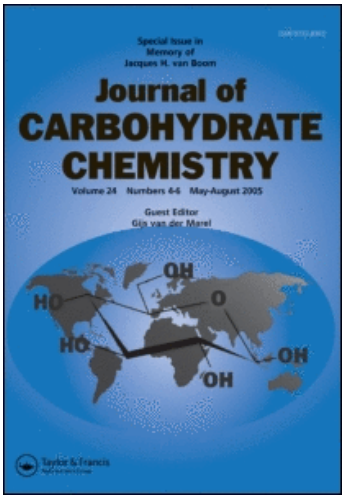

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Synthesis of an Optically Active Trisubstituted α,β-Butenolide, (*S*)-4, 6-Dihydroxy-2, 3-dimethyl-2-hexesoic Acid 1, 4-Lactone, from 2-Deoxy-D-ribose

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SYNTHESIS OF AN OPTICALLY ACTIVE TRISUBSTITUTED α,β-BUTENOLIDE, (*S*)-4,6-DIHYDROXY-2,3-DIMETHYL-2-HEXENOIC ACID 1,4-LACTONE, FROM 2-DEOXY-D-RIBOSE

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ABSTRACT

The title compound has been synthesized efficiently from 2-deoxy-D-ribose. The synthesis involves : 1) an aldol like carbon-carbon bond formation of (*S*)-3,5-dibenzyloxy-2-pentanone (8) with a lithium enolate of methyl propanoate, and 2) O-debenzylation of the aldol adducts (11) for a γ-lactonization followed by β-elimination of the desired butenolide skeleton.

INTRODUCTION

In many physiologically interesting natural products, α,β- and β,γ-butenolide structures are found as partial components,[1] and, in many cases, they are mono-, di- or trisubstituted. Although a variety of synthetic approaches toward substituted butenolides have appeared in the literature ,[2] more efficient

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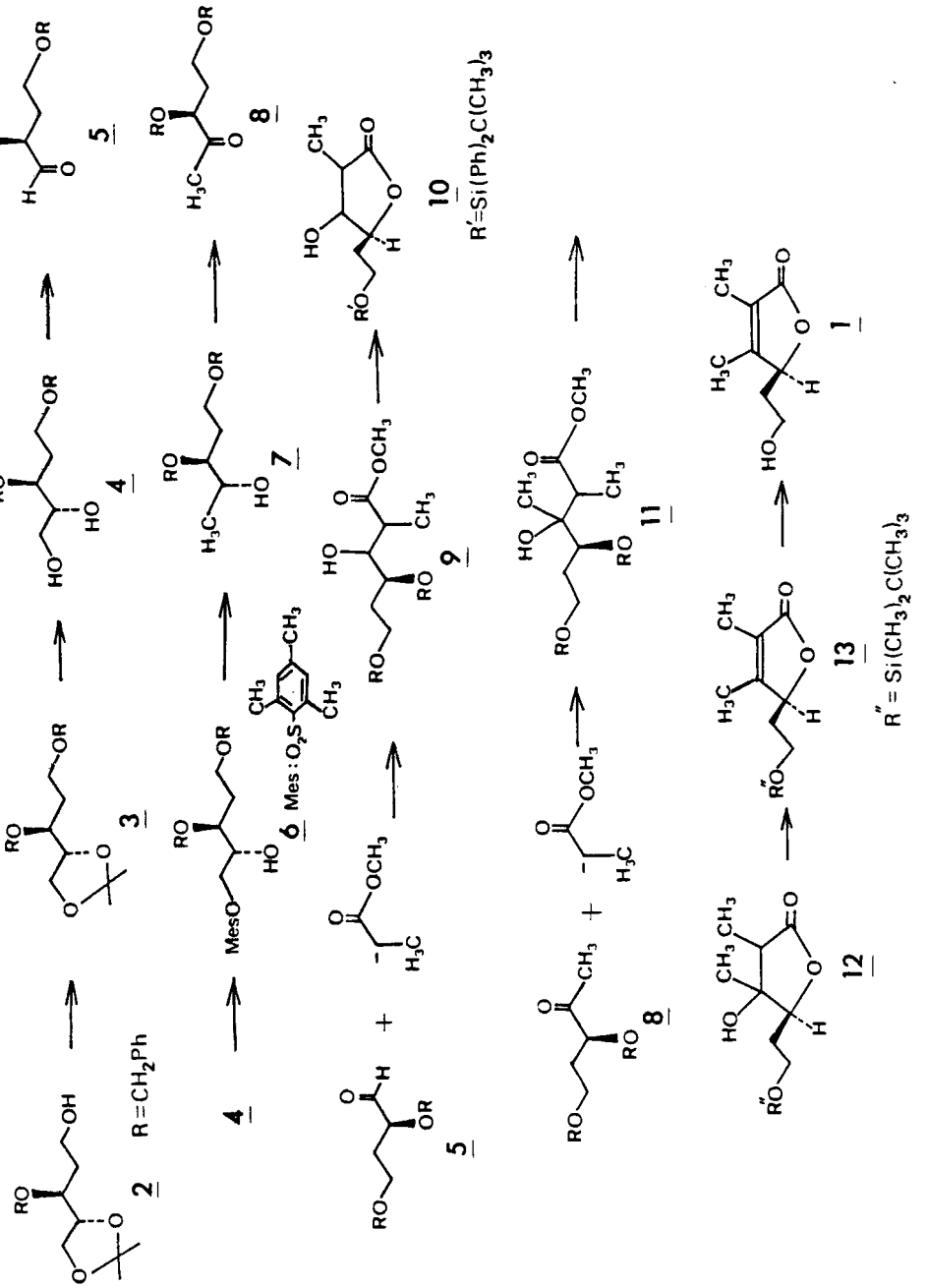
approaches are still desirable. Chiral syntheses of natural products employing readily available optically active compounds (carbohydrates, amino acids and so on) as starting materials have been investigated intensely in recent years.[3] The carbohydrate derived butenolides syntheses also have been described in the literature. Attwood and Barrett have reported a synthesis of some derivatives of (*S*)-3-hydroxy-5-hydroxymethyl-furan-2(5H)-one (2-hydroxylated 4-substituted α,β-butenolides) from properly acylated D-ribonic acid γ-lactones.[4] Similarly, some optically active 3-alkylated (4-hydroxylated) butyro-1,4-lactones have been synthesized from 2,3:4,5-di-O-isopropylidene-*aldehyde*-D-arabinose by Lawston and Inch.[5] As a part of chiral synthesis of synthetic intermediates for natural products such as highly substituted butenolides or butyrolactones, we wish to describe a synthesis of (*S*)-4,6-dihydroxy-2,3-dimethyl-2-hexenoic acid 1,4-lactone (1) from 2-deoxy-D-ribose.

RESULTS AND DISCUSSION

The synthesis of 1 was initiated from 3-O-benzyl-2-deoxy-4,5-O-isopropylidene-D-*erythro*-pentitol (2) which was recently prepared in our laboratory from 2-deoxy-D-ribose in a fairly good overall yield.[6] **Benzylation of 2 with benzyl bromide in the** presence of sodium hydride in DMF gave the 1,3-di-O-benzyl derivative (3) in 89% yield. O-Isopropylidene group in 3 was then removed with 85% trifluoroacetic acid to afford 1,3-di-O-benzyl-2-deoxy-D-*erythro*-pentitol (4) in 92% yield. The 4,5-diol in **4 was cleaved by periodate to give an aldehyde (5)** quantitatively, which served as an electrophile in the next aldol addition. **The aldol addition of 5 with a lithium enolate of** methyl propanoate, generated by lithium diisopropylamide (LDA), proceeded smoothly to give a diastereomeric mixture of (4*S*)-methyl 4,6-dibenzyloxy-3-hydroxy-2-methylhexanoate (9) in 61%



yield. The ^{1}H NMR spectrum of the mixture showed three doublets (each J=7.5 Hz) centered at δ 1.17, 1.20 and 1.22 which were attributed to 2-methyl groups of the aldol adducts. The approximate ratio of the diastereomers was 6:3:1. Those diastereomers could not be separated cleanly by SiO_2 chromatography, so the mixture was subjected to the next step. O-Debenzylation of the mixture 9 under the Hanessian Procedure[7] accompanied by γ-lactonization proceeded without difficulty, and the primary hydroxyl group of the product was protected as a silyl ether with *tert*-butylchlorodiphenylsilane to give an inseparable diastereomeric mixture (10) in 58% yield. To introduce an alkyl group at β-position of the carbonyl group, oxidation of the hydroxyl group in 10 was examined under several conditions. Pyridinium chlorochromate (PCC) or ruthenium tetroxide were virtually unreactive as oxidizing reagents, and 10 was recovered quantitatively. Dimethyl sulfoxide-acetic anhydride oxidation of 10 resulted in formation of a complex mixture, thus this method seems to be impractical. From these results, we abandoned the route to 1 from 10.

Next, we examined introduction of a methyl group at the β-position of the carbonyl group prior to γ-lactonization. Preferential sulfonylation of the primary hydroxyl group in 4 was achieved in 82% yield to give compound (6). Deoxygenation of 6 with lithium aluminium hydride afforded 1,3-di-O-benzyl-2,5-dideoxy-D-*erythro*-pentitol (7) in 92% yield. PCC oxidation of 7 gave compound 8 in 87% yield. The aldol addition of 8 with a lithium enolate of methyl propanoate, generated by LDA, afforded a diastereomeric mixture of (4*S*)-methyl 4,6-dibenzyloxy-3-hydroxy-2,3-dimethylhexanoate (11) in 96% yield. Owing to the multiplicity of the C-methyl signals in the ^{1}H NMR spectrum of the mixture, the ratio of each diastereomer could not be estimated. O-Debenzylation of the mixture by the Hanessian procedure[7] followed by silylation of the primary hydroxyl group in the resulting γ-lactone with *tert*-butylchlorodimethylsilane

gave a diastereomeric mixture of (4*S*)-6-(*tert*-butyldimethylsilyloxy)-3,4-dihydroxy-2,3-dimethylhexanoic acid 1,4-lactone (12) in 65% yield. The final stage to the α,β-butenolide was introduction of α,β-double bond by β-elimination. Treatment of 12 with mesyl chloride in pyridine at 40 °C gave the desired α,β-butenolide, (*S*)-6-(*tert*-butyldimethylsilyloxy)-4-hydroxy-2,3-dimethyl-2-hexenoic acid 1,4-lactone (13), in 58% yield. The formation of the α,β-butenolide proceeded presumably *via* the β-mesylate which could not be detected in the reaction mixture. Finally, O-desilylation of 13 with *p*-toluenesulfonic acid afforded the desired 1 in 71% yield. Thus, we achieved a convenient synthesis of a trisubstituted α,β-butenolide in an acceptable overall yield from 2-deoxy-D-ribose.

EXPERIMENTAL

General procedure. Solutions were concentrated under diminished pressure at a bath temperature below 40 °C. Specific rotations were measured in a 1-dm tube with a JEOL DIP-4 polarimeter. Column chromatography was performed with Wakogel C-300 (Wako Pure Chemicals), and TLC was carried out on glass plates coated with Wakogel B-5F, compounds being detected with UV light and by spraying with sulfuric acid followed by heating. Preparative TLC (PTLC) was performed on glass plates (20 x 20 cm) coated with Merck Kieselgel 60 PF_{254} and compounds were extratced with chloroform. IR spectra were recorded with a Hitachi Model-225 spectrometer (KBr) and JEOL Model A-202 spectrometer ($CHCl_3$). ^1H NMR spectra were recorded with a Varian EM-390 spectrometer, and chemical shifts for a $CDCl_3$ solution are recorded in δ values from internal tetramethylsilane. High resolution mass spectra were taken on a Hitachi M-80 mass spectrometer. Elemental analyses were performed by Mr. Saburo Nakada to whom our thanks are due.

1,3-Di-O-benzyl-2-deoxy-4,5-O-isopropylidene-D-*erythro*-pentitol (3). Sodium hydride (60% emulsion in mineral oil, 270 mg, 6.8 mmol) was washed with hexane (2 mL x 3), and suspended in DMF (15 mL). To the suspension was added a solution of 3-O-benzyl-2-deoxy-4,5-O-isopropylidene-D-*erythro*-pentitol (2)[6] (900 mg, 3.4 mmol) in DMF (10 mL), and the mixture was stirred for 25 min. Benzyl bromide (0.81 mL, 6.8 mmol) was added, and the mixture was stirred for 5 h. Then, ethanol (5 mL) was added, diluted with water (100 mL),and the solution was extracted with chloroform (100 mL x 3). The extracts were washed with water (100 mL x 2), dried (Na_2SO_4), and concentrated. The residue was chromatographed on SiO_2 (70 g, ethyl acetate:hexane= 1:10) and fractions corresponding to R_f 0.49 on TLC (ethyl acetate:hexane=1:5) were concentrated to afford 3 (1.08 g, 89%) as a syrup, $[\alpha]_D^{24}$-14.2° (*c* 1.27, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 1385, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34, 1.41 (each 3H, each s, $C(CH_3)_2$), 1.69-2.01 (2H, m, H-2,2'), 3.59 (2H, t, J=6 Hz, H-1,1'), 3.70-4.27 (4H, m, H-3,4,5,5'), 4.36 (2H, s, $OCH_2C_6H_5$), 4.62 (2H, ABq, $OCH_2C_6H_5$), 7.28-7.53 (10H, m, 2 x $OCH_2C_6H_5$).

Anal. calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.85; H, 7.89.

1,3-Di-O-benzyl-2-deoxy-D-*erythro*-pentitol (4). A solution of 3 (3.69 g, 10.4 mmol) in 85% trifluoroacetic acid (35 mL) was stirred at 0 °C for 1 h, and neutralized with 5 M NaOH solution. The solution was diluted with water (15 mL) and extracted with chloroform (150 mL x 3). The extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (100 g, ethanol:toluene=1:15), and fractions corresponding to R_f 0.17 on TLC (ethanol:toluene=1:10) were concentrated to afford 4 (3.00 g, 92%) as a syrup, $[\alpha]_D^{23}$+12.5° (*c* 1.61, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3450, 2930, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80-2.18 (2H, m, H-2,2'), 2.34-2.71 (1H, br s, OH), 3.11-3.39 (1H, br s, OH), 3.44-4.01 (6H, m, H-1,1',3,4,5,5'), 4.48-4.52 (4H, m, 2 x $OCH_2C_6H_5$), 7.32 (10H, m, 2 x $OCH_2C_6H_5$).

Anal. calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 71.98; H, 7.55.

1,3-Di-O-benzyl-2-deoxy-5-O-(2-mesitylenesulfonyl)-D-*erythro*-pentitol (6). To a solution of 4 (3.00 g, 9.5 mmol) in pyridine (20 mL) was added 2-mesitylenesulfonyl chloride (4.15 g, 19.0 mmol) at 0 °C. The mixture was stirred at the temperature for 3 h and concentrated. The residue was partitioned between ethyl acetate (200 mL) and water (100 mL), and the aqueous layer was extracted with ethyl acetate (200 mL x 3). The extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (150 g, ethyl acetate:toluene=1:20), and fractions corresponding to R_f 0.40 on TLC (ethyl acetate:toluene=1:5) were concentrated to afford 6 (3.88 g, 82%) as a syrup, $[\alpha]_D^{23}$+13.8° (*c* 1.04, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3450, 1600, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89 (2H, q, J=6 Hz, H-2,2'), 2.29 (3H, s, $OSO_2C_6H_2(CH_3)_2\underline{CH_3}$-4), 2.66 (6H, s, $OSO_2C_6H_2(\underline{CH_3}$-2,6)$CH_3$), 2.89-3.30 (1H, br s, OH), 3.38-4.00 (4H, m, H-1,1',3,4), 4.09 (2H, d, J=4 Hz, H-5,5'), 4.50 (4H, s, 2 x $OCH_2C_6H_5$), 6.95 (2H, s, $OSO_2C_6H_2(CH_3)_2CH_3$), 7.32 (10H, s, 2 x $OCH_2C_6H_5$). High resolution mass spectrum, calcd for $C_{28}H_{34}O_6S$: *m/z* 498.2074, found: M, 498.2071.

1,3-Di-O-benzyl-2,5-dideoxy-D-*erythro*-pentitol (7). To a solution of 6 (3.13 g, 6.3 mmol) in ether (20 mL) was added lithium aluminium hydride (0.48 g, 12.6 mmol), and the mixture was heated under reflux for 1 h. To the mixture were added water (0.5 mL), 15% aqueous NaOH (0.5 mL), and water (0.5 mL), successively. The insoluble materials were removed by filtration through Celite-pad, and washed with ethyl acetate (150 mL). The combined filtrate and washing were dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (80 g, ethyl acetate:toluene=1:10), and fractions corresponding to R_f 0.28 on TLC (ethyl acetate:toluene=1:10) were concentrated to afford 7 (1.74 g, 92%) as a syrup, $[\alpha]_D^{23}$-20.2° (*c* 0.89, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3430, 2860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3H, d, J=6 Hz, H-5,5',

5"), 1.84 (2H, q, J=6 Hz, H-2,2'), 2.37 -2.67 (1H, br s, OH), 3.38-3.72 (3H, m, H-1,1',3), 3.77-4.10 (1H, m, H-4), 4.47, 4.53 (each 2H, each s, 2 x $OCH_2C_6H_5$), 7.31 (10H, s, 2 x $OCH_2C_6H_5$). High resolution mass spectrum, calcd for $C_{19}H_{24}O_3$: *m/z* 300.1724, found: M, 300.1728.

(*S*)-3,5-Dibenzyloxy-2-pentanone (8). To a solution of 7 (123 mg, 0.40 mmol) in dry dichloromethane (5 mL) was added pyridinium chlorochromate (221 mg, 1.0 mmol). The mixture was stirred for 6 h, and applied on SiO_2 column (3 g). The column was eluted with ether, and the eluate was concentrated. The residue was purified by PTLC (ethyl acetate:toluene=1:8) to afford 8 (106 mg, 87%) as a syrup, R_f 0.42 on TLC (ethyl acetate: toluene=1:8), $[\alpha]_D^{24}$-43.1° (*c* 1.28, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 2860, 1355 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.97 (2H, q, J=6 Hz, H-4,4'), 2.15 (3H, s, H-1,1',1"), 3.58 (2H, t, J=6 Hz, H-5,5'), 3.98 (1H, t, J=6 Hz, H-3), 4.38-4.65 (4H, m, 2 x $OCH_2C_6H_5$), 7.17-7.57 (10H, m, 2 x $OCH_2C_6H_5$). High resolution mass spectrum, calcd for $C_{19}H_{22}O_3$: *m/z* 298.1568, found: M, 298.1575.

Diastereomeric mixture of (4*S*)-methyl 4,6-dibenzyloxy-3-hydroxy-2-methylhexanoate (9). To a solution of 4 (10.3 g, 3.2 mmol) in methanol (10 mL) was added a solution of sodium periodate (0.77 g, 3.6 mmol) in water (10 mL). The mixture was stirred for 45 min, diluted with water (50 mL), and extratced with chloroform (60 mL x 3). The extracts were dried (Na_2SO_4) and concentrated to afford 5 (0.92 g, 99%) as a syrup which was used in the next step without purification, $[\alpha]_D^{23}$-41.2° (*c* 0.68, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 2860, 1730, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84-2.14 (2H, m, H-3,3'), 3.60 (2H, t, J=6 Hz, H-4,4'), 3.97 (1H, br t, J=7 Hz, H-2), 4.45 (2H, s, $OCH_2C_6H_5$), 4.57-4.63 (2H, ABq, $OCH_2C_6H_5$), 6.97-7.60 (10H, m, 2 x $OCH_2C_6H_5$), 9.70 (1H, d, J=1 Hz, CHO).

The following reaction was carried out under argon atmosphere. To a solution of diisopropylamine (2.48 mL, 17.7 mmol) in dry THF (10 mL) was added butyllithium (1.2 M in

hexane, 14.8 mL, 17.7 mmol) at 0 °C, and the mixture was stirred for 10 min. The mixture was cooled to -78 °C, methyl propanoate (1.55 mL, 16.1 mmol) was added, and the mixture stirred at the temperature for 45 min. To the mixture was added a THF (10 mL) solution of 5 (916 mg, 3.42 mmol) at -78 °C. The mixture was gradually warmed to 0 °C, and quenched with 1% ammonium chloride solution (50 mL). The aqueous solution was extratced with ethyl acetate (50 mL x 3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (150 g, ethyl acetate:toluene=1:15), and fractions corresponding to R_f 0.51 on TLC (ethanol:toluene=1:10) were concentrated to afford the diastereomeric mixture 9 (737 mg, 61%) as a syrup, IR $\nu_{max}^{CHCl_3}$ 3440, 3000, 2940, 2860, 1725, 1450, 1435, 1170, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17, 1.20, 1.22 (total 3H, each d, J=7.5 Hz, CH_3-2), 1.96 (2H, q, J=6 Hz, H-5,5'), 2.71, 2.74 (total 2H, each t, J=5 Hz, H-2,2'), 2.96-3.05 (1H, m, OH), 3.49-4.14 (7H, m, $COOCH_3$, H-3,4,6,6'), 4.46-4.61 (4H, m, 2 x $OCH_2C_6H_5$), 7.18-7.60 (10H, m, 2 x $OCH_2C_6H_5$).

Anal. calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.74; H, 7.59.

Diastereomeric mixture of (4*S*)-6-(*tert*-butyl)diphenylsilyloxy-3,4-dihydroxy-2-methylhexanoic acid 1,4-lactone (10). To a solution of diastereomeric mixture of 9 (200 mg, 0.54 mmol) in ethanol (2 mL) were added cyclohexene (2.0 mL) and 20% $Pd(OH)_2$ on charcoal (100 mg). The mixture was heated under reflux for 6 h, and the catalyst was removed by filtration through Celite-pad. The filtrate was concentrated to afford a semi-crystalline syrup. The syrup was dissolved in DMF (1.5 mL) and *tert*-butylchlorodiphenylsilane (0.26 mL, 1.0 mmol) and imidazole (135 mg, 2.0 mmol) were added. The mixture was stirred for 1.5 h and diluted with water (20 mL). The solution was extracted with chloroform (25 mL x 3) and the extracts were washed with water (20 mL x 2). The extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on

SiO_2 (15 g, ethanol:toluene=1:10), and fractions corresponding to R_f 0.47 on TLC (ethanol:toluene=1:10) were concentrated to afford an inseparable mixture of 10 and (4*S*)-6-(*tert*-butyl)diphenylsilyloxy-3,4-dihydroxy-2-methylhexanoate (168 mg) as a syrup. The syrup was dissolved in dichloromethane (2.5 mL) and boron trifluoride etherate in dichloromethane (1% v/v, 1.2 mL, 0.096 mmol) was added. The mixture was stirred for 3 h, neutralized with saturated aqueous $NaHCO_3$ and diluted with water (15 mL). The solution was extracted with chloroform (15 mL x 3), and the extracts were dried (Na_2SO_4), and concentrated. The residue was purified on PTLC (ethanol:toluene=1:10) to afford 10 (124 mg, 58%) as a syrup, R_f 0.42 on TLC (ethanol:toluene=1:10); IR $\nu_{max}^{CHCl_3}$ 3430, 2930, 2860, 1775, 1460, 1425, 1115, 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (9H, s, $C(CH_3)_3$), 1.31 (3H, d, J=7 Hz, CH_3-2), 1.63-1.70 (total 1H, OH), 1.72-2.22 (2H, m, H-5,5'), 2.42-2.83 (1H, m, H-2), 3.63-4.40 (3H, m, H-3,6,6'), 4.37-4.72 (total 1H, m, H-4), 7.27-7.73 (10H, m, $OSi(C_6H_5)_2$).

Anal. calcd for $C_{23}H_{30}O_4Si$: C, 69.31; H, 7.59. Found: C, 69.16; H, 7.60.

Diastereomeric mixture of (4*S*)-methyl 4,6-dibenzyloxy-3-hydroxy-2,3-dimethylhexanoate (11). The reaction was carried out under argon atmosphere. To a solution of diisopropylamine (0.32 mL, 2.3 mmol) in dry THF (1.5 mL) was added butyllithium (1.6 M in hexane, 1.44 mL, 2.3 mmol), and the mixture was stirred for 10 min at 0 °C. After cooling to -78 °C, methyl propanoate (0.22 mL, 2.2 mmol) was added to the mixture and stirred at the temperature for 1 h. To the mixture was added a THF (2 mL) solution of 8 (135 mg, 0.45 mmol), and the mixture was stirred for 30 min at -78 °C. The mixture was quenched with 1% ammonium chloride (5 mL), and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layer and extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (30 g, ethyl acetate:toluene=1:20), and fractions corresponding

to R_f 0.22 on TLC (ethyl acetate:toluene=1:15) were concentrated to afford 11 (166 mg, 96%) as a syrup, IR $\nu_{max}^{CHCl_3}$ 3490, 3000, 2940, 2860, 1710, 1450, 1360, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07-1.47 (6H, m, CH_3-2, CH_3-3), 1.54-2.38 (2H, m, H-5,5'), 2.73 (1H, q, J=6 Hz, H-2), 3.20-3.25 (1H, br s, OH), 3.41-3.82 (6H, m, $COOCH_3$, H-4,6,6'), 4.43-4.82 (4H, m, 2 x $OCH_2C_6H_5$), 7.10-7.64 (10H, m, 2 x $OCH_2C_6H_5$).

Anal. calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.47; H, 7.74.

Diastereomeric mixture of (4*S*)-6-(*tert*-butyldimethylsilyloxy)-3,4-dihydroxy-2,3-dimethylhexanoic acid 1,4-lactone (12). To a solution of 11 (540 mg, 1.4 mmol) in ethanol (14 mL) were added cyclohexene (14 mL) and 20% $Pd(OH)_2$ on charcoal (540 mg). The mixture was heated under reflux for 24 h, and the catalyst was removed by filtration. The filtrate was concentrated and the residue was dissolved in DMF (4 mL). To the solution were added *tert*-butylchlorodimethylsilane (316 mg, 2.1 mmol) and imidazole (209 mg, 3.1 mmol). The mixture was stirred for 1.5 h and diluted with water (15 mL). The aqueous layer was extracted with ethyl acetate (20 mL x 3). The orgaic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (80 g, ethyl acetate:hexane=1:10) and the combined fractions corresponding to R_f 0.51 and 0.55 on TLC (ethanol:toluene=1:10) were concentrated to afford 12 (263 mg, 65%) as a syrup, ^1H NMR ($CDCl_3$) δ 0.09, 0.13 (total 6H, each s, $OSiC(CH_3)_3(C\underline{H}_3)_2$), 0.90 (9H, s, $OSiC(C\underline{H}_3)_3(CH_3)_2$), 1.11-1.31 (total 6H, m, CH_3-2, CH_3-3), 1.47-2.12 (total 2H, m, H-5,5'), 2.19-2.95 (total 1H, m, H-2), 3.48-3.95 (total 2H, H-6,6'), 3.99-4.48 (total 1H, m, H-4). High resolution mass spectrum, calcd for $C_{14}H_{28}O_4Si$: *m/z* 288.1755, found: M, 288.1755.

(*S*)-6-(*tert*-butyldimethylsilyloxy)-4-hydroxy-2,3-dimethyl-2-hexenoic acid 1,4-lactone (13). To a solution of 12 (210 mg, 0.73 mmol) in pyridine (4 mL) were added mesyl chloride (0.2 mL, 2.6 mmol) and 4-dimethylaminopyridine (36 mg, 0.29 mmol). The

mixture was stirred for 48 h at room temperature and for 2 h at 40 °C. Then, mesyl chloride (0.06 mL) was added and the mixture was heated at 40 °C for 4 h. The mixture was concentrated and the residue was partitioned between ethyl acetate (15 mL) and water (8 mL). The aqueous layer was extracted with ethyl acetate (15 mL x 2). The organic layer and extracts were dried (Na_2SO_4) and concentrated. The residue was purified on PTLC (ethyl acetate:toluene=1:10) to afford 13 (115 mg, 58%) as a syrup, R_f 0.61 on TLC (ethyl acetate:toluene=1:5), $[\alpha]_D^{23}$ -41.9° (*c* 1.85, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3020, 2955, 2930, 2855, 1740, 1670, 1250, 1220, 1200, 1100, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (6H, s, $OSiC(CH_3)_3(C\underline{H}_3)_2$), 0.88 (9H, s, $OSiC(C\underline{H}_3)_3(CH_3)_2$), 1.32-2.26 (2H, m, H-5,5'), 1.78, 1.95 (each 3H, each br s, CH_3-2, CH_3-3), 3.63-3.90 (2H, m, H-6,6'), 4.74-5.00 (1H, m, H-4). High resolution mass spectrum, calcd for $C_{14}H_{27}O_3Si$: *m/z* 271.1727, found: M+H, 271.1718.

(*S*)-4,6-Dihydroxy-2,3-dimethyl-2-hexenoic acid 1,4-lactone (1). To a solution of 13 (28 mg, 0.10 mmol) in methanol (1 mL) was added *p*-toluenesulfonic acid monohydrate (3.9 mg, 0.02 mmol), and the solution was stirred at 0 °C for 1.5 h. The solution was neutralized with saturated $NaHCO_3$ solution and concentrated. The residue was partitioned between water (8 mL) and dichloromethane (8 mL). The aqueous layer was extracted with dichloromethane (8 mL x 2). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by PTLC (ethyl acetate:hexane=1:2) to afford 1 (11 mg, 71%) as a syrup, $[\alpha]_D^{23}$ -51.6° (*c* 0.55, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3600, 3480, 2940, 1740, 1670, 1600, 1260, 1170, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38-2.36 (2H, m, H-5,5'), 1.81, 1.99 (each 3H, each br s, CH_3-2, CH_3-3), 2.40-2.62 (1H, m, OH), 3.86 (2H, bt, J=6 Hz, H-6,6'), 4.93 (1H, br d, J=10 Hz, H-4). High resolution mass spectrum, calcd for $C_8H_{13}O_3$: *m/z* 157.0863, found: M+H, 157.0836.

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