

STEREOSELECTIVE SYNTHESIS OF FULLY SUBSTITUTED δ -LACTONE; THE C1-C8 FRAGMENT OF DISCODERMOLIDE[†]

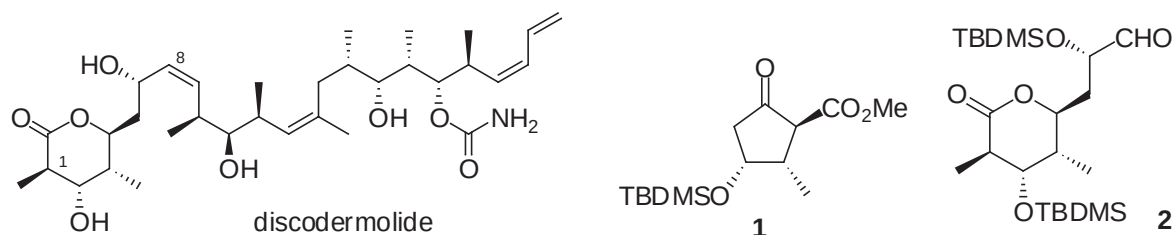
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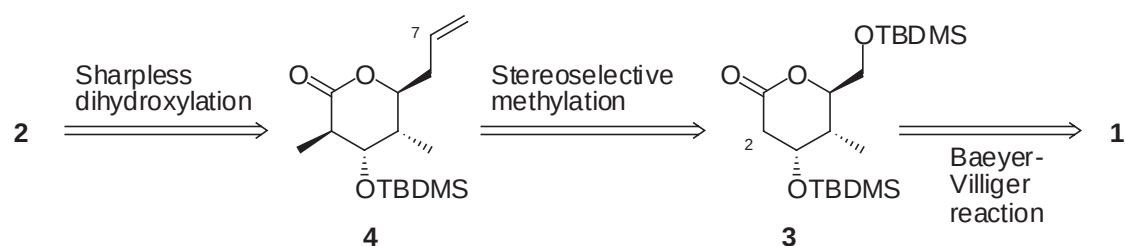
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Abstract — Baeyer-Villiger reaction of (2*R*,3*S*,4*R*)-4-*tert*-butyldimethylsilyloxy-2-*tert*-butyldimethylsilyloxymethyl-3-methylcyclopentanone (**5**) gave (4*R*,5*S*,6*R*)-4-*tert*-butyldimethylsilyloxy-6-*tert*-butyldimethylsilyloxymethyl-5-methyltetrahydropyran-2-one (**3**) in 96% yield, which was transformed into the C1-C8 fragment (**2**) of discodermolide *via* (3*R*,4*S*,5*S*,6*S*)-6-allyl-4-*tert*-butyldimethylsilyloxy-3,5-dimethyltetrahydropyran-2-one (**4**).

Considerable attention has recently been directed toward the stereoselective synthesis of lactones, since they are structural components of a large number of natural products and used as variable intermediates for the total syntheses.¹ Highly substituted stereo-defined δ -lactones are very important units in such natural products. The antitumor marine natural product (+)-discodermolide,²⁻⁶ which was isolated from the deep-water Caribbean sponge *Discodermia dissoluta* by Gunasekera and co-workers in 1990,² contains fully substituted δ -lactone and a polyhydroxylated acyclic portion. As a part of our interests in the stereoselective syntheses of functionalized cyclic compounds,⁷ we reported a novel stereoselective synthesis of an optically active cyclopentanone (**1**).⁸ Since **1** has three consecutive stereocenters on the cyclopentanone ring, we envisioned that **1** would be converted into an aldehyde (**2**), which is the C1-C8 intermediate⁹ in the total synthesis of discodermolide reported by Smith and co-workers.⁴ We describe here the synthesis of highly substituted δ -lactone (**2**) in a stereoselective manner. Our retrosynthetic plan for **2** is shown in Scheme 1. The key steps include the Baeyer-Villiger reaction, stereoselective methylation, and the Sharpless asymmetric dihydroxylation.

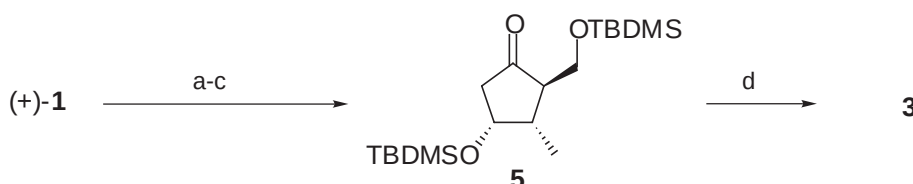


[†]This paper is dedicated to Professor Yuichi Kanaoka on the occasion of his 75th birthday.

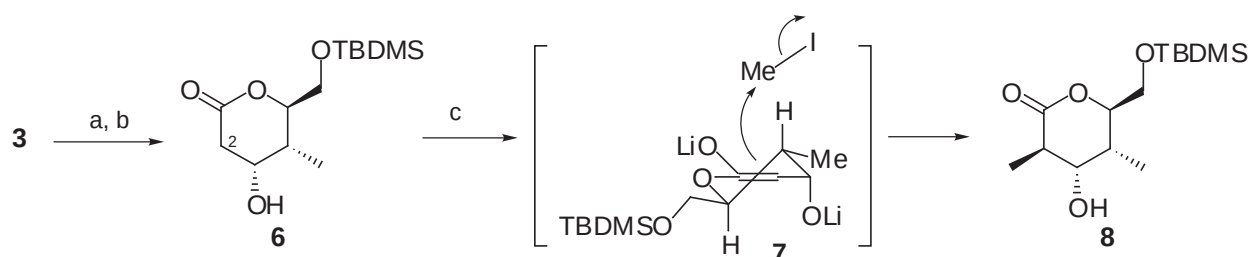


Scheme 1

The starting optically active cyclopentanone [(+)-**1**] was prepared from (*R*)-malic acid according to the procedure of the antipode [(−)-**1**].⁸ The following three-step sequence from (+)-**1** gave the Baeyer-Villiger precursor (**5**) shown in Scheme 2: (i) reduction of **1** with lithium aluminum hydride (LAH), (ii) selective silylation of the primary alcohol with TBDMSCl and triethylamine in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP), and (iii) oxidation by a catalytic amount of tetrapropylammonium perruthenate (TPAP) with *N*-methylmorpholine *N*-oxide (NMO). Because of the steric hindrance around the carbonyl group, the Baeyer-Villiger reaction of the optically active cyclopentanone (**5**) was considerably slow under standard conditions. This difficulty has been overcome by improved solvent-free conditions.¹⁰ Thus, treatment of **5** with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of sodium bicarbonate under solvent-free conditions using a dissolution and evaporation technique every 3 h produced **3** in 96% yield (Scheme 2).



Scheme 2 Reagents and conditions: a) LAH, THF, rt (quant.); b) TBDMSCl, Et₃N, DMAP, CH₂Cl₂, rt (88%); c) TPAP, NMO, MS 4A, CH₂Cl₂, rt (99%); d) *m*-CPBA, NaHCO₃, rt (96%)

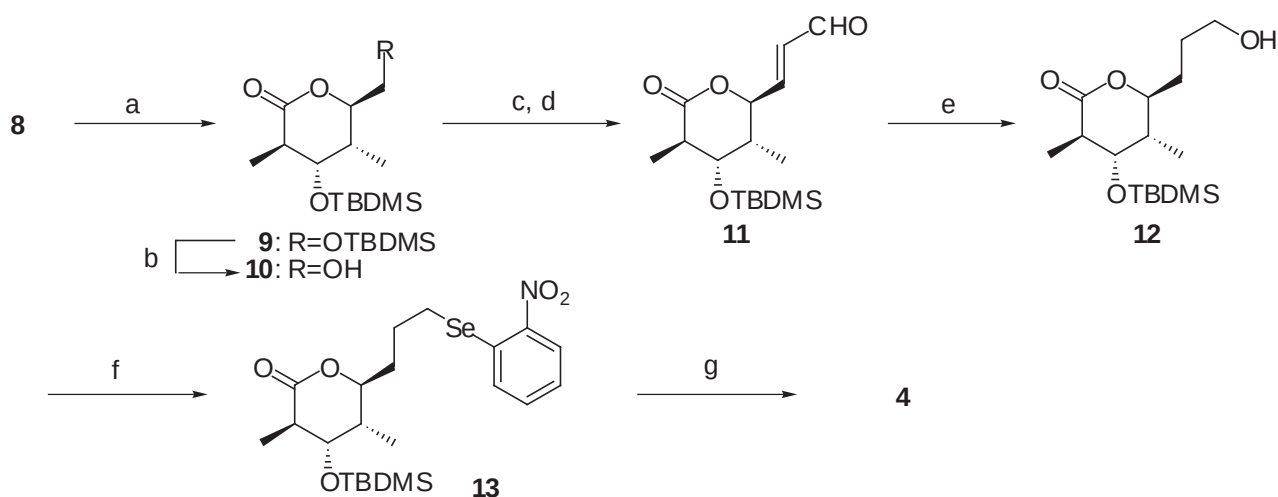


Scheme 3 Reagents and conditions: a) TsOH, MeCN, rt (88%); b) TBDMSCl, imidazole, DMF, rt (95%); c) LDA, THF-HMPA, −78 °C, then MeI, −78 °C (82%)

The stereoselective introduction of a methyl group at the C-2 position of **3** was achieved by methylation of dianion (**7**). Desilylation of both the TBDMS ethers of **3** followed by selective silylation of the primary alcohol gave β-hydroxy lactone (**6**) in 84% yield in 2 steps. Treatment of **6** with 2 equivalents of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) and hexamethylphosphamide (HMPA) (5:1) at −78 °C

afforded dianion (**7**), which was trapped with methyl iodide to furnish **8** as a sole product in 82% yield, while a similar reaction without HMPA gave **8** in only 56% yield along with 24% of unreacted **6**.¹¹ At this stage, all substituents and their stereocenters of **8** on the δ -lactone ring are properly arranged for the C1-C8 portion of **1**. These stereochemistries were confirmed by NOESY experiments; positive NOE effects were observed among 2-Me protons, H-3 proton, and H-4 proton, respectively. This high stereoselectivity was rationalized in terms of the axial attack of methyl iodide to **7** (Scheme 3).

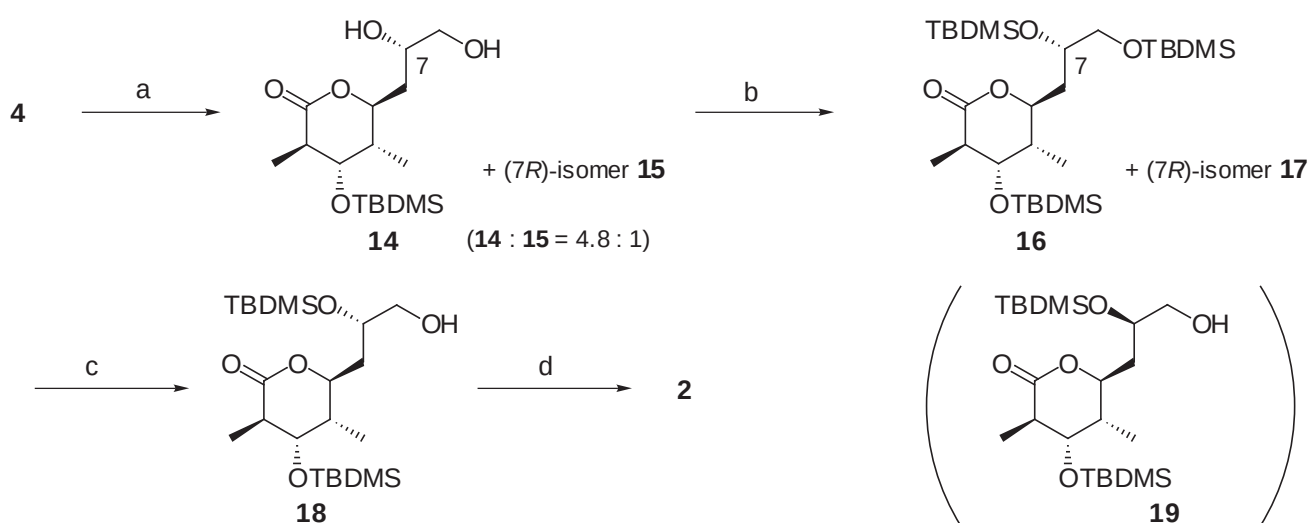
Next, a two-carbon extension and introduction of a chiral hydroxy center were performed by the following chemical transformations. Silylation of the C-3 secondary hydroxyl group of **8** with TBDMSOTf and 2,6-lutidine gave bisTBDMSoxylactone (**9**) in 88% yield. Selective desilylation¹² of the primary TBDMS ether was accomplished by the use of camphorsulfonic acid (CSA) in acetonitrile to give a primary alcohol (**10**). Since an attempt to substitute the hydroxyl group by a vinyl group *via* its tosylate or triflate¹³ failed, we turned our attention to the Wittig reaction for elongation of the side chain. Oxidation of **10** with Dess-Martin periodinane gave the corresponding aldehyde, which was treated with triphenylphosphoranylidene acetaldehyde without purification to give α,β -unsaturated aldehyde (**11**) in 73% yield in 2 steps. Catalytic hydrogenations of **11** followed by sodium borohydride reduction afforded a primary alcohol (**12**) in 90% yield, which was converted to terminal alkene (**4**) in two steps *via* seleno ether (**13**) by the standard procedure¹⁴ (Scheme 4).



Scheme 4 Reagents and conditions: a) TBDMSOTf, 2,6-lutidine, CH_2Cl_2 , -78°C (88%); b) CSA, MeCN, rt (90%); c) Dess-Martin periodinane, CH_2Cl_2 , rt; d) $\text{Ph}_3\text{P}=\text{CHCHO}$, benzene, rt (73% in 2 steps); e) H_2 , Pd-C, EtOAc, rt, then NaBH_4 , MeOH, rt (90%); f) $o\text{-NO}_2\text{C}_6\text{H}_4\text{SeCN}$, $n\text{-Bu}_3\text{P}$, THF, rt (95%); g) 30% H_2O_2 , THF, rt (84%)

The Sharpless asymmetric dihydroxylation¹⁵ of the allylic portion of **4** with AD-mix- α in *tert*-butanol-water (1:1) at 0°C for 2 days afforded diols in 90% yield as a 4.8:1¹⁶ inseparable mixture of desired (7*S*)-diol (**14**) and undesired (7*R*)-diol (**15**). The ratio of **14** and **15** was determined by a ^1H -NMR spectrum (see the experimental section). Oxidation with AD-mix- β gave a 1:1.7 mixture of **14** and **15**. The stereochemistries of **14** and **15** were assumed on the basis of the empirical rule for dihydroxylation of terminal alkene with AD-mix.¹⁷ After conversion of a mixture of the diols to bistriethylsilyl(TES) ether, an

attempt at selective oxidation of primary TES ether to the corresponding aldehyde under Swern oxidation conditions¹⁸ resulted in the formation of a mixture of the aldehyde and ketone. Therefore, the mixture of **14** and **15** was silylated with TBDMSCl to give a mixture of **16** and **17** in 95% yield, and then selective desilylation¹² of the bisTBDMSE ether was examined. Desilylation of the mixture of **16** and **17** with pyridinium *p*-toluenesulfonate (PPTS) in acetonitrile at room temperature for 12 h and successive careful separation gave a primary alcohol (**18**) (30%) and its (7*R*)-isomer (**19**) (6%), a mixture of unreacted **16** and **17** (50%), and recovery of diols (5%).¹⁹ Finally, oxidation of **18** with Dess-Martin periodinane gave aldehyde (**2**) in 72% yield. The aldehyde was identical with the spectroscopic data of an authentic sample reported by Smith's group⁴ (Scheme 5).



Scheme 5 Reagents and conditions: a) AD-mix- α , *tert*-BuOH-H₂O (1:1), 0 °C (90%); b) TBDMSCl, imidazole, DMF, rt (95%); c) PPTS, MeCN, rt (30% for **18**, 6% for **19**, 50% for recovered **16** and **17**, 5% for **14** and **15**); d) Dess-Martin periodinane, CH₂Cl₂, rt (72%)

In conclusion, trisubstituted cyclopentanone (**1**) was converted to a C1-C8 fragment (**2**) of discodermolide by ring expansion by the Baeyer-Villiger reaction, stereoselective methylation at the C-2 position, and introduction of the C-7 chiral center by the Sharpless asymmetric dihydroxylation as key steps.

ACKNOWLEDGEMENT

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EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded using a JASCO FT/IR-410 spectrophotometer. ¹H-NMR spectra were determined with a Varian XL-400 (400 MHz) and JEOL JNM-AL 300 (300 MHz) spectrometers using CDCl₃ as a solvent and tetramethylsilane as an internal standard. ¹³C-NMR spectra were determined with a Varian XL-400 (100 MHz) and JEOL JNM-AL 300 (75 MHz) spectrometers using CDCl₃ as a solvent and an internal standard. Specific rotations were recorded on a JASCO DIP-360 polarimeter. HRMS spectra (Exact FAB-MS) were obtained with a JEOL JMS-SX 102A instrument. Column chromatography was carried out on Silica gel 60 (0.063-0.200 mm) (Merck).

(2R, 3S, 4R)-4-tert-Butyldimethylsilyloxy-2-tert-butyldimethylsilyloxymethyl-3-methylcyclopentanone (5). A solution of (+)-**1** (500 mg, 1.75 mmol) [mp 62.0-63.0 °C (pentane), $[\alpha]_D^{24} +43.1^\circ$ (c 1.00, CHCl₃)]⁸ in THF (10 mL) was added to a suspension of LAH (199 mg, 5.24 mmol) in THF (33 mL) at 0 °C under a nitrogen atmosphere. After the mixture was stirred at rt for 2 h, 5% aqueous NaOH solution was added to it. The resulting mixture was dried (MgSO₄) and concentrated to give 4-tert-butyldimethylsilyloxy-2-hydroxymethyl-3-methylcyclopentanol, which was used without further purification in the next step. A mixture of the crude diol, TBDMSCl (389 mg, 2.59 mmol), Et₃N (209 mg, 2.07 mmol), and DMAP (21 mg, 0.17 mmol) in CH₂Cl₂ (12 mL) was stirred at rt overnight. The mixture was diluted with Et₂O and washed with saturated aqueous NH₄Cl solution, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel (5% in EtOAc in hexane) to give 4-tert-butyldimethylsilyloxy-2-tert-butyldimethylsilyloxymethyl-3-methylcyclopentanol (580 mg, 88% from **1**) as a colorless oil: ¹H-NMR δ: 0.05 (3H, s), 0.07 (3H, s), 0.09 (3H, s), 0.10 (3H, s), 0.88 (9H, s), 0.90 (9H, s), 1.02 (3H, d, *J* = 6.8 Hz), 1.65-1.70 (1H, m), 1.70-1.85 (1H, m), 1.85-1.95 (2H, m), 2.94 (1H, m), 3.52 (1H, dd, *J* = 9.9, 5.6 Hz), 3.78 (1H, dd, *J* = 9.9, 4.4 Hz), 3.99 (1H, br), 4.13 (1H, m). A mixture of the cyclopentanol (570 mg, 1.52 mmol), TPAP (160 mg, 0.46 mmol), MS 4A (100 mg), and NMO (445 mg, 3.80 mmol) in CH₂Cl₂ (20 mL) was stirred at rt for 2 h. The mixture was filtered through short silica gel pad and the filtrate was concentrated. The residue was chromatographed on silica gel (10% EtOAc in hexane) to give **5** (561 mg, 99%) as colorless crystals: mp <30 °C (hexane). $[\alpha]_D^{24} +31.7^\circ$ (c = 1.06, CHCl₃). IR (neat) cm⁻¹: 1750. ¹H-NMR (300 MHz) δ: 0.01 (3H, s), 0.03 (3H, s), 0.04 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 0.86 (9H, s), 1.11 (3H, d, *J* = 6.8 Hz), 1.94-2.02 (1H, m), 2.23-2.27 (2H, m), 2.31-2.42 (1H, m), 3.63 (1H, dd, *J* = 10.1, 3.1 Hz), 4.02 (1H, dd, *J* = 10.1, 3.1 Hz), 4.29-4.34 (1H, m). ¹³C-NMR (75 MHz) δ: -5.6 (2), -5.0, -4.7, 13.8, 18.1, 18.2, 25.7 (3), 25.8 (3), 38.5, 49.8, 54.2, 59.5, 71.5, 218.0. Exact FAB-MS *m/z*: 373.2600, Calcd for C₁₉H₄₁O₃Si₂: 373.2594.

(4R, 5S, 6R)-4-tert-Butyldimethylsilyloxy-6-tert-butyldimethylsilyloxymethyl-5-methyltetrahydropyran-2-one (3). To a solution of **5** (3.0 g, 8.05 mmol) and *m*-CPBA (2.8 g, 16.1 mmol) in CH₂Cl₂ (3 mL) was added NaHCO₃ (676 mg, 8.05 mmol) and then the suspension was concentrated under reduced pressure to give a solid residue. After 3 h, a small amount of CH₂Cl₂ was added to the mixture and the solvent was removed. This process (a dissolution and evaporation) was repeated twice every 3 h. After 10 h, EtOAc was added to the reaction mixture. The mixture was washed with saturated aqueous Na₂S₂O₃ solution, saturated aqueous NaHCO₃ solution, and brine, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel (10% EtOAc in hexane) to give **3** (3.0 g, 96%) as a white solid, mp 84-85 °C (hexane). $[\alpha]_D^{26} -6.6^\circ$ (c = 1.01, CHCl₃). IR (KBr) cm⁻¹: 1727. ¹H-NMR (300 MHz) δ: 0.06 (3H, s), 0.07 (6H, s), 0.08 (3H, s), 0.88 (18H, s), 1.01 (3H, d, *J* = 6.8 Hz), 2.08-2.11 (1H, m), 2.54 (1H, dd, *J* = 17.5, 3.1 Hz), 2.62 (1H, dd, *J* = 17.5, 3.1 Hz), 3.74 (1H, dd, *J* = 11.9, 2.4 Hz), 3.91 (1H, dd, *J* = 11.9, 2.2 Hz), 4.05 (1H, dd, *J* = 5.0, 3.1 Hz), 4.31 (1H, dt, *J* = 10.1, 2.2 Hz). ¹³C-NMR (75 MHz) δ: -5.5, -5.3, -4.9, -4.5, 13.9, 18.0, 18.3, 25.7 (3), 25.8 (3), 33.3, 39.9, 62.8, 68.8, 81.8, 170.1. Exact FAB-MS *m/z*: 389.2536, Calcd for C₁₉H₄₁O₄Si₂: 389.2543. *Anal.* Calcd for C₁₉H₄₀O₄Si₂: C, 58.71; H, 10.37. Found: C, 58.49; H, 10.31.

(4R,5R,6R)-4-Hydroxy-6-hydroxymethyl-5-methyltetrahydropyran-2-one. A mixture of **3** (669 mg, 1.72 mmol) and TsOH·H₂O (646 mg, 3.40 mmol) in MeCN (5 mL) was stirred at rt for 3 h, then powdered NaHCO₃ (314 mg, 3.73 mmol) was added. The mixture was concentrated, and the residue was chromatographed on silica gel (EtOAc) to give (4R,5R,6R)-4-hydroxy-6-hydroxymethyl-5-methyltetrahydropyran-2-one (242 mg, 88%) as colorless crystals: mp 109.5-110 °C (EtOAc-hexane). IR (KBr) cm⁻¹: 3420, 1685. ¹H-NMR (300 MHz) δ: 1.11 (3H, d, *J* = 7.6 Hz), 2.02-2.18 (3H, m), 2.69 (1H, dd, *J* = 18.1, 3.8 Hz), 2.77 (1H, dd, *J* = 18.1, 2.7 Hz), 3.70 (1H, ddd, *J* = 12.3, 7.9, 4.0 Hz), 3.96 (1H, ddd, *J* = 12.3, 6.0, 3.0 Hz), 4.10-4.16 (1H, br), 4.47 (1H, dt, *J* = 10.5, 3.0 Hz). ¹³C-NMR δ: 13.4, 32.7, 39.4, 62.6, 68.0, 81.2, 169.8. Exact FAB-MS *m/z*: 161.0818, Calcd for C₇H₁₃O₄: 161.0814. *Anal.* Calcd for C₇H₁₂O₄: C, 52.49; H, 7.55. Found: C, 52.44; H, 7.63.

(4R,5R,6R)-6-tert-Butyldimethylsilyloxy-4-hydroxy-5-methyltetrahydropyran-2-one (6). A mixture of (4R,5R,6R)-4-hydroxy-6-hydroxymethyl-5-methyltetrahydropyran-2-one (460 mg, 2.87 mmol), TBDMSCl (433 mg, 2.87 mmol), and imidazole (293 mg, 4.31 mmol) in DMF (30 mL) was stirred at rt overnight. The mixture was poured into H₂O and the mixture was extracted with Et₂O. The combined extracts were washed with brine, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel (50% EtOAc in hexane) to give **6** (750 mg, 95%) as colorless crystals: mp 74.5-75.5 °C (hexane). [α]_D²⁵ +6.6 ° (*c* = 1.45, CHCl₃). IR (KBr) cm⁻¹: 3444, 1717. ¹H-NMR (300 MHz) δ: 0.06 (3H, s), 0.07 (3H, s), 0.88 (9H, s), 1.09 (3H, d, *J* = 6.6 Hz), 2.11-2.25 (1H, m), 2.60 (1H, dd, *J* = 17.8, 3.7 Hz), 2.62 (1H, br s), 2.71 (1H, dd, *J* = 17.6, 3.0 Hz), 3.75 (1H, dd, *J* = 11.7, 2.6 Hz), 3.92 (1H, dd, *J* = 11.7, 2.2 Hz), 4.10 (1H, br s), 4.36 (1H, dt, *J* = 10.3, 2.4 Hz). ¹³C-NMR (75 MHz) δ: -5.5, -5.3, 13.4, 18.3, 25.8 (3), 32.6, 39.4, 62.8, 67.9, 81.5, 170.3. Exact FAB-MS *m/z*: 275.1674, Calcd for C₁₃H₂₇O₄Si: 275.1678. *Anal.* Calcd for C₁₃H₂₆O₄Si: C, 56.90; H, 9.55. Found: C, 56.62; H, 9.49.

(3R,4S,5R,6R)-6-tert-Butyldimethylsilyloxymethyl-4-hydroxy-3,5-dimethyltetrahydropyran-2-one (8). A solution of **6** (350 mg, 1.28 mmol) in THF-HMPA (5:1, 4 mL) was added to a solution of LDA in THF-HMPA (5:1, 20 mL), prepared from diisopropylamine (671 mg, 6.63 mmol) and butyllithium (1.6 M in hexane, 4.11 mL, 6.38 mmol), at -78 °C under a nitrogen atmosphere and the mixture was stirred for 1 h. Then MeI (1.81 g, 12.75 mmol) was added to the solution of the dianion at the same temperature. The whole mixture was stirred for 1 h, and then saturated aqueous NH₄Cl solution was added at the same temperature. After the mixture was warmed to rt, it was diluted with Et₂O and washed with H₂O and brine, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel (30% EtOAc in hexane) to give **8** (303 mg, 82%) as colorless crystals: mp 93.5-94.5 °C (EtOAc-hexane). [α]_D²⁵ +5.5 ° (*c* = 0.75, CHCl₃). IR (KBr) cm⁻¹: 3853, 1697. ¹H-NMR (300 MHz) δ: 0.07 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 1.09 (3H, d, *J* = 7.0 Hz), 1.31 (3H, d, *J* = 7.3 Hz), 1.73 (1H, br), 2.37 (1H, dqd, *J* = 9.9, 7.0, 3.0 Hz), 2.69 (1H, qd, *J* = 7.3, 3.0 Hz), 3.75 (1H, dd, *J* = 11.7, 2.5 Hz), 3.81 (1H, t, *J* = 3.0 Hz), 3.91 (1H, dd, *J* = 11.7, 2.5 Hz), 4.30 (1H, dt, *J* = 9.9, 2.5 Hz). ¹³C-NMR (75 MHz) δ: -5.9, -5.3, 12.8, 15.8, 18.3, 25.8 (3), 29.4, 43.4, 62.8, 73.5, 81.2, 173.8. Exact FAB-MS

m/z : 289.1841, Calcd for $C_{14}H_{29}O_4Si$: 289.1835. *Anal.* Calcd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78. Found: C, 58.37; H, 9.92.

(3R, 4S, 5S, 6R)-4-tert-Butyldimethylsilyloxy-6-tert-butyldimethylsilyloxymethyl-3,5-dimethyltetrahydropyran-2-one (9). A mixture of **8** (100 mg, 0.35 mmol), 2,6-lutidine (89 mg, 0.83 mmol), and TBDMSOTf (183 mg, 0.69 mmol) in CH_2Cl_2 (5 mL) was stirred at $-78\text{ }^{\circ}C$ for 1 h. Then H_2O was added to the mixture at the same temperature and allowed to warm to rt. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (20% EtOAc in hexane) to give **9** (123 mg, 88%) as colorless crystals: mp $70.5\text{--}71\text{ }^{\circ}C$ (hexane). $[\alpha]_D^{25} +8.8\text{ }^{\circ}$ ($c = 1.10$, $CHCl_3$). IR (KBr) cm^{-1} : 1722. 1H -NMR (300 MHz) δ : 0.02 (3H, s), 0.04 (3H, s), 0.07 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 0.89 (9H, s), 1.01 (3H, d, $J = 6.9$ Hz), 1.26 (3H, d, $J = 7.5$ Hz), 2.35 (1H, dqd, $J = 9.7, 6.6, 2.8$ Hz), 2.64 (1H, qd, $J = 7.5, 2.8$ Hz), 3.72 (1H, t, $J = 2.8$ Hz), 3.73 (1H, dd, $J = 11.7, 2.2$ Hz), 3.90 (1H, dd, $J = 11.7, 2.2$ Hz), 4.27 (1H, dt, $J = 9.7, 2.2$ Hz). ^{13}C -NMR (75 MHz) δ : $-5.6, -5.3, -4.9, -4.5, 13.6, 16.0, 17.9, 18.2, 25.7$ (3), 25.8 (3), $28.9, 43.9, 62.7, 74.4, 81.7, 174.0$. Exact FAB-MS m/z : 403.2694, Calcd for $C_{20}H_{43}O_4Si_2$: 403.2700. *Anal.* Calcd for $C_{20}H_{42}O_4Si_2$: C, 59.65; H, 10.51. Found: C, 59.31; H, 10.48.

(3R, 4S, 5S, 6R)-4-tert-Butyldimethylsilyloxy-6-hydroxymethyl-3,5-dimethyltetrahydropyran-2-one (10). A mixture of **9** (243 mg, 0.60 mmol) and CSA (140 mg, 0.60 mmol) in MeCN (8 mL) was stirred at rt overnight, then powdered $NaHCO_3$ (50 mg, 0.60 mmol) was added. The mixture was concentrated, the residue was chromatographed on silica gel (50% EtOAc in hexane) to give **10** (157 mg, 90%) as colorless crystals: mp $87.5\text{--}88.5\text{ }^{\circ}C$ (hexane). $[\alpha]_D^{25} +2.0\text{ }^{\circ}$ ($c = 0.85$, $CHCl_3$). IR (KBr) cm^{-1} : 3175, 1725. 1H -NMR (300 MHz) δ : 0.08 (3H, s), 0.09 (3H, s), 0.89 (9H, s), 1.02 (3H, d, $J = 6.6$ Hz), 1.29 (3H, d, $J = 7.7$ Hz), 1.98-2.16 (1H, br), 2.22 (1H, dqd, $J = 10.5, 6.6, 2.6$ Hz), 2.68 (1H, qd, $J = 7.7, 2.6$ Hz), 3.68 (1H, dd, $J = 12.8, 4.0$ Hz), 3.70 (1H, t, $J = 2.6$ Hz), 3.92 (1H, dd, $J = 12.8, 2.6$ Hz), 4.39 (1H, ddd, $J = 10.5, 4.0, 2.6$ Hz). ^{13}C -NMR (75 MHz) δ : $-4.8, -4.5, 13.7, 16.3, 17.9, 25.7$ (3), $29.3, 44.2, 62.6, 74.5, 81.7, 174.1$. Exact FAB-MS m/z : 289.1829, Calcd for $C_{14}H_{29}O_4Si$: 289.1835. *Anal.* Calcd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78. Found: C, 58.06; H, 10.06.

3-[(2S, 3S, 4S, 5R)-4-tert-Butyldimethylsilyloxy-3,5-dimethyl-6-oxotetrahydropyran-2-yl]-(E)-propenal (11). A mixture of **10** (380 mg, 1.32 mmol) and Dess-Martin periodinane (559 mg, 2.64 mmol) in CH_2Cl_2 (13 mL) was stirred at rt overnight. The mixture was diluted with EtOAc (25 mL), washed with 10% aqueous $NaHSO_3$ solution, saturated aqueous $NaHCO_3$ solution, H_2O , and brine, dried ($MgSO_4$) and concentrated to give crude 4-tert-butyldimethylsilyloxy-3,5-dimethyl-6-oxotetrahydropyran-2-carbaldehyde (500 mg), which was used without further purification in the next step. A mixture of the crude aldehyde (500 mg) and $Ph_3P=CHCHO$ (401 mg, 1.32 mmol) in benzene (13 mL) was stirred at rt. After 3 h, the mixture was concentrated and the residue was chromatographed on silica gel (20% EtOAc in hexane) to give **11** (301 mg, 73% from **10**) as a pale yellow oil: IR (neat) cm^{-1} : 1741, 1697. 1H -NMR

(300 MHz) δ : 0.09 (3H, s), 0.10 (3H, s), 0.90 (9H, s), 1.07 (3H, d, J = 6.6 Hz), 1.30 (3H, d, J = 7.7 Hz), 2.03 (1H, dqd, J = 10.0, 6.6, 2.5 Hz), 2.73 (1H, qd, J = 7.7, 2.5 Hz), 3.73 (1H, t, J = 2.5 Hz), 5.04 (1H, br dd, J = 10.0, 5.5 Hz), 6.40 (1H, ddd, J = 15.8, 7.5, 1.1 Hz), 6.78 (1H, dd, J = 15.8, 5.5 Hz), 9.62 (1H, d, J = 7.5 Hz). ^{13}C -NMR (75 MHz) δ : -4.8, -4.5, 13.5, 16.3, 18.0, 25.7 (3), 34.3, 44.0, 74.0, 79.1, 133.0, 151.2, 172.5, 192.5. Exact FAB-MS m/z : 335.1650, Calcd for $\text{C}_{16}\text{H}_{28}\text{O}_4\text{NaSi}$: 335.1654.

(3R, 4S, 5S, 6S)-4-tert-Butyldimethylsilyloxy-6-(3-hydroxypropyl)-3,5-dimethyltetrahydropyran-2-one (12). A mixture of **11** (62 mg, 0.20 mmol) and 10% Pd-C (10 mg) in EtOAc (2 mL) was stirred under H_2 (1 atm) at rt for 1 h. The mixture was diluted with EtOAc (20 mL), and the catalyst was filtered off. The filtrate was concentrated to give crude 3-(4-tert-butyldimethylsilyloxy-3,5-dimethyl-6-oxotetrahydropyran-2-yl)propanal (66 mg), which was used without further purification in the next step. A mixture of the crude aldehyde (66 mg) and NaBH_4 (7.5 mg, 0.20 mmol) in MeOH (2 mL) was stirred at rt. After 2 h, the mixture was diluted with Et_2O , washed with H_2O and brine, dried (MgSO_4), and concentrated. The residue was chromatographed on silica gel (20% EtOAc in hexane) to give **12** (57 mg, 90% from **11**) as a colorless oil: $[\alpha]_{\text{D}}^{24}$ -15.8 $^\circ$ (c = 0.85, CHCl_3). IR (neat) cm^{-1} : 3438, 1730. ^1H -NMR (300 MHz) δ : 0.07 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 1.00 (3H, d, J = 7.0 Hz), 1.27 (3H, d, J = 7.7 Hz), 1.55-1.98 (6H, m), 2.65 (1H, qd, J = 7.3, 2.9 Hz), 3.64-3.74 (3H, m), 4.33-4.41 (1H, m). ^{13}C -NMR (75 MHz) δ : -4.8, -4.5, 13.9, 16.3, 18.0, 25.7 (3), 27.8, 29.6, 33.7, 43.9, 62.6, 74.4, 80.6, 174.2. Exact FAB-MS m/z : 317.2140, Calcd for $\text{C}_{16}\text{H}_{33}\text{O}_4\text{Si}$: 317.2148.

(3R, 4S, 5S, 6S)-4-tert-Butyldimethylsilyloxy-3,5-dimethyl-6-[3-(2-nitrophenylseleno)propyl]tetrahydropyran-2-one (13). A mixture of **12** (120 mg, 0.38 mmol), *o*-nitrophenylcyano selenide (138 mg, 0.61 mmol), and tributylphosphine (123 mg, 0.61 mmol) in THF (4 mL) was stirred at rt. After 3 h, the mixture was concentrated, the residue was chromatographed on silica gel (50% EtOAc in hexane) to give **13** (180 mg, 95%) as a pale yellow oil: IR (neat) cm^{-1} : 1734, 1514. ^1H -NMR (300 MHz) δ : 0.07 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 0.99 (3H, d, J = 7.0 Hz), 1.26 (3H, d, J = 7.7 Hz), 1.65-2.16 (5H, m), 2.65 (1H, qd, J = 7.7, 2.5 Hz), 2.90-3.05 (2H, m), 3.66 (1H, t, J = 2.5 Hz), 4.38 (1H, ddd, J = 10.8, 8.2, 2.5 Hz), 7.28-7.37 (1H, m), 7.53-7.58 (2H, m), 8.29 (1H, d, J = 8.4 Hz). ^{13}C -NMR (75 MHz) δ : -4.8, -4.5, 14.0, 16.4, 17.9, 23.6, 25.7 (3), 25.8, 33.4, 33.7, 44.0, 74.5, 80.0, 125.4 (2), 126.5, 129.0, 133.3, 133.7, 174.0. Exact FAB-MS m/z : 502.1518, Calcd for $\text{C}_{22}\text{H}_{36}\text{O}_5\text{NSeSi}$: 502.1528.

(3R, 4S, 5S, 6S)-6-Allyl-4-tert-butyldimethylsilyloxy-3,5-dimethyltetrahydropyran-2-one (4). A 30% aqueous solution of hydrogen peroxide (0.5 mL, 4.4 mmol) was added to a solution of **13** (180 mg, 0.36 mmol) in THF (4 mL) at rt and the mixture was stirred for 3 h. Then the mixture was diluted with Et_2O and washed with 5% aqueous Na_2CO_3 solution and brine, dried (MgSO_4), and concentrated. The residue was chromatographed on silica gel (20% EtOAc in hexane) to give **4** (90 mg, 84%) as colorless crystals: mp 63-64.5 $^\circ\text{C}$ (hexane). $[\alpha]_{\text{D}}^{23}$ +14.5 $^\circ$ (c = 0.95, CHCl_3). [*lit.*,⁴ $[\alpha]_{\text{D}}^{23}$

+14.2 °($c = 0.12$, CHCl_3)]. IR (KBr) cm^{-1} : 2925, 1720, 1463, 1086, 832. ^1H -NMR (300 MHz) δ : 0.06 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 0.98 (3H, d, $J = 6.9$ Hz), 1.25 (3H, d, $J = 7.6$ Hz), 1.95 (1H, dqd, $J = 9.9, 6.9, 2.3$ Hz), 2.23-2.36 (1H, m), 2.51-2.63 (1H, m), 2.64 (1H, qd, $J = 7.6, 3.0$ Hz), 3.65 (1H, t, $J = 2.5$ Hz), 4.41 (1H, ddd, $J = 9.9, 5.6, 4.3$ Hz), 5.16-5.21 (2H, m), 5.88 (1H, dddd, $J = 17.5, 9.8, 7.9, 6.3$ Hz). ^{13}C -NMR (75 MHz) δ : -4.8, -4.5, 13.6, 16.3, 17.9, 25.7 (3), 32.4, 37.0, 43.9, 74.5, 80.1, 118.6, 132.6, 174.1. Exact FAB-MS m/z : 299.2035, Calcd for $\text{C}_{16}\text{H}_{31}\text{O}_3\text{Si}$: 299.2042. Anal. Calcd for $\text{C}_{16}\text{H}_{30}\text{O}_3\text{Si}$: C, 64.38; H, 10.13. Found: C, 64.27; H, 9.98.

(3R, 4S, 5S, 6S)-4-tert-Butyldimethylsilyloxy-6-[(2S)-2,3-dihydroxypropyl]-3,5-dimethyltetrahydropyran-2-one (14) and **(3R, 4S, 5S, 6S)-4-tert-Butyldimethylsilyloxy-6-[(2R)-2,3-dihydroxypropyl]-3,5-dimethyltetrahydropyran-2-one (15)**. A mixture of **4** (90 mg, 0.3 mmol) and AD-mix- α (422 mg) in $t\text{-BuOH-H}_2\text{O}$ (1:1, 1.5 mL) was stirred at rt. After 15 min, the mixture was cooled to 0 °C and stirred at the same temperature for 2 days. Then Na_2SO_3 (1.2 g) was added to the reaction mixture. The whole mixture was allowed to warm to rt and stirred for further 20 min. The mixture was diluted with EtOAc, washed with H_2O and brine, and concentrated, the residue was chromatographed on silica gel (50% EtOAc in hexane) to give a 4.8:1 mixture of **14** and **15** (90 mg, 90%) as a colorless oil: IR (neat) cm^{-1} : 3410, 1714. ^1H -NMR (400 MHz) for the major isomer δ : 0.07 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 1.01 (3H, d, $J = 6.8$ Hz), 1.27 (3H, d, $J = 7.7$ Hz), 1.58 (1H, ddd, $J = 14.5, 10.5, 2.8$ Hz), 1.79-1.96 (2H, m), 2.62-2.70 (1H, br), 2.66 (1H, qd, $J = 7.6, 3.2$ Hz), 3.00 (1H, br s), 3.45-3.56 (1H, m), 3.65-3.72 (2H, m), 4.08-4.15 (1H, m), 4.60 (1H, td, $J = 10.2, 2.0$ Hz). Selected signals for the minor isomer δ : 1.28 (3H, d, $J = 7.5$ Hz), 4.01-4.08 (1H, m), 4.50 (1H, td, $J = 9.4, 3.1$ Hz). The ratio of stereoisomers (**14** and **15**) was estimated from the integrated intensity of peak heights of the signals due to the 6-protons at δ 4.60 (td) and 4.50 (td), respectively. ^{13}C -NMR (100 MHz) for the major isomer δ : -4.7, -4.5, 13.9, 16.2, 18.0, 25.7 (3), 34.6, 37.0, 43.8, 66.9, 67.9, 74.2, 78.0, 174.2. Exact FAB-MS m/z : 333.2094, Calcd for $\text{C}_{16}\text{H}_{33}\text{O}_5\text{Si}$: 333.2097.

(3R, 4S, 5S, 6S)-6-[(2S)-2,3-Bis-tert-butyldimethylsilyloxypropyl]-4-tert-butyldimethylsilyloxy-3,5-dimethyltetrahydropyran-2-one (16) and **(3R, 4S, 5S, 6S)-6-[(2R)-2,3-Bis-tert-butyldimethylsilyloxypropyl]-4-tert-butyldimethylsilyloxy-3,5-dimethyltetrahydropyran-2-one (17)**. A mixture of **14** and **15** (90 mg, 0.27 mmol), TBDMSCl (122 mg, 0.81 mmol), and imidazole (66 mg, 0.97 mmol) in DMF (2.5 mL) was stirred at rt overnight. The mixture was poured into H_2O and the mixture was extracted with Et_2O . The extract was washed with brine, dried (MgSO_4), and concentrated. The residue was chromatographed on silica gel (5% EtOAc in hexane) to give a mixture of **16** and **17** (144 mg, 95%) as a colorless oil: IR (neat) cm^{-1} : 1737. ^1H -NMR (400 MHz) for the major isomer δ : 0.039 (3H, s), 0.042 (3H, s), 0.06 (3H, s), 0.07 (3H, s), 0.08 (3H, s), 0.09 (3H, s), 0.86 (9H, s), 0.88 (18H, s), 0.98 (3H, d, $J = 6.8$ Hz), 1.26 (3H, d, $J = 7.7$ Hz), 1.59-1.75 (2H, m), 1.80-1.91 (1H, m), 2.63 (1H, qd, $J = 7.7, 2.9$ Hz), 3.39 (1H, dd, $J = 10.0, 6.3$ Hz), 3.57 (1H, dd, $J = 10.0, 4.9$ Hz), 3.66 (1H, t, $J = 2.7$ Hz), 4.02-4.09 (1H, m), 4.51 (1H, td, $J = 10.4, 2.0$ Hz). ^{13}C -NMR (100 MHz) for the major isomer δ : -5.4, -5.3, -4.85, -4.83, -4.6, -4.2, 14.0, 16.4, 17.9, 18.0, 18.4, 25.7

(3), 25.9 (3), 26.0 (3), 34.6, 38.8, 43.9, 67.9, 68.4, 74.6, 77.1, 173.8. Exact FAB-MS m/z : 561.3822, Calcd for $C_{28}H_{61}O_5Si_3$: 561.3827.

(3R, 4S, 5S, 6S)-4-tert-Butyldimethylsilyloxy-6-[(2S)-2-tert-butyldimethylsilyloxy-3-hydroxypropyl]-3,5-dimethyltetrahydropyran-2-one (18) and **(3R, 4S, 5S, 6S)-4-tert-Butyldimethylsilyloxy-6-[(2R)-2-tert-butyldimethylsilyloxy-3-hydroxypropyl]-3,5-dimethyltetrahydropyran-2-one (19)**. A mixture of **16** and **17** (140 mg, 0.25 mmol) and PPTS (63 mg, 0.25 mmol) in MeCN (3 mL) was stirred at rt overnight. Then the mixture was diluted with Et_2O , washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (5% EtOAc in hexane). The first fraction gave a mixture of **16** and **17** (70 mg, 50%). The second fraction gave **19** (7 mg, 6%) as a colorless oil: IR (neat) cm^{-1} : 3434, 1725. 1H -NMR (400 MHz) δ : 0.06 (3H, s), 0.08 (3H, s), 0.09 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 0.90 (9H, s), 1.00 (3H, d, $J = 6.8$ Hz), 1.27 (3H, d, $J = 7.7$ Hz), 1.59 (1H, br s), 1.71 (1H, ddd, $J = 14.5, 10.3, 3.7$ Hz), 1.88 (1H, dqd, $J = 9.9, 6.8, 2.4$ Hz), 2.00 (1H, ddd, $J = 14.5, 8.7, 2.1$ Hz), 2.65 (1H, qd, $J = 7.7, 3.1$ Hz), 3.58 (1H, dd, $J = 11.8, 4.1$ Hz), 3.63-3.69 (1H, m), 3.66 (1H, t, $J = 2.7$ Hz), 4.12 (1H, dq, $J = 8.6, 3.8$ Hz), 4.42 (1H, td, $J = 10.2, 2.0$ Hz). ^{13}C -NMR (100 MHz) δ : -4.8, -4.7, -4.6, -4.5, 14.0, 16.3, 18.0, 21.4, 25.7 (3), 25.8 (3), 34.5, 37.5, 43.9, 64.8, 69.1, 74.3, 77.8, 173.7. The third fraction gave **18** (33 mg, 30%) as a colorless oil: IR (neat) cm^{-1} : 3451, 1732. 1H -NMR (400 MHz) δ : 0.07 (3H, s), 0.08 (3H, s), 0.115 (3H, s), 0.118 (3H, s), 0.89 (9H, s), 0.90 (9H, s), 1.00 (3H, d, $J = 6.8$ Hz), 1.27 (3H, d, $J = 7.7$ Hz), 1.54 (1H, ddd, $J = 14.3, 11.2, 2.2$ Hz), 1.80-1.85 (1H, br), 1.86 (1H, dqd, $J = 10.3, 6.8, 2.2$ Hz), 1.98 (1H, ddd, $J = 14.3, 10.3, 1.6$ Hz), 2.65 (1H, qd, $J = 7.7, 2.7$ Hz), 3.42-3.49 (1H, m), 3.63-3.69 (1H, m), 3.66 (1H, t, $J = 2.5$ Hz), 4.14-4.20 (1H, m), 4.46 (1H, td, $J = 10.7, 1.6$ Hz). ^{13}C -NMR (100 MHz) δ : -4.9, -4.8, -4.54, -4.51, 14.1, 16.5, 17.9 (2), 25.7 (3), 25.8 (3), 34.4, 38.3, 44.1, 67.0, 68.0, 74.7, 77.4, 173.7. Exact FAB-MS m/z : 447.2957, Calcd for $C_{22}H_{47}O_5Si_2$: 447.2962. The fourth fraction gave a mixture of **14** and **15** (4 mg, 5%)

(2S)-2-tert-Butyldimethylsilyloxy-3-[(2S, 3S, 4S, 5R)-4-tert-butyldimethylsilyloxy-3,5-dimethyl-6-oxotetrahydropyran-2-yl]propanal (2). A mixture of **18** (14 mg, 0.03 mmol) and Dess-Martin periodinane (27 mg, 0.06 mmol) in CH_2Cl_2 (0.3 mL) was stirred at rt overnight. The mixture was diluted with Et_2O (25 mL), washed with 10% aqueous $NaHSO_3$ solution, saturated aqueous $NaHCO_3$ solution, H_2O , and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (5% EtOAc in hexane) to give a mixture of **2** (10 mg, 72%) as a white solid: mp 57-59.5 $^{\circ}C$ (hexane). [*lit.*,⁴ mp 58-60 $^{\circ}C$ (hexane)]. $[\alpha]_D^{26} -57.1^{\circ}$ ($c = 0.48$, $CHCl_3$). [*lit.*,⁴ $[\alpha]_D^{23} -55.5^{\circ}$ ($c = 1.46$, $CHCl_3$)]. IR (neat) cm^{-1} : 1738. 1H -NMR (400 MHz) δ : 0.07 (3H, s), 0.09 (3H, s), 0.11 (3H, s), 0.13 (3H, s), 0.89 (9H, s), 0.92 (9H, s), 0.99 (3H, d, $J = 6.6$ Hz), 1.28 (3H, d, $J = 7.7$ Hz), 1.78 (1H, ddd, $J = 14.1, 10.5, 2.3$ Hz), 1.87 (1H, ddd, $J = 14.1, 10.5, 2.6$ Hz), 1.92 (1H, dqd, $J = 10.5, 6.6, 2.5$ Hz), 2.66 (1H, qd, $J = 7.7, 2.5$ Hz), 3.67 (1H, t, $J = 2.5$ Hz), 4.46 (1H, ddd, $J = 10.1, 2.6, 0.7$ Hz), 4.53 (1H, td, $J = 10.6, 2.3$ Hz), 9.67 (1H, d, $J = 0.7$ Hz). ^{13}C -NMR (100 MHz) δ : -5.2, -4.9, -4.6, -4.5, 14.0, 16.5, 17.9, 18.1, 25.67 (3), 25.73 (3), 34.1, 36.1, 44.2, 73.6, 74.6, 76.0, 173.2, 203.4. Exact FAB-MS m/z :

445.2802, Calcd for C₂₂H₄₅O₅Si₂: 445.2806. These data were identical to those reported for an authentic sample.⁴

REFERENCES

1. G. E. Keck, C. E. Knutson, and S. A. Wiles, *Org. Lett.*, 2001, **3**, 707; G. E. Keck, X.-Y. Li, and C. E. Knutson, *Org. Lett.*, 1999, **1**, 411; J. Tholander and E. M. Carreira, *Helv. Chim. Acta*, 2001, **84**, 613; S. Sano, T. Miwa, K. Hayashi, K. Nozaki, Y. Ozaki, and Y. Nagao, *Tetrahedron Lett.*, 2001, **42**, 4029; T. K. Chakraborty and S. Tapadar, *Tetrahedron Lett.*, 2001, **42**, 1375 and references cited therein.
2. S. P. Gunasekera, M. Gunasekera, R. E. Longley, and G. K. Schulte, *J. Org. Chem.*, 1990, **55**, 4912.
3. For total syntheses, see: J. B. Nerenberg, D. T. Hung, P. K. Somers, and S. L. Schreiber, *J. Am. Chem. Soc.*, 1993, **115**, 12621; A. B. Smith, III, Y. Qiu, D. R. Jones, and K. Kobayashi, *J. Am. Chem. Soc.*, 1995, **117**, 12011; D. T. Hung, J. B. Nerenberg, and S. L. Schreiber, *J. Am. Chem. Soc.*, 1996, **118**, 11054; S. S. Harried, G. Yang, M. A. Strawn, and D. C. Myles, *J. Org. Chem.*, 1997, **62**, 6098; J. A. Marshall and B. A. Johns, *J. Org. Chem.*, 1998, **63**, 7885; I. Paterson, G. J. Florence, K. Gerlach, and J. P. Scott, *Angew. Chem., Int. Ed.*, 2000, **39**, 377; I. Paterson and G. J. Florence, *Tetrahedron Lett.*, 2000, **41**, 6935; I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, and N. Sereinig, *J. Am. Chem. Soc.*, 2001, **123**, 9535.
4. For other total syntheses, see: A. B. Smith, III, M. D. Kaufman, T. J. Beauchamp, M. J. LaMarche, and H. Arimoto, *Org. Lett.*, 1999, **1**, 1823; A. B. Smith, III, T. J. Beauchamp, M. J. LaMarche, M. D. Kaufman, Y. Qiu, H. Arimoto, D. R. Jones, and K. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 8654.
5. For partial syntheses, see: D. L. Clark and C. H. Heathcock, *J. Org. Chem.*, 1993, **58**, 5878; J. M. C. Golec and S. D. Jones, *Tetrahedron Lett.*, 1993, **34**, 8159; P. L. Evans, J. M. C. Golec, and R. J. Gillespie, *Tetrahedron Lett.*, 1993, **34**, 8163; J. M. C. Golec and R. J. Gillespie, *Tetrahedron Lett.*, 1993, **34**, 8167; I. Paterson and S. P. Wren, *J. Chem. Soc., Chem. Commun.*, 1993, 1790; G. Yang and D. C. Myles, *Tetrahedron Lett.*, 1994, **35**, 1313; G. Yang and D. C. Myles, *Tetrahedron Lett.*, 1994, **35**, 2503; I. Paterson and A. Schlapbach, *Synlett*, 1995, 498; M. Miyazawa, S. Oonuma, K. Maruyama, and M. Miyashita, *Chem. Lett.*, 1997, 1193; J. A. Marshall, Z.-H. Lu, and B. A. Johns, *J. Org. Chem.*, 1998, **63**, 817; A. M. Misske and H. M. R. Hoffmann, *Tetrahedron*, 1999, **55**, 4315; D. A. Evans, D. P. Halstead, and B. D. Allison, *Tetrahedron Lett.*, 1999, **40**, 4461; S. A. Filla, J. J. Song, L. Chen, and S. Masamune, *Tetrahedron Lett.*, 1999, **40**, 5449; J. S. Yadav, S. Abraham, M. M. Reddy, G. Sabitha, A. R. Sankar, and A. C. Kunwar, *Tetrahedron Lett.*, 2001, **42**, 4713; O. Arjona, R. Menchaca, and J. Plumet, *Tetrahedron*, 2001, **57**, 6751; A. Arefolov, N. F. Langille, and J. S. Panek, *Org. Lett.*, 2001, **3**, 3281; S. BouzBouz and J. Cossy, *Org. Lett.*, 2001, **3**, 3995; T. K. Chakraborty and P. Laxman, *J. Indian Chem. Soc.*, 2001, **78**, 543; D. P. Curran and T. Furukawa, *Org. Lett.*, 2002, **4**, 2233; A. Arefolov and J. S. Panek, *Org. Lett.*, 2002, **4**, 2397; I. Paterson and T. Temal-Laieb, *Org. Lett.*, 2002, **4**, 2473; B. W. Day,

- C. O. Kangani, and K. S. Avor, *Tetrahedron: Asymmetry*, 2002, **13**, 1161.
6. For another partial synthesis, see: M. Miyazawa, S. Oonuma, K. Maruyama, and M. Miyashita, *Chem. Lett.*, 1997, 1191.
 7. T. Yakura, S. Yamada, Y. Kunimune, A. Ueki, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3643; T. Yakura, A. Ueki, T. Kitamura, K. Tanaka, M. Nameki, and M. Ikeda, *Tetrahedron*, 1999, **55**, 7470; T. Yakura, *Yakugaku Zasshi*, 2000, **120**, 1309 and references cited therein.
 8. T. Yakura, K. Tanaka, T. Kitano, J. Uenishi, and M. Ikeda, *Tetrahedron*, 2000, **56**, 7715.
 9. The numbering systems of discodermolide and pyrans are different. To avoid confusion in this discussion, we use the numbering system for discodermolide.
 10. T. Yakura, T. Kitano, M. Ikeda, and J. Uenishi, *Tetrahedron Lett.*, accepted.
 11. Miyashita and co-workers reported similar stereoselective methylation of δ -lactone using LDA-MeI in THF without HMPA.⁶
 12. T. D. Nelson and R. D. Crouch, *Synthesis*, 1996, 1031.
 13. H. Kotsuki, I. Kadota, and M. Ochi, *Tetrahedron Lett.*, 1989, **30**, 1281; H. Kotsuki, I. Kadota, and M. Ochi, *Tetrahedron Lett.*, 1990, **31**, 4609; H. Kotsuki, *J. Synth. Org. Chem., Jpn.*, 1999, **57**, 334.
 14. P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, 1976, **41**, 1485; T. Kametani, H. Matsumoto, H. Nemoto, and K. Fukumoto, *J. Am. Chem. Soc.*, 1978, **100**, 6218.
 15. K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, and X.-L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768; H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
 16. Smith and co-workers reported that attempts of dihydroxylation of **4** led, at best, a 3:1 mixture of diols.⁴
 17. Eventually, the stereochemistry of the isomer (**14**) was confirmed after the conversion to the known aldehyde (**2**).
 18. A. Rodríguez, M. Nomen, B. W. Spur, and J. J. Godfroid, *Tetrahedron Lett.*, 1999, **40**, 5161.
 19. A longer reaction time and use of CSA or TsOH instead of PPTS led to increase the yield of diols (**14** and **15**).