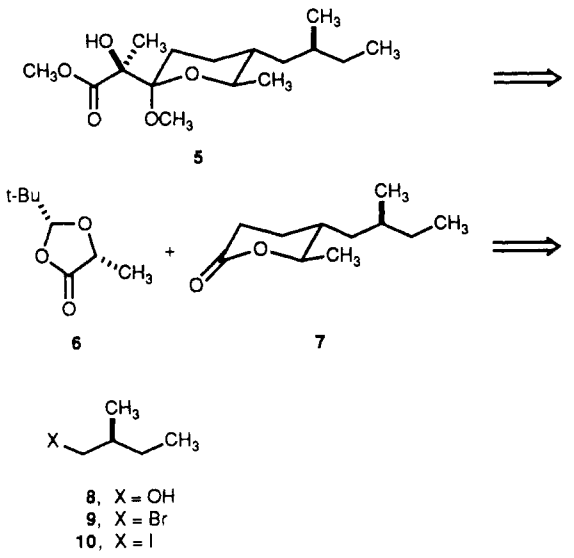
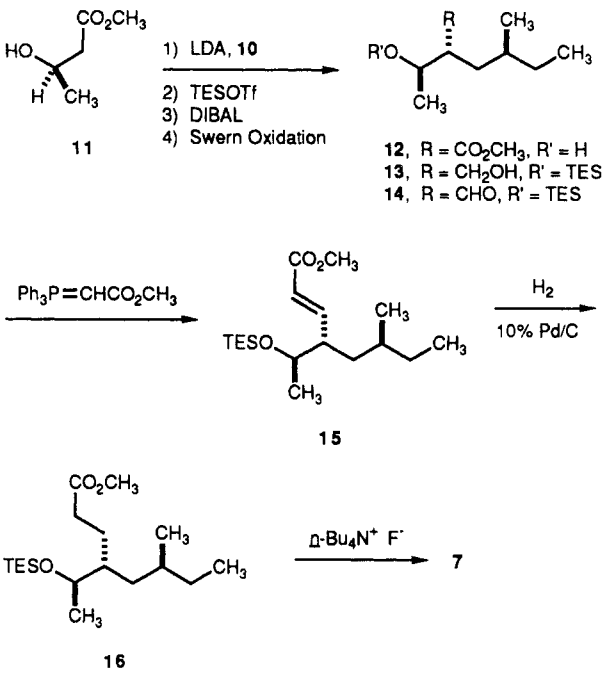
Scheme I



Scheme II



14-carbon side chain, prepared as the methyl ester methyl pyranoside derivative **5**. The anomeric center of the tetrahydropyran ring of L-156,602 is clearly in its preferred thermodynamic configuration, dictated by the preference of the hydroxyl group for the axial orientation and the preference of the three other substituents for the equatorial orientation. Control of the four remaining fixed stereocenters of the side chain was required in our synthetic approach. We planned to define the configuration at the tertiary hydroxyl center of alcohol **5** by the use of the chiral acetal **6**, developed by Seebach and co-workers,[13] in a condensation reaction with the valerolactone **7** (Scheme I). Related condensation reactions have been carried out in approaches to pederin without stereocontrol in the addition reaction.[14] The bromide **9** and iodide **10**, derived from chiral alcohol **8**, provide convenient sources of the (*S*)-2-methylbutyl moiety of lactone **7**. We now describe two asymmetric synthesis of the lactone **7** and its subsequent conversion to ester **5**.

The utility of the diastereoselective alkylation reactions of homochiral 3-hydroxybutyrate esters in the preparation of chiral compounds has been demonstrated.[15,16] Methodology described by Seebach and co-workers in their total synthesis of di-*O*-methylelaiophylidene[17] has been adapted for the conversion of methyl (*R*)-3-hydroxybutyrate (**11**) into aldehyde **14** (Scheme II). For use in this approach, (*S*)-1-bromo-2-methylbutane (**9**), obtained commercially or prepared from (*S*)-2-methyl-1-butanol (**8**),[18-20] was converted into iodide **10** by reaction with sodium iodide in acetone.[21] Deprotonation of methyl (*R*)-3-hydroxybutyrate (**11**) with 2 equiv of lithium diisopropylamide gave the corresponding alkoxide enolate, which was alkylated by iodide **10** in 46% yield. The alkylation product **12** contains the three asymmetric centers found in the valerolactone **7**. Protection of the hydroxyl function of **12** using triethylsilyl trifluoromethanesulfonate followed by DIBAL reduction of the methyl ester yielded primary alcohol **13**. Swern oxidation proceeded smoothly to give a 97% yield of aldehyde **14**. Elongation to unsaturated ester **15** was accomplished in 70% yield by condensation of aldehyde **14** with methyl (triphenylphosphoranylidene)acetate in refluxing tetrahydrofuran. Saturated ester **16** was obtained in quantitative yield by hydrogenation using 10% palladium on carbon as catalyst. Removal of the silyl protecting group by treatment with tetrabutylammonium fluoride[22] proceeded cleanly with spontaneous cyclization to the desired lactone intermediate **7**.

The second approach to the 11-carbon lactone (**7**) utilized diastereoselective reactions directed by the pinanediyldioxyboryl group[23] to establish both chiral centers in the lactone ring (Scheme III). In this route the Grignard reagent derived from (*S*)-1-bromo-2-methylbutane (**9**) was added to trimethylborate and the intermediate boronic acid was condensed with (1*R*,2*R*,3*R*,5*R*)-(−)-pinanediol.[24-26] The resulting cyclic ester product **17** was allowed to react with dichloromethyllithium, and the addition product was rearranged in situ under the influence of zinc chloride. Treatment of the crude α-chloroboronate **18** with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-di-

(13) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313–1324.
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(18) (*S*)-1-Bromo-2-methylbutane and (*S*)-2-methyl-1-butanol were obtained commercially from Aldrich Chemical Co. (*S*)-1-Bromo-2-methylbutane ($[\alpha]_D$ +4.50° (*c* = 5.7 $CHCl_3$)) was also conveniently prepared from (*S*)-2-methyl-1-butanol by the method described in ref 20.
(19) (*S*)-1-Iodo-2-methylbutane has recently become available from Aldrich Chemical Co.
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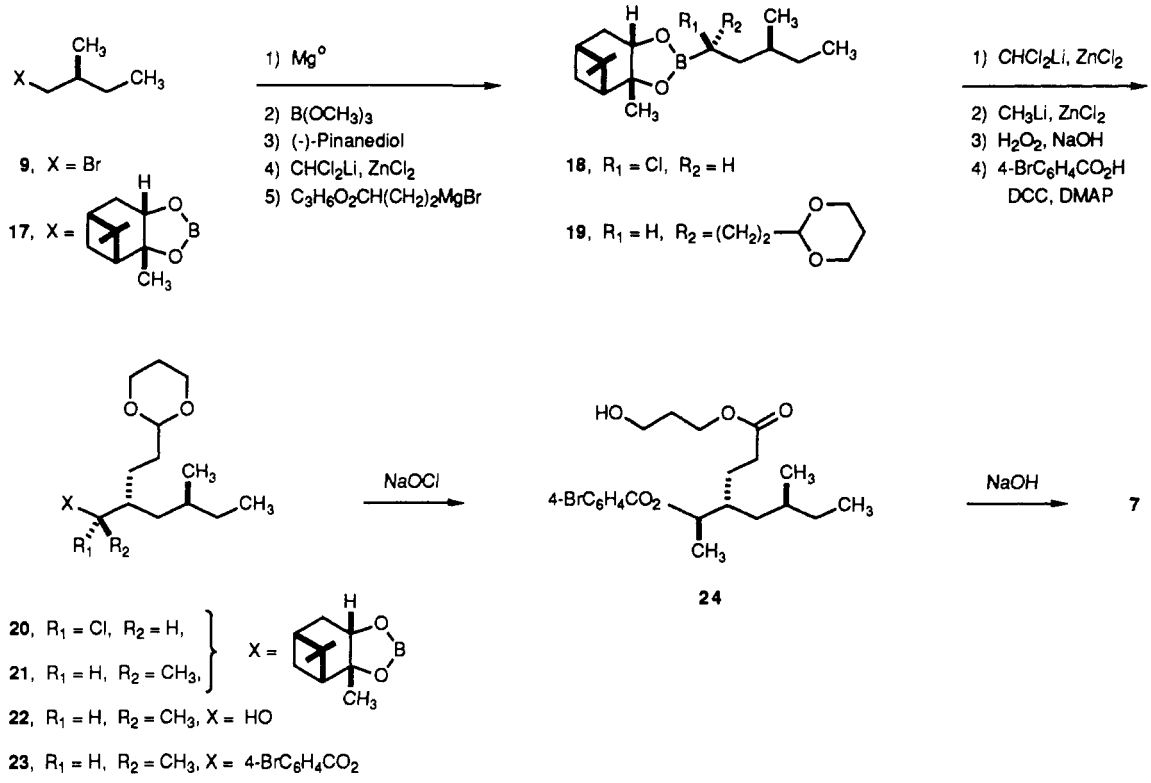
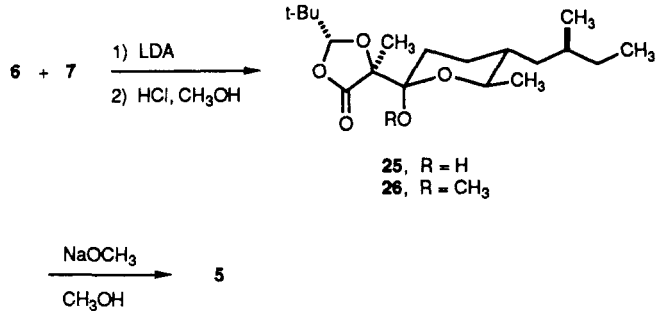
Scheme III



oxane[27] gave acetal **19** in 73% overall yield from ester **17**. Subsequent homologation by treatment with dichloromethyllithium and zinc chloride proceeded smoothly. Treatment of the intermediate α-chloroboronate **20** with methylmagnesium bromide resulted in formation of substitution product **21** in 39% yield. Use of methyllithium produced an improved yield (64%), while methyllithium followed by zinc chloride gave ester **21** in 79% overall yield from intermediate **17**. Oxidation with basic hydrogen peroxide cleanly gave alcohol **22**, which was esterified in 91% yield using 4-bromobenzoic acid in the presence of DCC and 4-(dimethylamino)pyridine.[28] Adjustment of the acetal moiety to the desired carboxylic acid oxidation level was accomplished by treatment with sodium hypochlorite in a mixture of aqueous acetone and acetic acid,[29] yielding the 3-hydroxypropyl ester **24** in 68% yield. Saponification of diester **24** followed by an acid workup provided an 87% yield of the lactone intermediate **7**.

The remaining three carbon atoms of the side chain were then introduced by condensation of the lithium enolate of (2*R*,5*R*)-2-*tert*-butyl-5-methyl-1,3-dioxolan-4-one (**6**)[13] with lactone **7** in THF at −70 to −25 °C (Scheme IV). The resulting addition product **25** was obtained as a single diastereomer in 75% yield, accompanied by 16% of the recovered lactone **7**. Treatment with methanolic HCl accomplished the smooth and quantitative conversion of **25** into the methyl pyranoside **26**. Saponification of the 2-*tert*-butyl-1,3-dioxolan-4-one moiety of **26** proved to be a sluggish reaction, and the free acid corresponding to the ester **5** was not sufficiently stable to allow isolation. We therefore sought to remove the pivalaldehyde group while preparing a stable ester derivative of the latent β-keto acid.

Scheme IV



Transesterification of dioxolanone **26** with excess sodium methoxide proceeded smoothly, and the desired methyl ester **5** was obtained in 78% yield.

The naturally occurring enantiomer of the 14-carbon tetrahydropyranyl side chain of L-156,602 has been prepared by asymmetric synthesis. Two complementary routes have been described for controlling the three chiral centers of the key intermediate lactone. The diastereoselective alkylation of the methyl 3-hydroxybutyrate alkoxide enolate provides an attractive, short synthesis of lactone **7**. Alternatively, the synthesis utilizing the pinanediyldioxyboryl group provides a route potentially amenable to preparation of related compounds. Stereocontrol at the tertiary hydroxyl center of the side chain was accomplished by condensation of the lactone with the chiral lactic acid enolate equivalent derived from dioxolanone **6**. Activation and coupling reactions of the acid corresponding to ester **5** will be described in a subsequent paper.

Experimental Section

General. All reactions were run under a positive pressure of dry nitrogen unless otherwise noted. Infrared (IR) spectra were obtained from 2–5% solutions. Proton NMR spectra were determined at 200 or 300 MHz. Melting points were determined

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in open capillary tubes and are uncorrected. Flash column chromatography[30] was carried out with the indicated solvent using Kieselgel 60 (EM Science, 230–400 mesh). High-pressure liquid chromatography (HPLC) was accomplished on a Waters LC3000 instrument. Analytical thin-layer chromatography (TLC) was performed with silica gel GHLF plates of 0.25 mm thickness obtained from Analtech, Inc.

In experiments requiring dry solvents, tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl. Triethylamine, diisopropylamine, dimethyl sulfoxide (DMSO), and 2,6-lutidine were distilled from calcium hydride, with the distillations of DMSO and 2,6-lutidine carried out at reduced pressure. Dichloromethane was dried over 3A molecular sieves unless otherwise indicated. Zinc chloride was dried under vacuum at 110 °C. Apparatus for experiments requiring anhydrous conditions was flame-dried under a stream of nitrogen.

(*S*)-1-Iodo-2-methylbutane (10). Sodium iodide (307.80 g, 2.05 mol) was suspended in acetone (275 mL), and (*S*)-1-bromo-2-methylbutane (**9**) (103.40 g, 684 mmol) was added dropwise over 35 min. The reaction was stirred 1 h at 25 °C followed by 3 h at reflux. After cooling to room temperature, the reaction mixture was diluted with water (1.5 L). After separation of the organic layer, the aqueous layer was divided into two portions and each was extracted with ether (3 × 100 mL). All of the organic layers were combined and washed with 1 N aqueous $NaHSO_3$ (50 mL) and saturated aqueous NaCl (100 mL). The solution was dried (Na_2SO_4), decanted, and distilled through a 1 × 10 cm Vigreaux column to yield 123.4 g (91% yield) of alkyl iodide **10** as a mobile liquid: bp 84–86 °C (100 mmHg) (lit.[31] bp 50–54 °C (20 mmHg)); $[\alpha]_D$ +6.20° (*c* = 5.6, $CHCl_3$) (lit.[31] $[\alpha]_D^{20}$ +5.8° (*c* = 7.0, CH_2Cl_2)).

Methyl (2*R*,4*S*)-2-[(1*R*)-1-Hydroxyethyl]-4-methylhexanoate (12). Diisopropylamine (92 mL, 66 g, 660 mmol) and THF (200 mL) were added under a nitrogen atmosphere to a flask fitted with an internal thermometer. The resulting solution was cooled to −50 °C, and *n*-butyllithium (2.5 *M* in hexane, 211 mL, 530 mmol) was added over 15 min. After an additional 15 min, methyl (*R*)-3-hydroxybutanoate (**11**) (24.0 g, 203 mmol) was added, keeping the temperature at −40 to −50 °C. The resulting mixture was stirred 3.5 h at −20 to −25 °C and then cooled to −78 °C. (*S*)-1-Iodo-2-methylbutane (**10**) (120 g, 606 mmol) was added dropwise over 30 min, keeping the temperature at −70 °C. The reaction was allowed to warm to room temperature overnight and stirred for a total of 60 h. The mixture was poured into saturated aqueous NH_4Cl (200 mL) at 0 °C. The aqueous layer was separated and extracted with 1:1 ether/petroleum ether (2 × 200 mL). The organic layers were washed in succession with saturated aqueous NH_4Cl (200 mL) followed by saturated aqueous NaCl (200 mL). The combined organic layers were dried (Na_2SO_4), decanted, and concentrated under vacuum. Bulb-to-bulb distillation yielded 17.45 g (46% yield) of product as a colorless oil collected at an oven temperature of 80–90 °C (0.05 mmHg); $[\alpha]_D$ +20.6° (*c* = 1.0, $CHCl_3$). Purification by HPLC (Whatman Partisil 10 silica gel column, 5% 2-propanol in hexane as eluant) yielded an analytical sample of ester **12**: $[\alpha]_D$ +23.3° (*c* = 0.55, $CHCl_3$); IR (CCl_4) 3650–3300, 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.84 (sextet, 1 H, *J* = 6.5 Hz, collapses to quintet upon addition of D_2O), 3.71 (s, 3 H), 2.33 (d, 1 H, *J* = 7 Hz, exchanges with D_2O), 1.78 (t, 1 H, *J* = 10 Hz), 1.38–1.10 (m, 4 H), 1.22 (d, 3 H, *J* = 6.5 Hz), 0.89 (d, 3 H, *J* = 6 Hz), 0.86 (t, 3 H, *J* = 6 Hz). Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.68; H, 10.98.

(2*S*,4*S*)-2-[(1*R*)-1-[(Triethylsilyl)oxy]ethyl]-4-methyl-1-hexanol (13). The alcohol **12** (5.70 g, 30.3 mmol) and CH_2Cl_2 (50 mL) were added to a flask fitted with an internal thermometer. The solution was then cooled to −40 to −50 °C as triethylsilyl trifluoromethanesulfonate (8.59 g, 32.5 mmol) was added over 20 min. After 5 min, a solution of 2,6-lutidine (4.06 g, 37.9 mmol) in CH_2Cl_2 (5 mL) was added over 20 min at −40 °C. The reaction was allowed to warm to 0 °C and maintained overnight at that temperature. The reaction was diluted with CH_2Cl_2 (50 mL) and washed with 0.5 N aqueous HCl (3 × 15 mL) and saturated aqueous NaCl (15 mL). The organic layer was dried (Na_2SO_4), decanted, and evaporated. The residue was dissolved in hexane, dried (Na_2SO_4), decanted, and evaporated to give 9.01 g of crude methyl (2*R*,4*S*)-2-[(1*R*)-1-[(triethylsilyl)oxy]ethyl]-4-methylhexanoate (**12**).

The crude ester was dissolved in dry toluene (90 mL) in a flask fitted with an internal thermometer. The solution was cooled to −65 to −70 °C as DIBAL (1.0 N in hexane, 86 mL, 86 mmol) was added over 45 min. The reaction was stirred for 1 h at −70 °C and for 30 min at −40 °C. The reaction was cooled to −70 °C and quenched by the addition of 2-propanol (5 mL), followed by saturated aqueous NH_4Cl (35 mL). The reaction was allowed to warm to 0 °C and stirred at that temperature for 30 min. The resulting suspension was poured into a flash column containing a pad of Celite, and the precipitate was washed with ether (300 mL). The combined organic washes were washed with saturated aqueous NH_4Cl (35 mL), dried (Na_2SO_4), and evaporated to give 8.36 g of crude product. A portion (7.36 g) was purified by flash column chromatography (silica gel, 3–5% ethyl acetate in hexane as eluant) to give 3.82 g (52% yield) of alcohol **13** as a colorless oil: $[\alpha]_D$ +9.6° (*c* = 1.0, $CHCl_3$); IR (CCl_4) 3640, 3540, 2980, 2940, 2920, 2890, 1470, 1420, 1380, 1245, 1125, 1075, 1020, 1010, 970, 725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.97–3.83 (m, 2 H), 3.54 (ddd, 1 H, *J* = 11.5, 6.5, 5 Hz), 3.19 (dd, 1 H, *J* = 6.5, 4.5 Hz, exchanges with D_2O), 1.57–1.07 (m, 5 H), 1.26 (t, 3 H, *J* = 6 Hz), 0.98 (t, 9 H, *J* = 8 Hz), 0.88 (t, 3 H, 7 Hz), 0.87 (d, 3 H, *J* = 6 Hz), 0.53 (q, 6 H, *J* = 8 Hz). Anal. Calcd for $C_{15}H_{34}O_2Si$: C, 65.63; H, 12.48. Found: C, 65.68; H, 12.16.

(2*S*,4*S*)-2-[(1*R*)-1-[(Triethylsilyl)oxy]ethyl]-4-methylhexanal (14). Oxalyl chloride (2.48 mL, 3.61 g, 28.4 mmol) was added to CH_2Cl_2 (45 mL) in a flask equipped with a mechanical stirrer and an internal thermometer. The solution was cooled to −70 °C, and dry DMSO (4.22 mL, 4.65 g, 78.1 mmol) was added over 10 min. After 1 min, alcohol **13** (5.0 g, 18.2 mmol) was added over 13 min as a solution in CH_2Cl_2 (15 mL), and the reaction was stirred for 5 min. Triethylamine (16.8 mL. 12.2 g, 120 mmol) was then added over 5 min. After the reaction was stirred for 10 min at −70 °C, the mixture was allowed to warm to −20 °C over 30 min. The contents of the flask were poured into saturated aqueous NH_4Cl (70 mL). The aqueous layer was separated and diluted with saturated aqueous NaCl (50 mL). The organic layer was washed with saturated aqueous NaCl (50 mL). The aqueous layers were extracted in succession with CH_2Cl_2 (2 × 50 mL). The organic layers were dried (Na_2SO_4), decanted, and evaporated. The residue was taken up in hexane (100 mL) and washed with water (2 × 50 mL) and saturated aqueous NaCl (50 mL). The hexane layer was dried (Na_2SO_4), decanted, and evaporated to give 4.85 g (98% yield) of crude aldehyde **14** as a pale yellow oil suitable for further transformations. Flash chromatography (silica gel, 20% CH_2Cl_2 in hexane as eluant) yielded an analytical sample of aldehyde **14**: $[\alpha]_D$ +4.6° (*c* = 0.5, $CHCl_3$); IR (CCl_4) 2960, 2925, 2910, 2880, 1720, 1460, 1375, 1235, 1150, 1120, 1075, 1000 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.63 (d, 1 H, *J* = 4 Hz), 4.05 (quintet, 1 H, *J* = 6 Hz), 2.40–2.26 (m, 1 H), 1.82 (ddd, 1 H, *J* = 13, 11, 3 Hz), 1.41–1.07 (m, 5 H), 1.21 (d, 3 H, *J* = 6 Hz), 1.03–0.81 (m, 15 H), 0.58 (q, 6 H, *J* = 7 Hz). Anal. Calcd for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84. Found: C, 66.04; H, 11.68.

Methyl (4*S*,6*S*)-(*E*)-4-[(1*R*)-1-[(Triethylsilyl)oxy]ethyl]-6-methyl-2-octenoate (15). Methyl (triphenylphosphoranylidene)acetate (10.39 g, 31.1 mmol) was added to a solution of aldehyde **14** (4.61 g, 16.9 mmol) in dry THF (32 mL). The reaction was heated to reflux for 7.5 h, cooled to room temperature, and allowed to stand overnight. After the mixture was diluted with hexane (100 mL), the precipitate was removed by filtration and washed with additional hexane (3 × 50 mL). The filtrate was evaporated, and the resulting residue was purified by flash column chromatography (silica gel, 1.5–3% ether in hexane as eluant) to give 3.90 g (70% yield) of unsaturated ester **15** as an almost colorless oil: $[\alpha]_D$ +44.9° (*c* = 1.02, $CHCl_3$); IR (CCl_4) 2960, 2930, 2910, 2880, 1730, 1460, 1435, 1375, 1325, 1270, 1215, 1175, 1150, 1080, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (dd, 1 H, *J* = 15.5, 9.5 Hz), 5.83 (d, 1 H, *J* = 15.5 Hz), 3.81 (qd, 1 H, *J* = 6, 4 Hz), 3.74 (s, 3 H), 2.32–2.20 (m, 1 H), 1.51 (t, 1 H, *J* = 10 Hz), 1.34–1.12 (m, 4 H), 1.10 (d, 3 H, *J* = 6 Hz), 0.95 (t, 9 H, *J* = 8 Hz), 0.85 (t, 3 H, *J* = 7 Hz), 0.80 (d, 3 H, *J* = 5.5

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Hz), 0.57 (q, 6 H, J = 8 Hz). Anal. Calcd for $C_{18}H_{36}O_3Si$: C, 65.80; H, 11.04. Found: C, 65.81; H, 11.08.

Methyl (4*R*,6*S*)-4-[(1*R*)-1-[(Triethylsilyl)oxy]ethyl]-6-methyloctanoate (16). Catalyst (650 mg of 10% palladium on carbon) was added to a solution of unsaturated ester **15** (3.80 g, 11.6 mmol) in ethyl acetate (81 mL). The theoretical amount of hydrogen was taken up within 10 min at 40 psi of pressure. The reaction was centrifuged, and the supernatant was filtered through a 0.45-μm membrane. Additional ethyl acetate (3 × 20 mL) was used to rinse the catalyst. The combined filtrate was evaporated to give 3.75 g (98% yield) of ester **16** as an almost colorless oil: $[\alpha]_D$ +14.6° (c = 0.98, $CHCl_3$); IR (CCl_4) 2960, 2930, 2910, 2880, 1745, 1460, 1375, 1240, 1170, 1080, 1010 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.81 (qd, 1 H, J = 6, 4 Hz), 3.66 (s, 3 H), 2.34 (t, 2 H, J = 6 Hz), 1.77–1.07 (m, 8 H), 1.07 (d, 3 H, J = 6 Hz), 0.96 (t, 9 H, J = 7 Hz), 0.86 (t, 3 H, J = 7 Hz), 0.83 (d, 3 H, J = 7 Hz), 0.57 (q, 6 H, J = 7 Hz). Anal. Calcd for $C_{18}H_{38}O_3Si$: C, 65.40; H, 11.59. Found: C, 65.53; H, 11.82.

(5*R*,6*R*)-6-Methyl-5-[(2*S*)-2-methylbutyl]tetrahydro-2*H*-pyran-2-one (7). Methyl ester **16** (3.61 g, 10.9 mmol) was dried by evaporation of a toluene solution and then dissolved in THF (18 mL). Tetra-*n*-butylammonium fluoride (1.0 N in THF, 18.1 mL, 18 mmol) was added, and the solution was stirred at room temperature for 2 h. The reaction was poured into 2 N aqueous HCl (100 mL) and extracted with petroleum ether (200 mL). The organic layer was washed with saturated aqueous NaCl (50 mL). The aqueous layers were extracted in succession with petroleum ether (100 mL). The combined organic layers were dried (Na_2SO_4), decanted, and evaporated. The residue was purified by flash column chromatography (silica gel, 20% ether in petroleum ether as eluant) to give 1.85 g (92% yield) of lactone **7** as an almost colorless oil: $[\alpha]_D$ +94.1° (c = 0.99, $CHCl_3$); IR (CCl_4) 2970, 2930, 2880, 1745, 1465, 1385, 1260, 1220, 1110, 1060 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.13 (dq, 1 H, J = 9, 6 Hz), 2.63 (ddd, 1 H, J = 17.5, 7, 5.5 Hz), 2.44 (ddd, 1 H, J = 17.5, 8.5, 6.5 Hz), 2.07–1.91 (m, 1 H), 1.72–1.11 (m, 7 H), 1.38 (d, 3 H, J = 6 Hz), 1.89 (t, 3 H, J = 7 Hz), 1.87 (d, 3 H, J = 6.5 Hz). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.35; H, 10.81.

(1*R*,2*R*,3*S*,5*R*)-Pinanediol (*R*)-(2-Methylbutyl)boronate (17). Magnesium turnings (1.61 g, 66.2 mg-atom) were crushed lightly and added to a nitrogen-filled flask. After addition of dry ether (35 mL) to the reaction flask, a portion (0.5-1.0 mL) of the alkyl bromide **9** (9.56 g, 63.3 mmol) was added and the reaction was warmed briefly with a heat gun to initiate the reaction. After the resulting exotherm began to subside, the remaining bromide was added over a 20-min period, maintaining a gentle reflux. The reaction was warmed to reflux in an oil bath for an additional 20 min and then allowed to cool to room temperature.

Dry ether (30 mL) was added to a nitrogen-filled flask fitted with a mechanical stirrer and internal thermometer. When the ether had cooled to −60 °C in a dry ice/2-propanol bath, trimethyl borate (7.15 mL, 6.54 g, 63.0 mmol) and the solution of Grignard reagent were added alternately (0.715 mL and 4.3 mL, respectively, 10 portions of each) over 20 min, with the reaction temperature remaining below −60 °C. The reaction was stirred an additional 25 min at dry ice temperature and then warmed to 0 °C in an ice bath. The dry ice was then used as needed to keep the reaction temperature at −10 to 0 °C as the reaction was quenched by addition of 4.4 mL of distilled water followed by a solution of 1.85 mL of concentrated H_2SO_4 in 40 mL of water. The resulting mixture was separated, and the aqueous layer was extracted with ether (3 × 50 mL). After concentrating to ether extracts to a volume of 125 mL by distillation at atmospheric pressure, water (10 mL) was added and distillation was continued until the head temperature reached 98 °C. After the mixture was cooled to room temperature, the residue was extracted with 2:1 CH_2Cl_2/ether (75 mL followed by 45 mL). The organic extracts were dried (Na_2SO_4), decanted, and evaporated to yield 3.67 g of crude (*R*)-2-methylbutaneboronic acid. (+)-Potassium bis(pinanediol) borate[23a] (6.47 g, 16.7 mmol) was stirred with water (21 mL) cooled in an ice bath, and then 1:1 ether/petroleum ether (42 mL) was added followed by 2 N aqueous HCl (18 mL). The mixture was removed from the ice bath and stirred until two clear layers were seen. The organic layer was separated, and the aqueous layer was saturated with NaCl. The aqueous layer was extracted with ether (15 mL, then 10 mL). The combined organic extracts were added to the crude alkylboronic acid and stirred at room temperature for 2 h. The solution was evaporated and the residue was distilled. The product boronic acid ester **17** was obtained as 5.67 g (36% yield) colorless oil: bp 86–90 °C (0.15 mmHg); $[\alpha]_D$ −21.1° (c = 1.0, $CHCl_3$); IR (CCl_4) 2960, 2920, 2870, 1450, 1380, 1345, 1280, 1240, 1205, 1190, 1120, 1075, 1030 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6) δ 4.11 (dd, 1 H, J = 8, 2.5 Hz), 2.18–1.78 (m, 5 H), 1.72–0.78 (m, 5 H), 1.32 (d, 1 H, J = 10 Hz), 1.26 (s, 3 H), 1.12 (d, 3 H, J = 6.5 Hz), 1.06 (s, 3 H), 0.95 (t, 3 H, J = 7 Hz), 0.52 (s, 3 H). Anal. Calcd for $C_{15}H_{27}BO_2$: C, 72.01; H, 10.88. Found: C, 71.57; H, 11.06.

2-[(3*R*,5*S*)-5-Methyl-3-[(1*R*,2*R*,3*R*,5*R*)-(pinanediyldioxy)boryl]heptyl]-1,3-dioxane (19). A flask fitted with an internal thermometer was charged with THF (40 mL) and CH_2Cl_2 (2.00 mL, 2.65 g, 31 mmol, distilled from P_2O_5). The flask was cooled to −95 °C by an ethanol/liquid nitrogen slush. *n*-Butyllithium (1.6 M in hexane, 14.6 mL, 21.2 mmol) was added via syringe over a 7-min period, letting the solution flow down the inside wall of the flask. After 10 min the internal temperature, which had risen to −87 °C during the addition, had returned to −95 °C. A solution of boronic acid ester **17** (5.31 g, 21.2 mmol) dissolved in ether (13.0 mL) at 25 °C was added over a 1-min period via a double-ended needle, causing the reaction temperature to rise to −65 °C. After 7 min, a solution of $ZnCl_2$ in ether (0.68 M, 22 mL, 15 mmol) was added and the reaction was allowed to warm slowly to 20 °C as it was stirred for 16 h. Most of the solvent was then removed on a rotary evaporator, keeping the bath temperature below 30 °C. The residue was stirred for 10 min with hexane (100 mL) and then shaken with saturated aqueous NH_4Cl (25 mL). The aqueous layer was extracted with additional hexane (2 × 25 mL). The three organic extracts were washed with saturated aqueous NH_4Cl (20 mL), combined, dried ($MgSO_4$), filtered, and evaporated. This yielded the crude α-chloroboronate **18** as 6.32 g (100% yield) of clear, colorless, mobile oil.

The crude α-chloroboronate was dissolved in 25 mL of toluene and evaporated at a bath temperature below 35 °C. After repeating this with two additional portions of toluene, the dried α-chloroboronate was dissolved in dry THF (25 mL). A Grignard reagent was prepared by addition of 2-(2-bromoethyl)-1,3-dioxane (3.17 mL, 4.54 g, 23.3 mmol) to magnesium (708 mg, 29.1 mg-atom) in THF (25 mL) at reflux. The solution of the Grignard reagent was cooled in an ice bath and then added via double-ended needle to the −78 °C solution of the α-chloroboronate over a 5-min period. After 15 min, the reaction was allowed to warm to 20 °C with stirring overnight. The reaction was concentrated on a rotary evaporator to remove most of the solvent and then stirred for 5 min with hexane (50 mL). The mixture was then shaken with saturated aqueous NH_4Cl (25 mL) and diluted with additional hexane (50 mL) and saturated aqueous NH_4Cl (25 mL). The aqueous layer was extracted with hexane (2 × 50 mL). The organic layers were washed in succession with saturated aqueous NaCl (25 mL), dried (Na_2SO_4), decanted, and evaporated to a crude weight of 7.75 g. Flash column chromatography on silica gel (290 g) eluting with 6% ethyl acetate/hexane (3 L) followed by 7% ethyl acetate/hexane (1 L) gave 5.82 g (73% yield) of product **19** as a clear, colorless, viscous oil: $[\alpha]_D$ −6.9° (c = 1.04, $CHCl_3$); IR (CCl_4) 2960, 2920, 2850, 1460, 1390, 1380, 1340, 1280, 1240, 1150, 1120, 1080, 1030 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6) δ 4.54 (t, 1 H, J = 5 Hz), 4.07 (dd, 1 H, J = 8.5, 2.5 Hz), 3.84 (dd, 2 H, J = 11, 5 Hz), 3.36 (bt, 2 H, J = 11 Hz), 2.19–0.84 (m, 16 H), 1.34 (d, 1 H, J = 10.5 Hz), 1.25 (s, 3 H), 1.02 (s, 3 H), 0.95 (d, 3 H, J = 6 Hz), 0.89 (t, 3 H, J = 7 Hz), 0.62 (dm, 1 H, J = 13 Hz), 0.50 (s, 3 H). Anal. Calcd for $C_{22}H_{39}BO_4$: C, 69.84; H, 10.39. Found: C, 69.77; H, 10.36.

2-[(3*R*,5*S*)-5-Methyl-3-[(1*R*)-1-[(1*R*,2*R*,3*S*,5*R*)-(pinanediyldioxy)boryl]ethyl]heptyl]-1,3-dioxane (21). Via the procedure described above for the preparation of intermediate **18**, the boronic acid ester **19** (5.82 g, 15.4 mmol) was allowed to react with dichloromethyllithium to yield the crude α-chloroboronate **20** as 6.84 g of clear, colorless oil. A portion (5.68 g) of this α-chloroboronate was dissolved in 15 mL of toluene and evaporated at a bath temperature below 30 °C. After repeating this with two additional portions of toluene, the dried α-chloroboronate was dissolved in dry THF (40 mL). The solution was cooled in a dry ice/2-propanol bath, and methyllithium (1.4 M in ether, 11.0 mL, 15 mmol) was added in one portion via syringe.

After 10 min, a solution of $ZnCl_2$ (1.49 g, 10.9 mmol) in ether (16 mL) was added. After 10 min, the reaction mixture was allowed to warm to 20 °C with stirring overnight. The reaction was concentrated on a rotary evaporator to remove most of the solvent and then stirred for 5 min with hexane (100 mL). The mixture was then shaken with saturated aqueous NH_4Cl (25 mL). The aqueous layer was extracted with hexane (50 mL). The organic layers were washed in succession with saturated aqueous NaCl (25 mL), dried (Na_2SO_4), decanted, and evaporated to a crude weight of 5.44 g. Flash column chromatography on silica gel (250 g), eluting with 5% ethyl acetate/hexane (4 L), gave 4.11 g (79% yield) of boronic acid ester **21** as a clear, colorless oil: $[\alpha]_D$ −4.9° (c = 1.0, $CHCl_3$); IR (CCl_4) 1465, 1380, 1285, 1240, 1150, 1080, 1030 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 4.53 (t, 1 H, J = 5 Hz), 4.12 (dd, 1 H, J = 8, 2 Hz), 3.86 (dd, 2 H, J = 11.5, 5 Hz), 3.38 (tm, 2 H, J = 12 Hz), 2.19–0.85 (m, 17 H), 1.35 (d, 1 H, J = 10 Hz), 1.28 (s, 3 H), 1.23 (d, 3 H, J = 7 Hz), 1.05 (s, 3 H), 1.01 (d, 3 H, J = 6.5 Hz), 0.90 (t, 3 H, J = 7.5 Hz), 0.65 (dm, 1 H, J = 13 Hz), 0.51 (s, 3 H). Anal. Calcd for $C_{24}H_{43}BO_4$: C, 70.93; H, 10.66. Found: C, 70.88; H, 10.63.

2-[(3*R*,5*S*)-3-[(1*R*)-1-Hydroxyethyl]-5-methylheptyl]-1,3-dioxane (22). The boronic acid ester **21** (4.06 g, 9.99 mmol) was dissolved in THF (70 mL) and stirred in an ice bath. Aqueous NaOH (9.1 mL, 2.5 N, 23 mmol) and then 30% aqueous hydrogen peroxide (4.2 mL, 9.8 M, 41 mmol) were added dropwise from a pipet. The reaction, containing a precipitate, was stirred at 0 °C for 30 min, 1 h with the ice bath removed, and 1 h at 45–50 °C. The reaction was cooled to room temperature and concentrated in a rotary evaporator using a vacuum pump (bath temperature ≤30 °C) to a volume of 30 mL. The residue was partitioned between ether (50 mL) and water (25 mL) and centrifuged to separate the layers. The aqueous layer was extracted with additional ether (3 × 50 mL). The ether extracts were washed in succession with saturated aqueous NaCl (25 mL), dried (Na_2SO_4), decanted, and evaporated. The residue was purified by flash column chromatography on silica gel (75 g), eluting with 30% ethyl acetate in hexane (1 L), yielding 2.32 g (95% yield) of alcohol **22** as a colorless oil: $[\alpha]_D$ +19.5° (c = 1.0, $CHCl_3$); IR (CCl_4) 3620, 3580–3260, 1465, 1380, 1245, 1150, 1080 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 4.43 (t, 1 H, J = 5 Hz), 3.83 (dd, 2 H, J = 11.5, 5 Hz), 3.61 (quintet, 1 H, J = 6 Hz), 3.35 (tm, 1 H, J = 12 Hz), 1.96–1.06 (m, 11 H), 1.02 (d, 3 H, J = 6.5 Hz), 0.86 (t, 3 H, J = 7 Hz), 0.85 (d, 3 H, J = 6 Hz), 0.64 (dm, 1 H, J = 13 Hz). Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 68.99; H, 11.71.

2-[(3*R*,5*S*)-3-[(1*R*)-1-[(4-Bromobenzoyl)oxy]ethyl]-5-methylheptyl]-1,3-dioxane (23). 4-Bromobenzoic acid (1.00 g, 4.97 mmol) and 4-(dimethylamino)pyridine (75 mg, 0.61 mmol) were added to a solution of alcohol **22** (1.00 g, 4.11 mmol) in 20.0 mL of CH_2Cl_2. 1,3-Dicyclohexylcarbodiimide (1.23 g, 5.96 mmol) was added in two portions 15 min apart, and the reaction was stirred at 25 °C for 22 h. The reaction was then stirred for 1 h with water (500 mg, 28 mmol) and filtered. The precipitate was washed with ether (3 × 7 mL), and the combined filtrate was evaporated to give 2.34 g of crude product. Flash column chromatography on silica gel (50 g), eluting with 7% ethyl acetate/hexane (500 mL) followed by 10% ethyl acetate/hexane (300 mL), gave ester **23** as 1.61 g (91% yield) of clear, colorless oil: $[\alpha]_D$ −10.3° (c = 1.1, $CHCl_3$); IR (CCl_4) 1725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.89 (d, 2 H, J = 8.5 Hz), 7.58 (d, 2 H, J = 8.5 Hz), 5.21 (qd, 1 H, J = 6, 4 Hz), 4.55 (t, 1 H, J = 5 Hz), 4.12 (dd, 2 H, J = 11, 5 Hz), 3.78 (bt, 2 H, J = 12 Hz), 2.24–1.94 (m, 1 H), 1.88–1.04 (m, 11 H), 1.30 (d, 3 H, J = 6.5 Hz), 0.86 (t, 3 H, J = 7 Hz), 0.82 (d, 3 H, J = 6 Hz). Anal. Calcd for $C_{21}H_{31}BrO_4$: C, 59.02; H, 7.31. Found: C, 58.79; H, 7.28.

3-Hydroxypropyl (4*R*,6*S*)-4-[(1*R*)-1-[(4-Bromobenzoyl)oxy]ethyl]-6-methyloctanoate (24). The acetal **23** (163 mg, 0.381 mol) was dissolved in a mixture of acetone (3.0 mL) and glacial acetic acid (0.6 mL) and cooled to 0 °C. Household bleach (Clorox, 5.25% aqueous NaOCl, 1.3 mL) was added, and the resulting mixture was stirred 30 min at 0 °C. An additional portion of bleach (1.3 mL) was added, and the reaction was stirred 4 h at 0 °C. The reaction was then diluted with hexane (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 15 mL) and saturated aqueous NaCl (2 × 15 mL). The hexane solution was dried (Na_2SO_4), decanted, and evaporated. The residue was purified by flash column chromatography on silica gel (6.5 g), eluting with 25% ethyl acetate in hexane (100 mL) and 30% ethyl acetate in hexane (50 mL) to give the diester **24** as 115 mg (68% yield) of colorless oil: $[\alpha]_D$ −16° (c = 1.0, $CHCl_3$); IR (CCl_4) 3630, 3540, 2960, 2920, 2860, 1720, 1270, 1175, 1110, 1100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.87 (d, 2 H, J = 8.5 Hz), 7.58 (d, 2 H, J = 8.5 Hz), 5.19 (qd, 1 H, J = 6.5, 3.5 Hz), 4.25 (t, 2 H, J = 6 Hz), 3.70 (q, 2 H, J = 6 Hz), 2.42 (t, 2 H, J = 7 Hz), 2.00–1.66 (m, 6 H), 1.54–1.02 (m, 5 H), 1.31 (d, 3 H, J = 6.5 Hz), 0.87 (t, 3 H, J = 7 Hz), 0.82 (d, 3 H, J = 6 Hz). Anal. Calcd for $C_{21}H_{31}BrO_5$: C, 56.89; H, 7.05. Found: C, 56.61; H, 7.07.

(5*R*,6*R*)-6-Methyl-5-[(2*S*)-2-methylbutyl]tetrahydro-2*H*-pyran-2-one (7). The diester **24** (0.78 g, 1.76 mmol) was dissolved in ethanol (10 mL), and aqueous NaOH (1.75 mL, 4.0 N, 7.0 mmol) was added. After stirring the solution for 3 days at room temperature, most of the solvent was removed on a rotary evaporator. Aqueous HCl (10 mL, 2 N, 20 mmol) and ether (20 mL) were added to the concentrated reaction mixture. After stirring for 1 h, the layers were separated and the aqueous layer was extracted with 20 mL of ether. The ether layers were washed in succession with 10 mL of aqueous NaCl, dried (Na_2SO_4), decanted, and evaporated. Purification by flash column chromatography on silica gel (10 g), eluting with 20% ether/petroleum ether (200 mL), yielded product containing a small amount of 4-bromobenzoic acid. This material was combined with product similarly obtained from 115 mg (0.26 mmol) of diester **24** and dissolved in ether (10 mL). The solution was washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and saturated aqueous NaCl (5 mL). The aqueous layers were extracted in succession with ether (10 mL). The organic layers were dried ($MgSO_4$), filtered, and evaporated. Bulb-to-bulb distillation yielded 322 mg (87% yield) of lactone **7** as a colorless oil: bp 100–120 °C (1.5 mmHg); $[\alpha]_D$ +93.2° (c = 1.1, $CHCl_3$); IR (CCl_4) and ^1H NMR (200 MHz, $CDCl_3$) spectra were identical with those described for compound **7** above.

(2*R*,5*S*)-5-[(2*R*,5*R*,6*R*)-2-Hydroxy-6-methyl-5-[(2*S*)-2-methylbutyl]tetrahydro-2*H*-pyran-2-yl]-5-methyl-2-(1,1-dimethylethyl)-1,3-dioxolan-4-one (25). *n*-Butyllithium (1.63 M in hexane, 13.50 mL, 22.0 mmol) was added to a −70 °C solution of diisopropylamine (3.70 mL, 2.67 g, 26.4 mmol) in THF (125 mL). The resulting solution was allowed to warm to −10 °C and then cooled to −70 °C. (2*R*,5*R*)-5-Methyl-2-(1,1-dimethylethyl)-1,3-dioxolan-4-one (**6**) (3.35 mL, 3.26 g, 20.6 mmol) was then added over 4 min via syringe. The solution was stirred at −70 °C for 45 min, and then lactone **7** (2.89 g, 15.7 mmol) was added over 5 min as a solution in THF (10 mL), with additional THF (5 mL) being used to rinse the last lactone into the reaction. The reaction was allowed to warm to −25 °C (internal temperature) over 45 min and then maintained at −35 to −25 °C for 1 h. The reaction was poured into a 1:1 mixture of water and saturated aqueous NH_4Cl (500 mL) and then extracted with ether (2 × 500 mL). The ether layers were washed with saturated aqueous NaCl (250 mL), combined, dried (Na_2SO_4), decanted, and evaporated. The residue was dissolved in hexane, dried (Na_2SO_4), decanted, and evaporated to give 6.08 g of crude product. Flash column chromatography on silica gel (300 g), eluting with 1.5% ethyl acetate/hexane (6 L), gave 4.05 g (75% yield) of the condensation product **25** as a colorless oil, which crystallized upon standing: mp 43–47 °C; $[\alpha]_D$ +86° (c = 0.9, $CHCl_3$); IR (CCl_4) 3530, 2975, 2920, 2880, 1785, 1490, 1460, 1405, 1380, 1355, 1290, 1270, 1180, 1160, 1085, 990, 915 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.29 (s, 1 H), 3.66 (dq, 1 H, J = 9.5, 6 Hz), 3.16 (d, 1 H, J = 1.5 Hz), 1.81–1.68 (m, 3 H), 1.43 (s, 3 H), 1.42–1.12 (m, 5 H), 1.11 (d, 3 H, J = 6 Hz), 1.07–0.99 (m, 2 H), 0.96 (s, 9 H), 0.87 (t, 3 H, J = 7 Hz), 0.83 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_{19}H_{34}O_5$: C, 66.64; H, 10.01. Found: C, 66.84; H, 10.08.

Continued elution of the column with 33% ether/petroleum ether (3.1 L) gave 474 mg (16% recovery) of the starting lactone **7**, $[\alpha]_D$ +91.4° (c = 1.1, $CHCl_3$).

(2*R*,5*S*)-5-[(2*R*,5*R*,6*R*)-2-Methoxy-6-methyl-5-[(2*S*)-2-methylbutyl]tetrahydro-2*H*-pyran-2-yl]-5-methyl-2-(1,1-dimethylethyl)-1,3-dioxolan-4-one (26). The hemiacetal **25** (1.00 g, 2.92 mmol) was dissolved in dry methanol (16.0 mL) and cooled to 0 °C. Acetyl chloride (1.0 mL, 1.1 g, 14 mmol) was added dropwise over 5 min. The reaction was stirred 20 min at 0 °C, followed by 75 min at room temperature. The reaction was diluted with petroleum ether (100 mL) and washed with water (100 mL),

saturated aqueous $NaHCO_3$ (50 mL), and saturated aqueous NaCl (50 mL). The solution was dried (Na_2SO_4), decanted, and evaporated. After drying overnight under vacuum, the weight of the crude product was 1.00 g. This material was used in subsequent steps without further purification. Flash chromatography of a portion (200 mg) of the crude product on silica gel eluting with 2% ethyl acetate in hexane produced an analytical sample (186 mg, 89% yield) of the methyl pyranoside **26**: $[\alpha]_D$ +79.8° (c = 1.0, $CHCl_3$); IR (CCl_4) 2960, 2920, 2870, 1800, 1375, 1345, 1175, 1135, 1080, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.26 (s, 1 H), 3.39 (s, 3 H), 3.33 (dq, 1 H, J = 9, 6 Hz), 1.90 (td, 1 H, J = 13, 4.5 Hz), 1.73 (broad dq, 1 H, J = 13, 3 Hz). 1.63 (dt, 1 H, J = 13, 3 Hz), 1.46-1.08 (m, 5 H), 1.37 (s, 3 H), 1.16 (d, 3 H, J = 6 Hz), 1.07-0.99 (m, 2 H), 0.95 (s, 9 H), 0.88 (t, 3 H, J = 7 Hz), 0.84 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.20; H, 10.12.

(2*S*)-2-[(2*R*,5*R*,6*R*)-2-Methoxy-6-methyl-5-[(2*S*)-2-methylbutyl]tetrahydro-2*H*-pyran-2-yl]propanoic Acid Methyl Ester (5). Methanolic sodium methoxide was prepared by adding sodium (970 mg, 42 mg-atom) to dry methanol (20 mL, distilled from magnesium methoxide). The methyl pyranoside **26** was dried by repeatedly evaporating a toluene solution (3 × 12 mL) under vacuum. The residue was then dissolved in 10.0 mL of the methanolic sodium methoxide solution and stirred for 2 days. The reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with saturated aqueous NaCl (25 mL), dried (Na_2SO_4), decanted, and evaporated. Flash column chromatography on silica gel (40 g), eluting with 12% ethyl acetate/hexane (800 mL), gave the methyl ester **5** as 658 mg (78% yield) of colorless oil: $[\alpha]_D$ +89.8° (c = 1.0, $CHCl_3$); IR (CCl_4) 3560, 2960, 2930, 1740, 1450, 1380, 1250, 1175, 1150, 1125, 1080, 1030, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3 H), 3.39 (s, 1 H), 3.38 (dq, 1 H, J = 9, 6.5 Hz), 3.37 (s, 3 H), 1.97-1.87 (m, 1 H), 1.79-1.60 (m, 2 H), 1.49-0.94 (m, 7 H), 1.43 (s, 3 H), 1.19 (d, 3 H, J = 6 Hz), 0.87 (t, 3 H, J = 7 Hz), 0.82 (d, 3 H, J = 6.5 Hz). Anal. Calcd for $C_{16}H_{30}O_5$: C, 63.55; H, 10.00. Found: C, 63.85; H, 9.94.

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Reactivity of Biologically Important Reduced Pyridines. 7.† Energetics and Effect of Substitution on Hydride versus Electron Transfer in Dihydropyridines, Dihydroquinolines, and Dihydroisoquinolines

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The hydridic and electronic oxidation of a variety of 1-methyl-3-substituted-1,4-dihydropyridines, 1-methyl-3-substituted-1,4-dihydroquinolines, 1-methyl-3-substituted-1,2-dihydroquinolines, 2-methyl-4-substituted-1,2-dihydroisoquinolines, and 1-(4-substituted-phenyl)-1,4-dihydronicotinamides were examined using a semiempirical molecular orbital (AM1) method. The data obtained indicate that a significant correlation (r > 0.97) is generated when the energies associated with either electron loss or hydride transfer are compared. The slope of such relationships approaches unity. In addition, the relative stabilities of various derivatives determined theoretically are consistent with experimentally derived kinetic stabilities. A group of five substituents ($(CH_3)_2N$, CH_3O, CH_3S, Cl, F) invariably deviate from the relationship defined by the remaining compounds. This deviation may be due to the differential effect of electron donation on the ground state which controls electronic oxidation and on the hydride-transferring transition state which determines hydridic oxidative reactivity.

Introduction

Dihydropyridines constitute the basic operational subunit of a number of biologically important coenzymes.[1] These compounds can accept a pair of electrons from the respiratory chain resulting in pyridinium salt formation. The nature of this oxidation, which is fundamental to the understanding of biochemical respiration, has been extensively studied through the use of various model systems.[2] In these investigations, the mechanism of this oxidation has been narrowed to two main possibilities, namely, concerted hydride transfer or sequential elec-

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