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STEREOSELECTIVE SYNTHESIS OF THE 3-HYDROXY-TETRAHYDROPYRAN PART OF MUCOCIN, AN ANTITUMOR AGENT, BASED ON REARRANGEMENT-RING EXPANSION REACTION OF A TETRAHYDROFURAN DERIVATIVE

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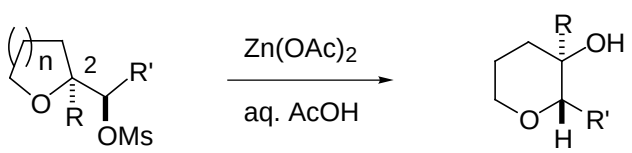
Abstract – The synthesis of the 2,6-disubstituted 2,3-*trans*-3-hydroxy-tetrahydropyran part of mucocin, a potent antitumor agent, was accomplished based on the zinc acetate-induced ring expansion reaction of a tetrahydrofuran having a cholоromethanesulfonate on the C2-side chain.

Recently, we reported the novel rearrangement reaction of cyclic ethers (**i**) having a leaving group on the C2-side chain with zinc acetate in aqueous acetic acid to afford the ring-expanded ethers (**ii**) (Scheme 1).[1] This new method is highly efficient for the synthesis of a tetrahydropyran or oxepane ring found in biologically active marine polycyclic ethers such as hemibrevetoxin B[2a] and maitotoxin.[2b,c] In order to extend the utility of the present reaction, our attention was next directed towards the synthesis of the 2,6-disubstituted 3-hydroxytetrahydropyran moiety of mucocin (**1**), a potent antitumor acetogenin isolated from *Rollinia mucosa* (Figure 1).[3] In the synthetic studies of mucocin (**1**), the construction of the 3-hydroxytetrahydropyran part was achieved by several methods, which included (1) the reductive cleavage of 6,6-spiroketals,[4] (2) the radical cyclization of an acyl selenide,[5] (3) *C*-glycosidation to a sugar derivative,[6] and (4) a 6-*endo* hydroxy epoxide opening.[7-9] We now describe an alternative and novel approach to the synthesis of a 2,6-*syn*-disubstituted 2,3-*trans*-3-hydroxytetrahydropyran derivative (**2**), starting from 2,5-anhydro-D-mannitol (**3**), based on the zinc acetate-induced rearrangement reaction.

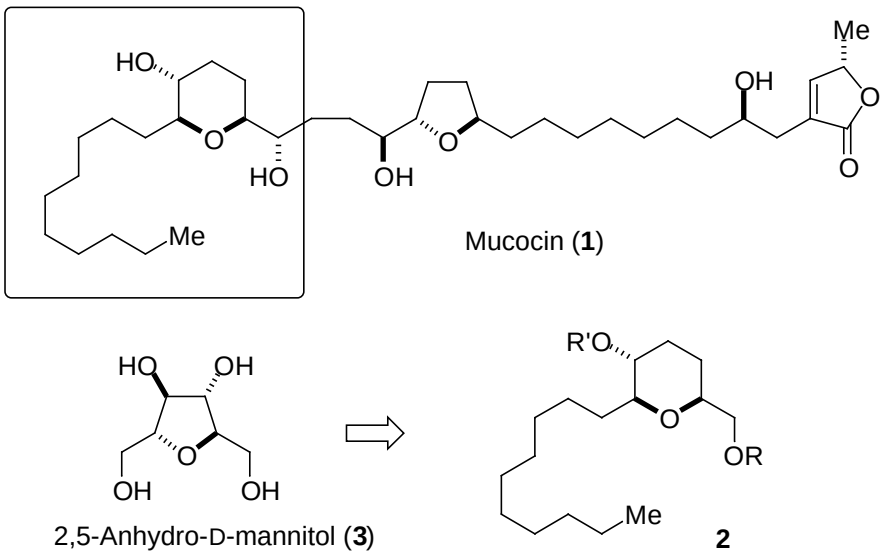
Scheme 1



i: R=H or Me
n=1 or 2

ii: R=H or Me
n=1 or 2

Figure 1

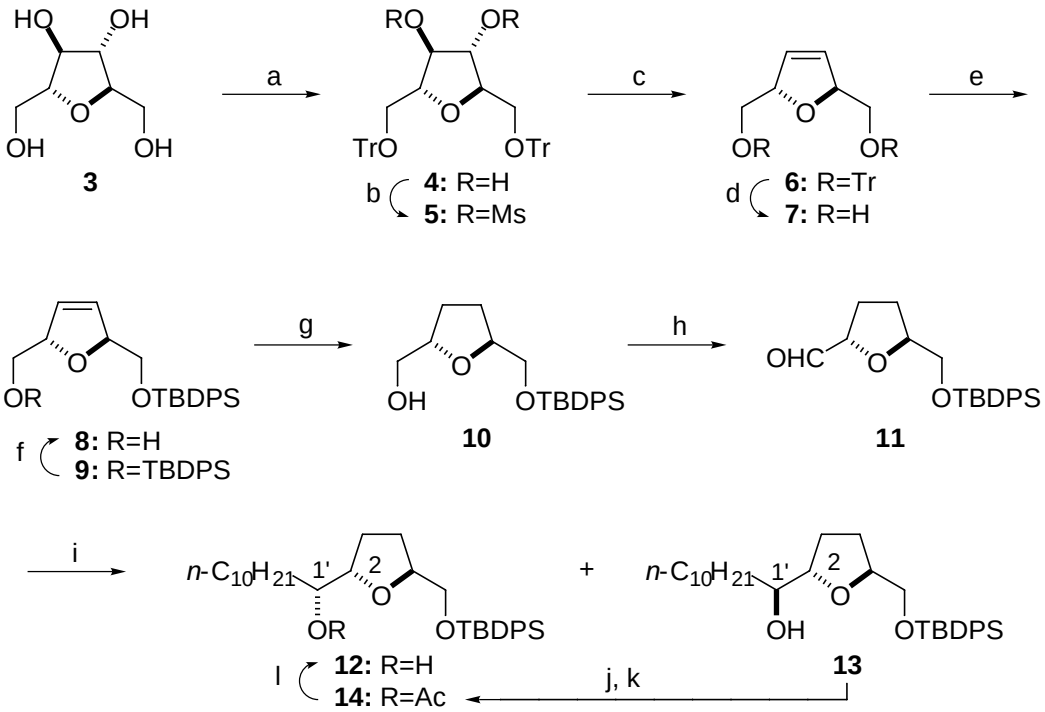


2,5-Anhydro-D-mannitol (**3**) was chosen as the starting material, because it bears the requisite carbon framework and functionalities, leading to a key intermediate (**12**) for the rearrangement-ring expansion reaction. The synthesis began with the deoxygenation reaction of the secondary hydroxyl groups in **3** (Scheme 2). Prior to the reaction, the two primary hydroxyl groups of **3** were protected as the trityl ether. The obtained diol (**4**) was converted into a dimesylate (**5**), which was treated with Zn-NaI in DMF,[10] giving an olefin (**6**) in 77% overall yield from **3**. After detritylation, the resulting diol (**7**) was silylated with *tert*-butyldiphenylsilyl chloride (TBDPSCl) (1.3 equiv.) and imidazole (2.0 equiv.) in acetonitrile-THF (1:1) at -78 °C, furnishing the desired monosilyl ether (**8**) in 46% yield along with a disilyl ether (**9**) (44%). These compounds were easily separated by column chromatography on silica gel. Treatment of the disilyl ether (**9**) with 1.0 equiv. of *n*-tetrabutylammonium fluoride (TBAF) afforded the monosilyl ether (**8**) in 87% yield based on the consumed **9**. By repetition of this simple procedure, multigrams of **8** could be obtained. The monosilyl ether (**8**) was subjected to hydrogenation, followed by the Swern oxidation with oxalyl chloride to give the aldehyde (**11**)[11] in 90% yield.

The 1'α-alcohol (**12**) having a decyl side chain with an *erythro*-configuration between the C1' and C2 positions was required for the ring-expansion reaction. The stereoselective introduction of the *n*-decyl group to the aldehyde (**11**) was first examined by a Grignard reaction. The reaction of **11** with *n*-decylmagnesium bromide in ether at -78 °C gave the desired 1'α-alcohol (**12**) [δ_H 3.78 (H-1'), δ_C 71.8 (C-1')] and the undesired 1'β-isomer (**13**) [δ_H 3.38 (H-1'), δ_C 74.0 (C-1')] in 12 and 42 % yields, respectively. These stereochemistries were determined by the application of Born's rule[12] and by comparison with the ^{13}C-NMR chemical shifts of related compounds.[13] This stereochemical assignment was also confirmed by chemical conversion of **12** into the desired tetrahydropyran derivative (**2**) (*vide infra*). In order to obtain **12** with high *erythro*-selectivity, we examined several conditions using a variety of additives.[14-16] The addition of cerium chloride[15] in Et_2O-THF at –78 °C to room temperature slightly improved the yield (combined yield; 61%), but the major product was still the undesired alcohol (**13**) (**12**:**13**=39:61). On the other hand, reversed selectivity was observed when methylaluminum bis(2,6-di-*tert*-butyl-1,4-methyl-phenoxide) (MAD)[16] or HMPA was added, although the ratio and yield were moderate: (1) Et_2O-toluene,

MAD, -78 °C (**12**:**13**=68:32, 44%), (2) Et_2O-THF-HMPA, -78 to 0 °C (**12**:**13**=83:17, 34% yield). In these cases, the Felkin-Ahn model would provide a reasonable explanation for the selectivity.

Scheme 2



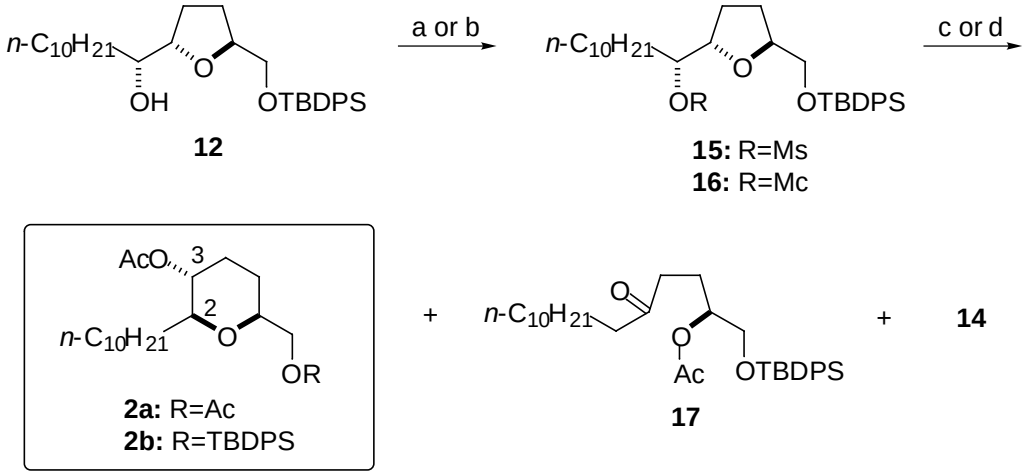
Reagents and conditions: (a) TrCl (2.3 equiv.), pyridine, rt (93%); (b) MsCl (3.0 equiv.), pyridine, 0 °C-rt (99%); (c) Zn (15.0 equiv.), NaI (8.0 equiv.), DMF, 140 °C (84%); (d) AcOH-H_2O (20:1), 50 °C (92%); (e) TBDPSCl (1.3 equiv.), imidazole (2.0 equiv.), THF-MeCN (1:1), -78 °C (46% for **8**, 44% for **9**); (f) TBAF, THF, 0 °C (87% based on the consumed **9**); (g) 10% Pd/C, H_2, EtOAc, rt (96%); (h) oxalyl chloride (3.0 equiv.), DMSO (6.0 equiv.), CH_2Cl_2, -78 °C and then Et_3N, -78-0 °C (94%); (i) *n*-$C_{10}H_{21}MgBr$, $CeCl_3$, ether-THF, -78 °C-rt (61%); (j) McCl (2.0 equiv.), 2,6-lutidine (2.0 equiv.), CH_2Cl_2, 0 °C; (k) CsOAc (8.6 equiv.), 18-crown-6 (2.0 equiv.), toluene, 60-80 °C; (l) NaOMe, MeOH, rt (65% from **13** in 3 steps).

We next examined the stereoselective transformation of the 1'β-alcohol (**13**) into the desired 1'α-isomer (**12**). Initial attempts for the stereoselective reduction of the corresponding ketone derived from **13** resulted in unsatisfactory results.[17] Consequently, the conversion of **13** into **12** was performed by the inversion reaction of the hydroxyl group in **13** *via* the chloromethanesulfonate (monochlate), which was recently found by us as an efficient leaving group.[18] The sulfonylation of **13** with chloromethanesulfonyl chloride ($ClCH_2SO_2Cl$=McCl) and 2,6-lutidine and subsequent treatment of the resulting monochlate with cesium acetate in the presence of 18-crown-6 in toluene[18,19] effected inversion of the 1'β-hydroxyl group to give the 1'α-acetate (**14**), which was subjected to methanolysis with sodium methoxide to give the desired 1'α-alcohol (**12**) in 65% overall yield from **13**.

With the requisite 1'α-alcohol (**12**) in hand, we proceeded to the ring-expansion reaction to obtain the desired tetrahydropyran (**2**). The mesylate derivative (**15**) was first examined for the rearrangement reaction (Scheme 3). A mixture of **15** and zinc acetate (4.0 equiv.) in aqueous acetic acid was gradually

heated with stirring. Although no reaction occurred at 50-80 °C, all the starting material (**15**) was consumed at 100-110 °C after 12 h. The usual work-up gave a complex mixture from which a diacetate (**2a**) was isolated in 16% yield. In the ^{1}H-NMR spectra of **2a**, the signals corresponding to the protons of H-2 and H-3 were observed at δ 3.25 ppm (td, *J* = 9.6, 2.3 Hz) and 4.48 ppm (td, *J* = 9.6, 5.0 Hz), respectively. The large coupling constant of the two protons indicates that the compound (**2a**) has the desired six-membered ether ring. Next, we applied a more efficient leaving group, monochlate, to this reaction.[1d,18] The reaction of the monochlate (**16**) with zinc acetate proceeded under milder conditions (80 °C for 2 h) to give the desired tetrahydropyran (**2b**) in 33% yield after acetylation. In this reaction, an acyclic ketone (**17**), which was produced by a 1,2-hydride shift, and a tetrahydrofuran derivative (**14**) were also isolated in 17 and 15 % yields, respectively.[1c]

Scheme 3



Reagents and conditions: (a) MsCl (2.0 equiv.), Et_3N, DMAP, pyridine, CH_2Cl_2, 0 °C-rt (73%); (b) McCl (2.0 equiv.), 2,6-lutidine, CH_2Cl_2, 0 °C-rt (99%); (c) $Zn(OAc)_2{\cdot}2H_2O$ (4.0 equiv.), aq. AcOH, 110 °C (16% for **2a**); (d) $Zn(OAc)_2{\cdot}2H_2O$ (4.0 equiv.), aq. AcOH, 80 °C, and then Ac_2O, pyridine, rt (33% for **2b**, 16% for **17**, 15% for **14**).

In summary, an alternative and unique procedure for the synthesis of the 2,6-*syn*-disubstituted 2,3-*trans*-3-hydroxytetrahydropyran (**2**) of mucocin (**1**), a potent antitumor agent, was developed based on a rearrangement-ring expansion reaction of the monochlate (**16**), prepared from 2,5-anhydro-D-mannitol (**3**).

ACKNOWLEDGMENT

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EXPERIMENTAL

Melting points were determined in a capillary with an Ishii melting-point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 polarimeter at 23±2 °C. IR spectra were recorded with a JASCO VALOR-III spectrophotometer. ^{1}H-NMR spectra were recorded at 270 MHz or 400 MHz with JEOL EX-270 or JNM-α 400 spectrometer, using tetramethylsilane as the internal standard. Column chromatography was performed on silica gel 60 (230-400 mesh; E. Merck, Darmstadt, Germany). The solvent extracts were dried with magnesium sulfate, and the solutions were evaporated under diminished pressure at 40-45 °C.

(2*R*,3*R*,4*R*,5*R*)-3,4-Dihydroxy-2,5-di(trityloxymethyl)tetrahydrofuran (4). To a stirred solution of **3** (1.64 g, 10.0 mmol) in pyridine (12 mL) was added trityl chloride (5.85 g, 21.0 mol) at rt, and then the mixture was stirred at rt for 5 h. After more trityl chloride (0.59 g, 2.1 mol) being added, stirring was further continued for 2 h. The resulting mixture was poured into ice-water with stirring, and then extracted with ether. The extracts were washed successively with water, cold dil. HCl solution, sat. $NaHCO_3$ solution, water, and brine, dried, and concentrated. Chromatography on silica gel with hexane-ethyl acetate (4:1→2:1) as the eluent gave **4** (6.01 g, 93%) as a white foam. $[\alpha]_D$ +18.7° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3430, 3060, 3012, 2940, 1597, 1491, 1448, 1217, 1069, 750 cm^{-1}; ^{1}H-NMR δ 3.20 (1H, d, *J* = 7.2 Hz, OH), 3.24 (1H, dd, *J* = 10.0, 3.3 Hz), 3.56 (1H, dd, *J* = 10.0, 4.5 Hz), 4.01 (1H, m), 4.19 (1H, br d), 7.26-7.34 (9H, m, Ar), 7.37-7.49 (6H, m, Ar). *Anal.* Calcd for $C_{44}H_{40}O_5$: C, 81.46; H, 6.21. Found: C, 81.45; H, 6.21.

(2*R*,3*R*,4*R*,5*R*)-3,4-Dimesyloxy-2,5-di(trityloxymethyl)tetrahydrofuran (5). To a stirred solution of **4** (4.0 g, 6.2 mmol) in pyridine (40 mL) was added dropwise methanesulfonyl chloride (2.16 mL, 18.5 mmol) at 0 °C and then the mixture was stirred at 0 °C to rt for 13 h. Crashed ice was added, and after 3 h the mixture was extracted with dichloromethane. The extracts were washed successively with water, cold dil. HCl solution, sat. $NaHCO_3$ solution, water, and brine, dried, and concentrated. The residue was treated with dichloromethane-ethyl acetate to afford 1.96 g of **5** (39%) as a white solid. The mother liquor was concentrated, and chromatographed on silica gel with toluene-ethyl acetate (50:1) as the eluent to give additional **5** (3.00 g, 60%) as a white solid. mp 183-184.5 °C (EtOAc); $[\alpha]_D$ +35.6° (*c* 0.43, $CHCl_3$); IR ($CHCl_3$) 3060, 3031, 2940, 1367, 1179, 1078, 958, 750 cm^{-1}; ^{1}H-NMR δ 2.90 (3H, s, Ms), 3.31 (1H, dd, *J* = 10.0, 4.7 Hz), 3.46 (1H, dd, *J* = 10.0, 4.4 Hz), 4.40 (1H, br d), 5.34 (1H, m), 7.24-7.33 (9H, m, Ar), 7.42-7.50 (6H, m, Ar). *Anal.* Calcd for $C_{46}H_{44}O_9S_2$: C, 68.64; H, 5.51; S, 7.97. Found: C, 68.62; H, 5.47; S, 7.91.

(2*S*,5*S*)-2,5-Di(trityloxymethyl)-2,5-dihydrofuran (6). To a stirred solution of **5** (2.00 g, 2.5 mmol) in DMF (20 mL) was added zinc powder (2.44 g, 37.3 mmol) and NaI (2.98 g, 19.9 mmol) and then the mixture was stirred at 140 °C for 19 h. After cooling, the reaction mixture was filtered through a pad of Celite. The filtrate was extracted with ether. The extracts were washed with water and brine, dried, and concentrated. Chromatography on silica gel with toluene-ethyl acetate (80:1) as the eluent gave **6** (1.29 g,

84%) as a white foam. $[\alpha]_D$ -88.0° (*c* 1.00, $CHCl_3$); ^{1}H-NMR δ 3.12 (1H, dd, *J* = 9.3, 2.9 Hz), 3.20 (1H, dd, *J* = 9.3, 2.3 Hz), 5.04 (1H, br d), 5.92 (1H, br s), 7.19-7.32 (9H, m, Ar), 7.44-7.52 (6H, m, Ar). *Anal.* Calcd for $C_{44}H_{38}O_3 \cdot 1/2H_2O$: C, 84.72; H, 6.30. Found: C, 84.67; H, 6.41.

(2*S*,5*S*)-2,5-Di(hydroxymethyl)-2,5-dihydrofuran (7). A mixture of **6** (1.18 g, 1.92 mmol) in 95% AcOH (21 mL) was stirred at 50 °C for 2 h. The mixture was cooled and concentrated. Chromatography on silica gel with toluene-ethyl acetate (1:2) as the eluent gave **7** (230 mg, 92%) as a syrup. $[\alpha]_D$ -219° (*c* 0.27, $CHCl_3$); IR (neat) 3376, 2873, 1090, 1067, 1037 cm^{-1}; ^{1}H-NMR δ 2.08-2.33 (1H, br s), 3.57 (1H, dd, *J* = 12.0, 4.6 Hz), 3.75 (1H, dd, *J* = 12.0, 2.0 Hz), 5.00 (1H, br s), 5.89 (1H, br s); HRMS (FAB) calcd for $C_6H_{10}O_3Na$: 153.0528. Found: 153.0519.

(2*S*,5*S*)-2-[(*tert*-Butyldiphenylsilyl)oxymethyl]-5-hydroxymethyl-2,5-dihydrofuran (8) and (2*S*,5*S*)-2,5-di[(*tert*-butyldiphenylsilyl)oxymethyl]-2,5-dihydrofuran (9). To a stirred solution of **7** (15.5 mg, 119 μmol) and imidazole (16.2 mg, 238 μmol) in acetonitrile-THF (1:1, 1.0 mL) was added TBDPSCl (40.2 μL, 155 μmol) at -78 °C. The mixture was stirred at -78 °C for 1 h, and then concentrated. Chromatography on silica gel with hexane-ethyl acetate (4:1) as the eluent gave **8** (20.0 mg, 46%) and **9** (32.0 mg, 44%). **8**: oil; $[\alpha]_D$ -115° (*c* 0.78, $CHCl_3$); IR (neat) 3440, 2931, 2859, 1113, 1074 cm^{-1}; ^{1}H-NMR δ 1.05 (9H, s), 1.88 (1H, t, *J* = 6.5 Hz, OH), 3.55 (1H, m), 3.70 (2H, br d), 3.75 (1H, m), 4.96 (2H, br s), 5.83 (1H, d, *J* = 6.3 Hz), 5.95 (1H, d, *J* = 6.3 Hz), 7.35-7.45 (6H, m, Ar), 7.61-7.71 (4H, m, Ar). *Anal.* Calcd for $C_{22}H_{28}O_3Si$: C, 71.69; H, 7.66. Found: C, 71.59; H, 7.73. **9**: oil; $[\alpha]_D$ -106° (*c* 0.63, $CHCl_3$); IR (neat) 2931, 2858, 1138, 1113, 1090 cm^{-1}; ^{1}H-NMR δ 1.05 (9H, s), 3.68 (1H, dd, *J* = 10.0, 4.9 Hz), 3.73 (1H, dd, *J* = 10.0, 4.3 Hz), 4.93 (1H, br s), 5.91 (1H, br s), 7.34-7.45 (6H, m, Ar), 7.66-7.69 (4H, m, Ar); HRMS (FAB) calcd for $C_{38}H_{46}O_3Si_2Na$: 629.2883, Found: 629.2868.

Transformation of 9 into 8. A solution of TBAF (1.0 M solution in THF, 1.66 mL) was added slowly to a stirred solution of **9** (1.01 g, 1.66 mmol) in THF (5 mL) at 0 °C. After stirring at 0 °C for 1 h, the mixture was diluted with water and extracted with ether. The extracts were washed with water and brine, dried, and concentrated. Chromatography on silica gel with hexane-ethyl acetate (4:1) as the eluent gave **8** (185 mg, 87% yield based on the consumed **9**) and **9** (661 mg).

(2*S*,5*S*)-2-[(*tert*-Butyldiphenylsilyl)oxymethyl]-5-(hydroxymethyl)tetrahydrofuran (10). A mixture of **8** (4.20 g, 13.6 mmol) and 10% Pd/C (400 mg) in EtOAc (10 mL) was stirred vigorously at rt under hydrogen atmosphere for 24 h. The mixture was filtered through a pad of Celite and then concentrated. Chromatography on silica gel with hexane-ethyl acetate (1:1) as the eluent gave **10** (4.04 g, 96%) as an oil. $[\alpha]_D$ +6.3° (*c* 0.21, $CHCl_3$); IR (neat) 3420, 2931, 2858, 1113, 1081 cm^{-1}; ^{1}H-NMR δ 1.06 (9H, s), 1.65-2.05 (5H, m), 3.48 (1H, m), 3.66 (2H, br d), 3.75 (1H, m), 4.06-4.18 (2H, m), 7.25-7.45 (6H, m, Ar), 7.66-7.71 (4H, m, Ar). *Anal.* Calcd for $C_{22}H_{30}O_3Si$: C, 71.31; H, 8.16. Found: C, 71.22; H, 8.19.

(2*S*,5*S*)-2-[1-(*tert*-Butyldiphenylsilyl)oxymethyl]-5-(1-formyl)tetrahydrofuran (11). To a stirred solution of oxalyl chloride (1.13 mL, 12.9 mmol) in dichloromethane (60 mL) was added dropwise a solution of DMSO (1.84 mL, 23.8 mmol) in dichloromethane (4 mL) at -78 °C under Ar and the mixture was stirred for 20 min at -78 °C. A solution of **10** (1.60 g, 4.31 mmol) in dichloromethane (10 mL) was added dropwise at -78 °C and the mixture was stirred at the same temperature for 1 h. Triethylamine (3.47 mL, 24.9 mmol) was added and the resulting mixture was gradually warmed to 0 °C with stirring, and poured into ice-water. The mixture was extracted with ether and the extracts were successively washed with cold sat. oxalic acid solution, sat. $NaHCO_3$ solution, water, and brine, dried, concentrated, and co-evaporated with toluene to give **11** (1.49 g, 94%) as a syrup, which was used for the next step without further purification. ^{1}H-NMR δ 1.06 (9H, s), 1.90-2.23 (4H, m), 3.65-3.78 (2H, m), 4.26 (1H, m), 4.35 (1H, m), 7.25-7.45 (6H, m, Ar), 7.66-7.71 (4H, m, Ar), 9.67 (1H, br d, *J* = 2.2 Hz).

(2*S*,5*S*)-2-[1-(*tert*-Butyldiphenylsilyl)oxymethyl]-5-[(1*R*)-(1-hydroxy)decyl]tetrahydrofuran (12) and (2*S*,5*S*)-2-[1-(*tert*-Butyldiphenylsilyl)oxymethyl]-5-[(1*S*)-(1-hydroxy)decyl]tetrahydrofuran (13).

i) Reaction of 11 with *n*-$C_{10}H_{21}$MgBr-$CeCl_3$. To a stirred suspension of $CeCl_3$ (104 mg, 0.42 mmol) in THF (1 mL) was added dropwise a solution of *n*-decylmagnesium bromide in ether (1M solution, 0.42 mL) at 0 °C and the mixture was stirred at 0 °C for 1 h. To the mixture was added a solution of **11** (39 mg, 0.11 mmol) in THF (0.4 mL) at -78 °C and the mixture was stirred at -78 °C for 3 h and -78 °C to rt for 17 h. After quenching with addition of sat. ammonium chloride solution, the resulting mixture was extracted with ether. The extracts were washed with water and brine, dried, and concentrated. Chromatography on silica gel with hexane-ethyl acetate (10:1) as the eluent gave **12** (13 mg, 24%) and **13** (20 mg, 37%).

ii) Reaction of 11 with *n*-$C_{10}H_{21}$MgBr-MAD. To a stirred solution of **11** (535 mg, 1.44 mmol) in ether (10 mL) was added dropwise a solution of MAD in toluene (0.4 M solution, 5.25 mL) at -78 °C under Ar and the mixture was stirred at the same temperature for 0.5 h. To this solution was added a solution of *n*-decylmagnesium bromide in ether (1M solution, 4.19 mL) and the mixture was stirred at - 78°C for 9 h. The same work-up as described above gave **12** (221 mg, 30%) and **13** (105 mg, 14%). **12**: oil; $[\alpha]_D$ -0.9° (*c* 0.45, $CHCl_3$); IR (neat) 3448, 2928, 2856, 1113, 1082 cm^{-1}; ^{1}H-NMR δ 0.88 (3H, t, *J* = 6.7 Hz), 1.06 (9H, s), 1.20-2.10 (23H, m), 3.65 (2H, br d), 3.78 (1H, m), 3.87 (1H, m), 4.15 (1H, m), 7.25-7.45 (6H, m, Ar), 7.66-7.71 (4H, m, Ar); ^{13}C-NMR δ 14.2, 19.3, 22.7, 24.8, 26.0, 26.9, 28.2, 29.4, 29.6, 29.8, 31.9, 32.7, 66.6, 71.8, 79.9, 82.3, 127.6, 129.6, 133.7, 135.6. *Anal.* Calcd for $C_{32}H_{50}O_3Si$: C, 75.23; H, 9.87. Found: C, 75.04; H, 9.86. **13**: oil; $[\alpha]_D$ -3.4° (*c* 0.48, $CHCl_3$); IR (neat) 3460, 2928, 2856, 1113, 1081 cm^{-1}; ^{1}H-NMR δ 0.88 (3H, t, *J* = 6.7 Hz), 1.05 (9H, s), 1.20-2.05 (22H, m), 2.32 (1H, br d, *J* = 4.3 Hz, OH), 3.38 (1H, m), 3.65 (2H, br d), 3.81 (1H, m), 4.10 (1H, m), 7.25-7.45 (6H, m, Ar), 7.66-7.71 (4H, m, Ar); ^{13}C-NMR δ 14.1, 19.3, 22.7, 25.7, 26.8, 28.3, 28.4, 29.3, 29.6, 29.8, 31.9, 33.7, 66.4, 74.0, 79.5, 82.7, 127.6, 129.6, 133.7, 135.6. *Anal.* Calcd for $C_{32}H_{50}O_3Si$: C, 75.23; H, 9.87. Found: C, 75.20; H, 10.06.

Transformation of 13 into 12. To a stirred mixture of **13** (537 mg, 1.05 mmol) and 2,6-lutidine (0.25 mL, 2.15 mmol) in dichloromethane (5 mL) was added dropwise chloromethanesulfonyl chloride (0.19 mL,

2.15 mmol) at 0 °C and then the mixture was stirred at 0 °C for 3.5 h. After addition of ice-water, the resulting mixture was stirried for 3 h, and extracted with ether. The extracts were washed successively with cold dil. HCl solution, sat. $NaHCO_3$ solution, water, and brine, dried, and concentrated to give a monochlate derivative (772 mg), which was dissolved in toluene (5 mL). To this solution were added CsOAc (1.73 g, 9.0 mmol) and 18-crown-6 (561 mg, 2.12 mmol) and the mixture was heated with stirring at 60 °C for 1.5 h and 80 °C for 2 h. After cooling, the mixture was diluted with ether and then washed with water, sat. $NaHCO_3$ solution, water, and brine, dried, and concentrated. Chromatography on silica gel with hexane-ethyl acetate (50:1) as the eluent gave **14** (378 mg, 65% from **13**) as a syrup. $[\alpha]_D$ +13.6° (*c* 0.46, $CHCl_3$); IR (neat) 2928, 2857, 1740, 1239, 1113, 1086 cm^{-1}; ^{1}H-NMR δ 0.88 (3H, t, *J* = 6.7 Hz), 1.05 (9H, s), 1.18-2.04 (22H, m), 2.05 (3H, s), 3.63 (2H, br d), 4.00 (1H, q, *J* = 6.0 Hz), 4.10 (1H, m), 4.92 (1H, m), 7.26-7.44 (6H, m, Ar), 7.65-7.69 (4H, m, Ar). *Anal.* Calcd for $C_{34}H_{52}O_4Si$: C, 73.86; H, 9.48. Found: C, 74.00; H, 9.69. To a stirred solution of **14** (20.0 mg, 0.04 mmol) in methanol (0.5 mL) was added NaOMe (7.8 mg, 0.14 mmol) and the mixture was stirred at rt for 16 h. To the mixture was added Dowex 50W X-8 (H^+) resin and the suspension was filtered. The filtrate was evaporated to a syrup that was chromatographed on silica gel with hexane-ethyl acetate (10:1→4:1) as the eluent, giving **12** (18.2 mg) quantitatively.

(2*S*,3*R*,6*S*)-3-Acetoxy-6-acetoxymethyl-2-decyltetrahydropyran (2a). The alcohol (**12**) (99 mg, 0.19 mmol) was mesylated with methanesulfonyl chloride (91 μL, 0.77 μmol), Et_3N (0.27 mL, 1.90 mmol) and *N*,*N*-dimethylaminopyridine (23.7 mg, 0.19 mmol) in pyridine-dichloromethane (1:1, 4 mL) at 0 °C-rt for 24 h. A usual work-up followed by chromatography on silica gel with toluene-dichloromethane (4:1) gave a mesylate (**15**) (84 mg, 73%) as a syrup. ^{1}H-NMR δ 0.88 (3H, t, *J* = 6.0 Hz), 1.04 (9H, s), 1.20-2.00 (22H, m), 3.02 (3H, s), 3.60 (1H, dd, *J* = 11 and 5.0 Hz), 3.68 (1H, dd, *J* = 11 and 4.3 Hz), 4.02 (1H, m), 4.08 (1H, m), 4.75 (1H, m), 7.36-7.42 (6H, m, Ar), 7.65-7.69 (4H, m, Ar). A mixture of **15** (84 mg, 0.14 mmol) and $Zn(OAc)_2 \cdot 2H_2O$ (124 mg, 0.57 mmol) in 50% AcOH (2 mL) was heated at 110 °C for 12 h with stirring, cooled, and then concentrated. The residue was diluted with water and then extracted with chloroform. The extracts were washed with sat. $NaHCO_3$ solution, water, and brine, dried, and concentrated. Chromatographed on silica gel with hexane-ethyl acetate (10:1→4:1) as the eluent gave **2a** (8.0 mg, 16%) as a syrup. $[\alpha]_D$ -33.1° (*c* 0.48, $CHCl_3$): IR (neat) 2930, 2850, 1740, 1235, 1038 cm^{-1}; ^{1}H-NMR δ 0.88 (3H, t, *J* = 6.7 Hz), 1.18-2.20 (22H, m), 2.05 (3H, s), 2.09 (3H, s), 3.25 (1H, dt, *J* = 9.6, 2.3 Hz), 3.55 (1H, m), 4.02 (1H, dd, *J* = 12, 4.6 Hz), 4.09 (1H, dd, *J* = 12, 6.6 Hz), 4.48 (1H, dt, *J* = 9.6, 5.0 Hz). HRMS (FAB) calcd for $C_{20}H_{36}O_5Na$: 379.2460. Found: 379.2466.

(2*S*,3*R*,6*S*)-3-Acetyl-6-[1-(*tert*-butyldiphenylsilyl)oxymethyl]-2-decyltetrahydropyran (2b), (2*S*,5*S*)-5-[(1*R*)-1-Acetoxydecyl]-2-[1-(*tert*-butyldiphenylsilyl)oxymethyl]tetrahydrofuran (14) and (2*S*)-2-Acetoxy-1-(*tert*-butyldiphenylsilyl)oxy-5-hexadecanone (17). The alcohol (**12**) (2.99 g, 5.85 mmol) was treated with chloromethanesulfonyl chloride (1.04 mL, 11.7 mmol), 2,6-lutidine (8.16 mL, 70.1 mmol) in dichloromethane (25 mL) at 0 °C-rt for 12 h. A usual work-up gave a monochlate (**16**) (3.76 g) as a syrup, which was used for the next step without further purification. ^{1}H-NMR δ 0.88 (3H, t, *J* = 6.6 Hz), 1.05

(9H, s), 1.19-2.05 (22H, m), 3.60 (1H, dd, *J* = 11.0 and 5.0 Hz), 3.70 (1H, dd, *J* = 11.0, 3.7 Hz), 3.92 (1H, ddd, *J* = 8.6, 5.9, 3.9 Hz), 4.20 (1H, m), 4.53 (1H, d, *J* = 12.0 Hz), 4.80 (1H, d, *J* = 12.0 Hz), 4.85 (1H, m), 7.32-7.46 (6H, m, Ar), 7.65-7.69 (4H, m, Ar). A mixture of **16** (3.76 g, *ca*. 5.85 mmol) and $Zn(OAc)_2 \cdot 2H_2O$ (5.14 g, 23.4 mmol) in 80% AcOH (240 mL) was heated at 80 °C for 2 h with stirring, cooled and then concentrated. The residue was diluted with water and extracted with chloroform. The extracts were washed with sat. $NaHCO_3$ solution, water, and brine, dried, and concentrated. The residue (3.57 g) was acetylated with Ac_2O (10 mL) in pyridine (30 mL) at rt for 24 h. A usual work-up followed by chromatography on silica gel with hexane-EtOAc (40:1→20:1→10:1) gave **2b** (1.08 g, 33%), **17** (594 mg, 18%) and **14** (469 mg, 15%). **2b**: syrup; $[\alpha]_D$ -30.7° (*c* 0.48, $CHCl_3$); IR (neat) 2927, 2856, 1741, 1239, 1113, 1039 cm^{-1}; ^{1}H-NMR δ 0.87 (3H, t, *J* = 6.6 Hz), 1.05 (9H, s), 1.18-1.60 (20H, m), 1.76 (1H, br d, *J* = 7.6 Hz), 2.05 (3H, s), 2.15 (1H, br s), 3.24 (1H, dd, *J* = 9.2, 7.9 Hz), 3.45 (1H, m), 3.55 (1H, dd, *J* = 10.0, 5.0 Hz), 3.71 (1H, dd, *J* = 10.0, 5.6 Hz), 4.45 (1H, ddd, *J* = 9.9, 9.2, 5.2 Hz), 7.31-7.44 (6H, m, Ar), 7.67-7.71 (4H, m, Ar). *Anal.* Calcd for $C_{34}H_{52}O_4Si$: C, 73.86; H, 9.48. Found: C, 73.83; H, 9.64. **17**: syrup; $[\alpha]_D$ -9.0° (*c* 0.20, $CHCl_3$); IR (neat) 2928, 2856, 1740, 1716, 1239, 1113 cm^{-1}; ^{1}H-NMR δ 0.88 (3H, t, *J* = 6.6 Hz), 1.06 (9H, s), 1.15-1.35 (16H, m), 1.45-1.60 (2H, m), 1.75-2.05 (2H, m), 2.00 (3H, s), 2.35 (2H, t, *J* = 7.2 Hz), 2.39 (2H, t, *J* = 7.6 Hz), 3.65 (2H, br d), 4.96 (1H, m), 7.32-7.42 (6H, m, Ar), 7.63-7.72 (4H, m, Ar). *Anal.* Calcd for $C_{34}H_{52}O_4Si$: C, 73.86; H, 9.48. Found: C, 73.98; H, 9.66.

REFERENCES AND NOTES

1. (a) T. Nakata, S. Nomura, and H. Matsukura, *Tetrahedron Lett.*, 1996, **37**, 213; (b) T. Nakata, S. Nomura, H. Matsukura, and M. Morimoro, *Tetrahedron Lett.*, 1996, **37**, 217; (c) K. Nagasawa, N. Hori, K. Koshino, and T. Nakata, *Heterocyles*, 1999, **50**, 919; (d) N. Hori, K. Nagasawa, T. Shimizu, and T. Nakata, *Tetrahedron Lett*., 1999, **40**, 2145.
2. (a) M. Morimoro, H. Matsukura, and T. Nakata, *Tetrahedron Lett.*, 1996, **37**, 6365; (b) T. Nakata, S. Nomura, and H. Matsukura, *Chem. Pharm. Bull*., 1996, **44**, 627; (c) K. Nagasawa, N. Hori, R. Shiba, and T. Nakata, *Heterocycles*, 1997, **44**, 105.
3. G. Shi, D. Alfonso, M. O. Fatope, L. Zeng, Z-m. Gu, G-x. Zhao, K. He, J. M. MacDougal, and J. L. McLaughlin, *J. Am. Chem. Soc.*, 1995, **117**, 10409.
4. M. T. Crimmins and S. W. Rafferty, *Tetrahedron Lett.*, 1996, **37**, 5649.
5. P. A. Evans and J. D. Roseman, *Tetrahedron Lett.*, 1997, **38**, 5249.
6. S. Takahashi and T. Nakata, *Tetrahedron Lett.*, 1999, **40**, 723.
7. P. Neogi, T. Doundoulakis, A. Yazbak, S. C. Sinha, S. C. Sinha, and E. Keinan, *J. Am. Chem. Soc.*, 1998, **120**, 11279.
8. S. Baurle, S. Hoppen, and U. Koert, *Angew. Chem., Int. Ed. Eng.*, 1999, **38**, 1263.
9. P. A. Evans and V. S. Murthy, *Tetrahedron Lett.*, 1999, **40**, 1253.
10. S. Tipson and A. Cohen, *Carbohydr. Res.*, 1965, **1**, 338.
11. The overall yield of **11** from **3** was 30% in seven steps. Synthesis of **11** from L-glutamic acid was also reported by Koert *et al*. (21% overall yiled, eight steps); U. Koert, M. Stein, and K. Harms, *Liebig. Ann.*, 1995, 1415, and references cited therein.

12. L. Born, F. Lieb, J. P. Lorentzen, H. Moeschler, M. Nonfon, R. Sollner, and D. Wendisch, *Planta Med.*, 1990, **56**, 312.
13. Y. Fujimoto, C. Murasaki, H. Shimada, S. Nishioka, K. Kakinuma, S. Singh, M. Singh, Y. K. Gupta, and M. Sahai, *Chem. Pharm. Bull.*, 1994, **42**, 1175.
14. B. Reitstoenm, L. Kilaas, and T. Anthonsen, *Acta Chem. Scand.*, 1986, **B 40**, 440.
15. T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima, and Y. Kamiya, *J. Am. Chem. Soc.*, 1989, **111**, 4392.
16. K. Maruoka, T. Itoh, M. Sakurai, K. Nonoshita, and H. Yamamoto, *J. Am. Chem. Soc.*, 1988, **110**, 3588.
17. The results are as follows; (1) $Zn(BH_4)_2$, toluene, -78 °C, **12**/**13** = 20/80 (87%), (2) $Zn(BH_4)_2$, Et_2O, -78 °C, **12**/**13** = 44/56 (99%), (3) $NaBH_4$, EtOH, 0 °C, **12**/**13** = 56/44 (89%), (4) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH-THF, 0 °C, **12**/**13** = 57/43 (99%), (5) L-Selectride, THF, -78 °C, **12**/**13** = 8/92 (99%).
18. (a) T. Simizu, S. Hiranuma, and T. Nakata, *Tetrahedron Lett.*, 1996, **37**, 6145; (b) T. Shimizu, T. Ohzeki, K. Hiramoto, N. Hori, and T. Nakata, *Synthesis*, 1999, 1373.
19. Y. Torisawa, H. Okabe, and S. Ikegami, *Chem. Lett.*, 1984, 1555.