The Asymmetric Syntheses of Methyl D-Digitoxoside, L-Oleandrose and L-Cymarose from Methyl Sorbate, an Achiral Precursor

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The addition of 4 eq of chloral to osmundalactone (4*S*,5*R*)-4 gave quantitative formation of the hemiacetal derivative (4*S*,5*R*)-8, which was treated with methane sulfonic acid to afford the intramolecular Micheal addition product (+)-(3*S*,4*S*,5*R*)-9 possessing a 3,4-*cis*-dihydroxy-*δ*-lactone in 78% overall yield from (4*S*,5*R*)-4. The obtained (+)-(3*S*,4*S*,5*R*)-9 was subsequently converted to methyl D-digitoxoside (pyranoside) (12) in 13% overall yield and methyl D-digitoxoside (furanoside) (12) in 20% overall yield. The reaction of benzyl-osmundalactone (4*R*,5*S*)-3 and MeOH in the presence of Amberlyst A-26 as a basic catalyst gave 3,4-*trans*-*δ*-lactone (−)-(3*S*,4*R*,5*S*)-20 in 28% yield and 3,4-*cis*-*δ*-lactone (−)-(3*R*,4*R*,5*S*)-21 in 45% yield. Dibal-H reduction of (−)-(3*S*,4*R*,5*S*)-20 followed by catalytic hydrogenation gave L-oleandrose (6) in 86% overall yield, while Dibal-H reduction of (−)-(3*R*,4*R*,5*S*)-21 followed by catalytic hydrogenation provided L-cymarose (7) in 85% overall yield.

Key words osmundalactone; methyl D-digitoxoside; L-oleandrose; L-cymarose

We previously reported the syntheses of (4*S*,5*R*)- and (4*R*,5*S*)-4-benzyloxy-5-hydroxyhexen-2(*E*)-oates (**2**) based on a chemoenzymatic method from methyl sorbate (**1**).[1)] Hydrolysis of (4*S*,5*R*)- and (4*R*,5*S*)-**2** gave the corresponding *δ*-hydroxy-*trans*-*α*,*β*-unsaturated carboxylic acids, which were converted to osmundalactones (4*S*,5*R*)- and (4*R*,5*S*)-**4** *via* the formation of *δ*-lactones (4*S*,5*R*)- and (4*R*,5*S*)-**3** accompanied by *trans*–*cis* isomerization, respectively.[2)]

Introduction of an oxygen functional group at C-3 position of (4*S*,5*R*)- and (4*R*,5*S*)-**4** may enable the synthesis of D-gigitoxose (**5**) and L-oleandrose (**6**), L-cymarose (**7**), respectively, possessing three contiguous chiral centers as shown in Chart 1. D-Digitoxose (**5**) is an important structural component of cardiac glycoside, digoxin,[3–5)] while L-oleandrose (**6**) is a component of several antibiotics such as oleandomycin[6–8)] and the avermectin series.[9–11)] L-Cymarose (**7**) is a glycosidic component of a number of cardiac glycosides. Several syntheses of methyl D-digitoxoside (**12**) (Chart 2) and L-oleandrose (**6**) have been reported,[12)] but the synthesis of L-cymrose (**7**) has scarcely been reported. Herein we report the asymmetric syntheses of methyl D-digitoxoside (**12**), L-oleandrose (**6**) and L-cymarose (**7**) from methyl sorbate, an achiral precursor.

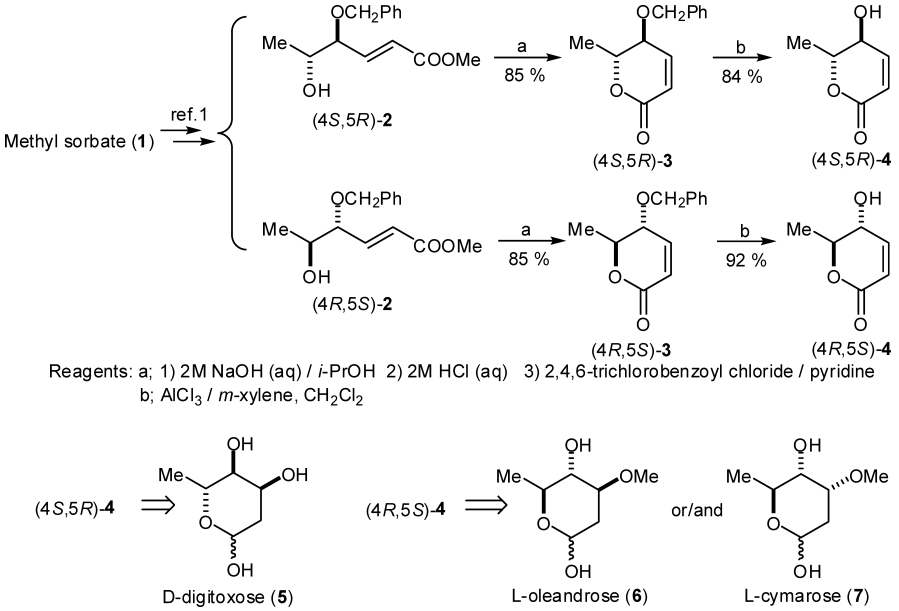

Chart 1

The authors declare no conflict of interest.

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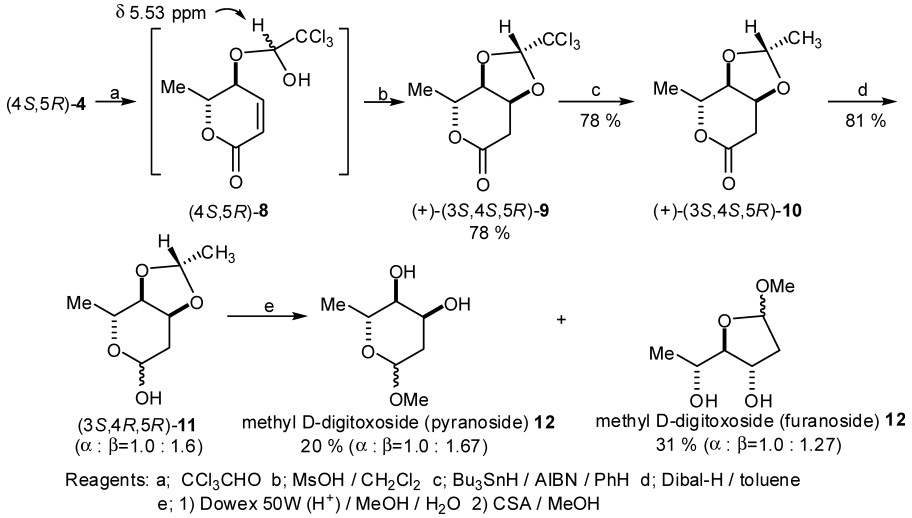

Chart 2

Synthesis of Methyl D-Digitoxoside (12) For the synthesis methyl D-digitoxoside (**12**), the construction of a 3,4-*cis*-dihydroxy-*δ*-lactone moiety is required from (4*S*,5*R*)-**4**. The oxymercuration–demercuration reaction of a trichloroacetaldehyde hemiacetal derivative derived from an unsaturated cyclic alcohol possessing an allylic alcohol moiety for a neighboring carbon–carbon double bond was reported to give an acetal possessing a 1,2-*cis*-dihydroxy-structure.[13] Owing to its high tendency for formation of hemiacetal, trichloroacetaldehyde (chloral) was selected for this study. The addition of 4 eq of chloral to (4*S*,5*R*)-**4** resulted in quantitative formation of the hemiacetal derivative (4*S*,5*R*)-**8** as shown in Chart 2. Hemiacetal formation was easily monitored by observing the appearance of the characteristic singlet (*δ* 5.53 ppm) of the methine hydrogen attached to the trichloromethyl-bearing carbone in nuclear magnetic resonance (NMR) spectrum. To promote the Micheal addition of the hemiacetal hydroxyl group to the neighboring *α*,*β*-unsaturated double bond, methane sulfonic acid (MsOH) was added and the intramolecular Micheal addition product (+)-(3*S*,4*S*,5*R*)-**9** possessing the 3,4-*cis*-dihydroxy-structure was obtained in 78% overall yield from (4*S*,5*R*)-**4**. The structure of (+)-(3*S*,4*S*,5*R*)-**9** was confirmed by nuclear Overhauser effect (NOE) spectroscopy as shown in Fig. 1.

Treatment of (+)-(3*S*,4*S*,5*R*)-**9** with tributyltin hydride (Bu_3SnH) in the presence of azoisobutyronitrile (AIBN) gave an acetal (+)-(3*S*,4*S*,5*R*)-**10** in 78% yield. Treatment of (+)-(3*S*,4*S*,5*R*)-**10** with diisobutylaluminum hydride (Dibal-H) gave a 1.0 : 1.6 mixture of *α*- and *β*-epimers of lactol (3*S*,4*R*,5*R*)-**11** in 81% yield. Acid treatment of this mixture with Dowex 50W (H^+) in MeOH followed by addition of camphor sulfonic acid (CSA) in MeOH afforded a 1.0 : 1.67 mixture of *α*- and *β*-epimers of methyl D-digitoxoside (pyranoside)-**12** (20% yield) and a 1.0 : 1.27 mixture of *α*- and *β*-epimers of methyl D-digitoxoside (furanoside)-**12** (31% yield). ^{1}H-NMR data of both epimers of (pyranoside)-**12** and both epimers of (furanoside)-**12** were identical with those of the reported compounds.[14] The $[\alpha]_D$ value of the 1.0 : 1.67 mixture of *α*- and *β*-epimers (pyranoside)-**12** $\{[\alpha]_D^{20}$ +35.4 (*c*=0.85, $CHCl_3)\}$ were consistent with the calculated value $\{[\alpha]_D$ +41.7 $(CHCl_3)\}$. The calculated value was obtained based on the reported pure *α*-epimer (pyranoside)-**12** $\{[\alpha]_D^{20}$ +174 (*c*=1.0, $CHCl_3)\}$[14] and *β*-epimer (pyranoside)-**12** $\{[\alpha]_D^{20}$ −36 (*c*=1.0, $CHCl_3)\}$[14] using the following equation.

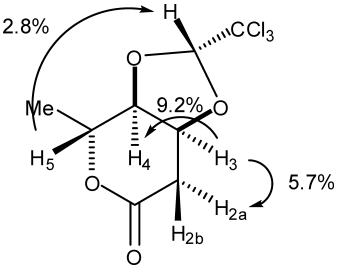

Fig. 1. NOE Correlation of (+)-(3*S*,4*S*,5*R*)-**9**

$$\text{calculated value } ([\alpha]_D) = +174 \times 0.37 + (-36) \times 0.63 = +41.7$$

The $[\alpha]_D$ value of the 1.0 : 1.27 mixture of *α*- and *β*-epimers (furanoside)-**12** $\{[\alpha]_D^{25}$ +1.4 (*c*=0.44, $CHCl_3)\}$ was consistent with the calculated one $\{[\alpha]_D$ +2.24 $(CHCl_3)\}$. The calculated value was obtained based on the reported pure *α*-isomer (furanoside)-**12** $\{[\alpha]_D^{20}$ +140 (*c*=1.0, $CHCl_3)\}$[14] and *β*-isomer (furanoside)-**12** $\{[\alpha]_D^{20}$ −106 (*c*=1.0, $CHCl_3)\}$[14] as follows.

$$\text{calculated value } ([\alpha]_D) = +140 \times 0.44 + (-106) \times 0.56 = +2.24$$

Thus the structure of the synthetic methyl D-digitoxoside (**12**) was unequivocally confirmed.

Synthesis of L-Oleandrose (6) and L-Cymarose (7) For the synthesis of L-oleandrose (**6**) and L-cymarose (**7**), the construction of a 3,4-*trans*-dihydroxy-*δ*-lactone moiety is required from (4*R*,5*S*)-**4**. The reaction of (±)-**4** and mercury(II) trifluoroacetate $[Hg(OCOCF_3)_2]$ followed by addition of an oxygen nucleophile such as water or methanol could give compound (±)-**14**, which could be reduced with sodium borohydride ($NaBH_4$) to afford compound (±)-**15** possessing the 3,4-*trans*-dihydroxy-*δ*-lactone moiety as shown in Chart 3. In this case, the structure of intermediary (±)-**13** could be either 2,3-*cis*- and 3,4-*cis* because of the chelation between hydroxyl group and mercury ion.

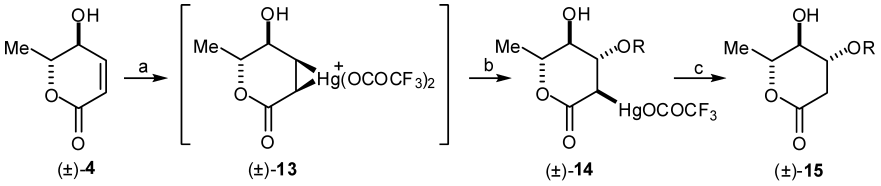

Chart 3

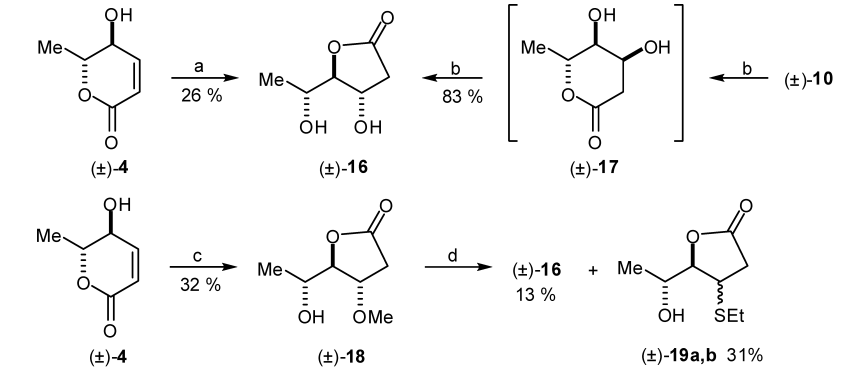

Chart 4

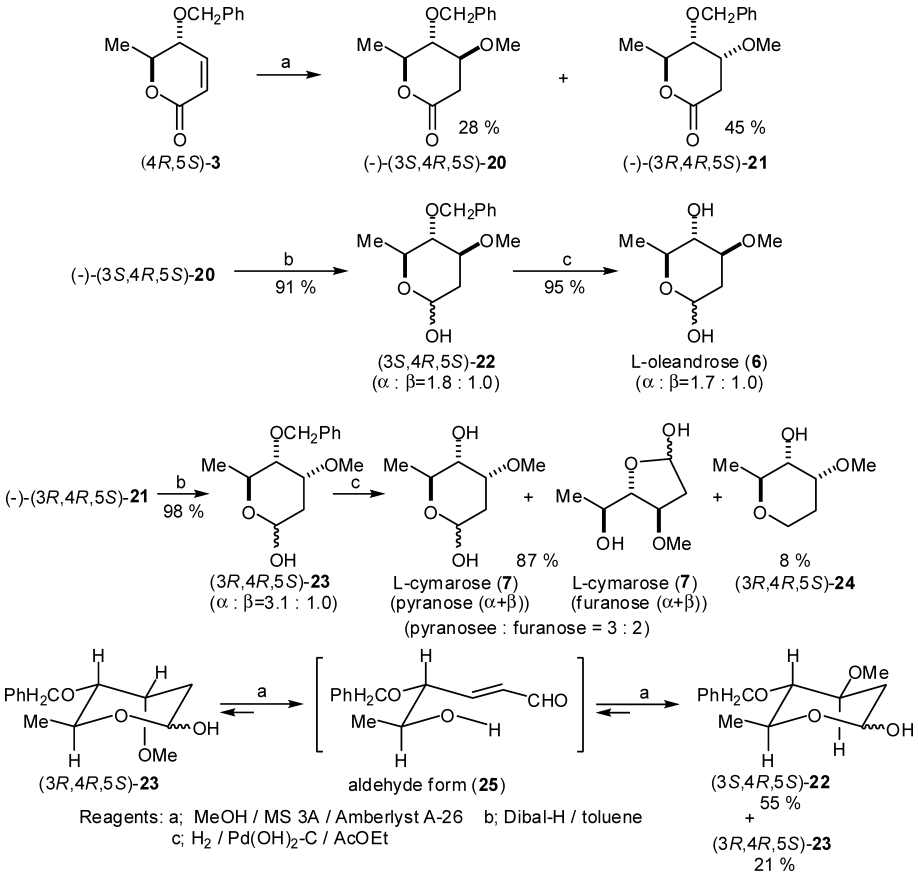

Chart 5

In order to examine this working hypothesis, the reaction of (±)-**4** and $Hg(OCOCF_3)_2$ in the presence of 70% $HClO_4$ solution followed by the reduction with alkaline $NaBH_4$ was carried out to afford compound (±)-**16** in 26% overall yield as shown in Chart 4. In this case, no other products were obtained.

The synthetic (±)-**16** was identical with the authentic (±)-**16**, which was obtained by treatment of previously mentioned (±)-**10** (Chart 2) with aqueous 1 M H_2SO_4 in 83% overall yield. The reaction of (±)-**4**, $Hg(OCOCF_3)_2$ and MeOH in the presence of 70% $HClO_4$ solution followed by the reduction with alkaline $NaBH_4$ was carried out to give compound (±)-**18** in 32% overall yield (Chart 4). In this case, no other products were obtained. $AlCl_3$-assisted demethylation of (±)-**18** in ethane thiol (EtSH) afforded (±)-**16** (13%) and a mixture of *α*- and *β*-isomers of (±)-**19a**, **b** (31%). Consequently, the structure of (±)-**18** was confirmed. From these fact, the structure of intermediary (±)-**13** could be either 2,3-*cis*- and 3,4-*trans* because stereic repulsion of between hydroxyl group and mercury ion could be larger than the above mentioned chelation effect. Consequently, water could attack at C(3)-position from *β*-side to give 3,4-*cis* (±)-**17**, which could be immediately converted to (±)-**16**.

Due to the low yield of (±)-**16** and (±)-**18**, the introduction of methoxyl group at the 3-position of the benzyl ether (4*R*,5*S*)-**3** *via* the Michael addition was examined. The reaction of (4*R*,5*S*)-**3** and MeOH in the presence of Amberlyst A-26 as a basic catalyst gave 3,4-*trans*-*δ*-lactone (−)-(3*S*,4*R*,5*S*)-**20** {$[\alpha]_D^{22}$ −112 (*c*=1.73, $CHCl_3$)} in 28% yield and 3,4-*cis*-*δ*-lactone (−)-(3*R*,4*R*,5*S*)-**21** {$[\alpha]_D^{24}$ −72 (*c*=1.5, $CHCl_3$)} in 45% yield. The structures of both products were confirmed by the fact that (−)-(3*S*,4*R*,5*S*)-**20** and (−)-(3*R*,4*R*,5*S*)-**21** were converted to natural products L-oleandrose (**6**) and L-cymarose (**7**), respectively, as shown in Chart 5.

Dibal-H reduction of (−)-(3*S*,4*R*,5*S*)-**20** provided a 1.8 : 1.0 mixture of *α*- and *β*-epimers (3*S*,4*R*,5*S*)-**22** {$[\alpha]_D^{23}$ −73 (*c*=0.55, $CHCl_3$)} in 91% yield, which was subjected to catalytic hydrogenation to give a 1.7 : 1.0 mixture of *α*- and *β*-L-oleandroses (**6**) in 95% yield. The specific rotation of the synthetic L-oleandrose (**6**) {$[\alpha]_D^{23}$ +10 (*c*=0.51, H_2O)} was consistent with the reported data {$[\alpha]_D^{23}$ +11.2 (*c*=1.0, H_2O)}.[9] ^{1}H-NMR data and ^{13}C-NMR data of the synthetic L-oleandrose (**6**) were identical with those of the reported data.[15]

Dibal-H reduction of (−)-(3*R*,4*R*,5*S*)-**21** provided a 3.1 : 1.0 mixture of *α*- and *β*-epimers (3*R*,4*R*,5*S*)-**23** {$[\alpha]_D^{24}$ −87.7 (*c*=1.46, $CHCl_3$)} in 98% yield, which was subjected to catalytic hydrogenation to give a 3 : 2 mixture of L-cymarose (pyranose) (**7**) and L-cymarose (furanose) (**7**) in 87% yield and (3*R*,4*R*,5*S*)-**24** in 8% yield. The specific rotation of the synthetic mixture L-cymarose (**7**) {$[\alpha]_D^{24}$ −52 (*c*=0.42, H_2O)} was consistent with the reported data {$[\alpha]_D^{23}$ −50 (*c*=1.0, H_2O)}.[16] ^{1}H-NMR data and ^{13}C-NMR data of the synthetic L-cymarose (**7**) were identical with those of the reported data.[16]

The reaction of the 3.1 : 1.0 mixture of *α*- and *β*-epimers (3*R*,4*R*,5*S*)-**23** and MeOH in the presence of Amberlyst A-26 gave a 1.8 : 1.0 mixture of *α*- and *β*-epimers (3*S*,4*R*,5*S*)-**22** in 55% yield and the recovery of (3*R*,4*R*,5*S*)-**23** in 21% yield. It was found that an equilibrium relationship was established between (3*R*,4*R*,5*S*)-**23** and (3*S*,4*R*,5*S*)-**22** *via* the aldehyde intermediate (**25**). This process could be explained in the following manner. Acid-promoted *trans* double bond and aldehyde group formations based on MeOH elimination could afford *α*,*β*-unsaturated aldehyde **25**, which could be accompanied by Micheal addition of MeOH and hemiaetal formation to afford (3*S*,4*R*,5*S*)-**22** possessing more stable all equatorial configurations.

Conclusion

The addition of 4 eq of chloral to osmundalactone (4*S*,5*R*)-**4** gave quantitative formation of the hemiacetal derivative (4*S*,5*R*)-**8**, which was treated with methane sulfonic acid (MsOH) to afford the intramolecular Micheal addition product (+)-(3*S*,4*S*,5*R*)-**9** possessing a 3,4-*cis*-dihydroxy-*δ*-lactone moiety in 78% overall yield from (4*S*,5*R*)-**4**. Thus obtained (+)-(3*S*,4*S*,5*R*)-**9** was converted to actal-*δ*-lactone (+)-(3*S*,4*S*,5*R*)-**10**, which was reduced with Dibal-H to provide lactol (3*S*,4*R*,5*R*)-**11** in 81% yield. Deprotection of the acetal in (3*S*,4*R*,5*R*)-**11** followed by acid treatment in MeOH gave methyl D-digitoxoside (pyranoside) (**12**) in 20% yield and methyl D-digitoxoside (furanoside) (**12**) in 31% yield.

The reaction of benzyl-osmundalactone (4*R*,5*S*)-**3** and MeOH in the presence of Amberlyst A-26 as a basic catalyst gave 3,4-*trans*-*δ*-lactone (−)-(3*S*,4*R*,5*S*)-**20** in 28% yield and 3,4-*cis*-*δ*-lactone (−)-(3*R*,4*R*,5*S*)-**21** in 45% yield. Dibal-H reduction of (−)-(3*S*,4*R*,5*S*)-**20** followed by catalytic hydrogenation gave L-oleandrose (**6**) in 86% overall yield, while Dibal-H reduction of (−)-(3*R*,4*R*,5*S*)-**21** followed by catalytic hydrogenation provided L-cymarose (**7**) in 85% overall yield.

Experimental

^{1}H- and ^{13}C-NMR spectra were recorded on JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by distortionless enhancement by polarization transfer (DEPT) pulse sequence. The fast atom bombardment-mass spectra (FAB-MS) were obtained with a JEOL JMS 600H spectrometer. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

Synthesis of Methyl D-Digitoxoside (11) i) A mixture of (4*S*,5*R*)-**4** (0.601 g, 4.7 mmol) and CCl_3CHO (3.46 g 23.5 mmol) was stood for 24 h at rt and a solution of MsOH (1.36 g, 14.1 mmol) in CH_2Cl_2 (10 mL) was added to the above reaction mixture. All reaction mixture was stirred for 8 h at rt. The reaction mixture was diluted with Et_2O and the organic layer was washed with brine. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (35 g, *n*-hexane–AcOEt=1 : 3) to give (+)-(3*S*,4*S*,5*R*)-**9** (1.010 g, 78%) as a colorless oil. (+)-(3*S*,4*S*,5*R*)-**9**: IR ($CHCl_3$): 1755 cm^{-1}; $[\alpha]_D^{30}$ +58.7 (*c*=0.34, $CHCl_3$), ^{1}H-NMR *δ*: 1.51 (3H, d, *J*=6 Hz), 2.81 (1H, dd, *J*=16, 6 Hz), 3.02 (1H, dd, *J*=16, 6 Hz), 4.42 (1H, qd, *J*=6, 6 Hz), 4.52 (1H, dd, *J*=6, 6 Hz), 5.07 (1H, ddd, *J*=6, 6, 6 Hz), 5.55 (1H, s). *Anal.* Calcd for $C_8H_9O_4Cl_3$: C, 34.88; H, 3.27. Found: C, 34.59; H, 3.26. MS (FAB) *m/z*: 276 (M^++1).

ii) To a solution of (+)-(3*S*,4*S*,5*R*)-**9** (0.453 g, 1.64 mmol) and AIBN (70 mg, 0.43 mmol) in benzene (40 mL) under argon atmosphere were added *n*-Bu_3SnH (2.16 g, 7.42 mmol) and the reaction mixture was stirred for 2.5 h at 90°C. The reaction mixture was evaporated to give a residue, which was chromatographed on silica gel (55 g, *n*-hexane–AcOEt=1 : 3)

to give (+)-(3*S*,4*S*,5*R*)-**10** (0.222 g, 78%) as a colorless oil. (+)-(3*S*,4*S*,5*R*)-**10**: IR (neat): 1756 cm^{-1}; $[\alpha]_D^{26}$ +105.9 (*c*=0.43, $CHCl_3$), ^{1}H-NMR δ: 1.34 (3H, d, *J*=5 Hz), 1.47 (3H, d, *J*=6 Hz), 2.72 (1H, dd, *J*=16, 8 Hz), 2.93 (1H, dd, *J*=16, 6 Hz), 4.08 (1H, dd, *J*=8.4, 8 Hz), 4.33 (1H, qd, *J*=8.4, 6 Hz), 4.59 (1H, ddd, *J*=8.4, 8, 6 Hz), 5.30 (1H, q, *J*=5 Hz). *Anal.* Calcd for $C_8H_{12}O_4 \cdot 0.25H_2O$: C, 54.37; H, 7.08. Found: C, 54.49; H, 7.25. MS (FAB) *m/z*: 173 (M^++1).

iii) To a solution of (+)-(3*S*,4*S*,5*R*)-**10** (0.173 g, 1.0 mmol) in toluene (15 mL) was added 1 M Dibal-H toluene solution (2.7 mL, 2.7 mmol) under argon atmosphere at −20°C and the reaction mixture was stirred for 1 h at −20°C. The reaction mixture was diluted with 2 M HCl solution and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (10 g, *n*-hexane–AcOEt=5 : 1) to give a 1 : 1.6 mixture of *α*- and *β*-epimers of (+)-(3*S*,4*R*,5*R*)-**11** (0.141 g, 81%) as a colorless oil. (+)-(3*S*,4*R*,5*R*)-**11**: IR (neat): 3432 cm^{-1}; $[\alpha]_D^{24}$ +82.03 (*c*=0.79, $CHCl_3$), *Anal.* Calcd for $C_8H_{14}O_4 \cdot 0.25H_2O$: C, 53.75; H, 8.12. Found: C, 53.76; H, 8.19. MS (FAB) *m/z*: 175 (M^++1). ^{1}H-NMR of each epimer was analyzed based on NOE and proton–proton decoupling (homo decoupling) analysis technique. *α*-Epimer δ: 1.26 (3H, d, *J*=6 Hz), 1.32 (3H, d, *J*=6 Hz), 1.80 (1H, ddd, *J*=14, 9, 4 Hz), 2.32 (1H, ddd, *J*=14, 4, 3 Hz), 3.15 (1H, d, *J*=5.8 Hz), 3.53 (1H, qd, *J*=9, 6 Hz), 3.78 (1H, dd, *J*=10, 4 Hz), 4.25–4.35 (1H, m), 5.03 (1H, ddd, *J*=9, 5.8, 2 Hz), 5.38 (1H, q, *J*=5.2 Hz). *β*-epimer δ: 1.26 (3H, d, *J*=6 Hz), 1.32 (3H, d, *J*=6 Hz), 2.06–2.20 (2H, m), 3.75 (1H, dd, *J*=10, 5 Hz), 3.97 (1H, qd, *J*=9, 6 Hz), 4.25–4.35 (1H, m), 5.15 (1H, ddd, *J*=8, 4, 4 Hz), 5.42 (1H, q, *J*=5.2 Hz).

iv) To a solution of a 1 : 1.6 mixture of *α*- and *β*-epimers of (+)-(3*S*,4*R*,5*R*)-**11** (0.107 g, 0.61 mmol) in MeOH (0.5 mL) was added H_2O (3.6 mL) and Dowex 50W(H+) (0.4 g), and the reaction mixture was stirred for 1.5 h at 70°C. The reaction mixture was filtered and the filtrate was evaporated to give a crude oil. To a solution of the above oil in MeOH (2 mL) was added CSA (0.12 g, 0.52 mmol) and the reaction mixture was stood for 1 h at rt. The reaction mixture was condensed to give a crude oil, which was chromatographed on silica gel (10 g, *n*-hexane–AcOEt=1 : 1) to give a 1 : 1.67 mixture of *α*- and *β*-epimers of (+)-methyl D-digitoxoside (**12**) (pyranoside, 0.020 g, 20%) as a colorless oil and a 1 : 1.27 mixture of *α*- and *β*-epimers of (+)-methyl D-digitoxoside (**12**) (furanoside, 0.031 g, 31%) as a colorless oil in elution order: D-digitoxoside (**12**) (pyranoside): IR (neat): 3445 cm^{-1}; $[\alpha]_D^{24}$ +35.4 (*c*=0.85, $CHCl_3$), *Anal.* Calcd for $C_7H_{14}O_4 \cdot 0.25H_2O$: C, 50.44; H, 8.77. Found: C, 50.65; H, 8.84. MS (FAB) *m/z*: 163 (M^++1). ^{1}H- and ^{13}C-NMR of each epimer were assigned by comparison of the reported data. *α*-Epimer, ^{1}H-NMR δ: 1.31 (3H, d, *J*=6 Hz), 1.89 (1H, ddd, *J*=14.5, 3.4, 3.4 Hz), 2.15 (1H, ddd, *J*=14.5, 5.3, 1 Hz), 3.12 (1H, d, *J*=7 Hz), 3.35 (3H, s), 3.69 (1H, qd, *J*=10, 6 Hz), 3.92 (1H, br s), 4.75 (1H, d, *J*=3.4 Hz). ^{13}C-NMR δ: 98.21 (d), 72.51 (d), 67.54 (d), 64.29 (d), 55.20 (s), 35.20 (t), 17.90 (s). *β*-Epimer δ: 1.29 (3H, d, *J*=6 Hz), 1.68 (1H, ddd, *J*=14, 10, 3 Hz), 2.08 (1H, ddd, *J*=14, 4, 2 Hz), 3.28 (1H, d, *J*=9 Hz), 3.45 (3H, s), 3.71 (1H, qd, *J*=9, 6 Hz), 4.08 (1H, dd, *J*=5, 3 Hz), 4.69 (1H, dd, *J*=10, 2 Hz). ^{13}C-NMR δ: 98.71 (d), 73.00 (d), 69.52 (d), 68.00 (d), 56.49 (s), 37.70 (t), 18.22 (s). D-digitoxoside (**12**) (furanoside): IR (neat): 3445 cm^{-1}; $[\alpha]_D^{24}$ +1.37 (*c*=0.44, $CHCl_3$), MS (FAB) *m/z*: 163 (M^++1). ^{1}H-NMR and ^{13}C-NMR of each epimer were assigned by comparison of the reported data. *α*-Epimer, ^{1}H-NMR δ: 1.22 (3H, d, *J*=6 Hz), 1.96 (1H, dd, *J*=14, 2 Hz), 2.07 (1H, ddd, *J*=14, 7, 2 Hz), 3.35 (3H, s), 3.80–3.90 (2H, m), 4.22 (1H, br s), 5.06 (1H, d, *J*=4 Hz). ^{13}C-NMR δ: 105.20 (d), 90.80 (d), 71.16 (d), 67.64 (d), 54.80 (s), 42.05 (t), 18.72 (s). *β*-Epimer δ: 1.21 (3H, d, *J*=6 Hz), 2.04–2.14 (1H, m), 2.24 (1H, ddd, *J*=14, 7, 2 Hz), 3.34 (3H, s), 3.75–3.85 (2H, m), 4.56 (1H, br s), 5.04 (1H, d, *J*=6 Hz). ^{13}C-NMR δ: 105.40 (d), 91.00 (d), 70.97 (d), 68.58 (d), 55.40 (s), 42.74 (t), 18.98 (s).

(±)-(3*S′*,4*R′*,5*R′*)-3,5-Dihydroxyhexano-4-lactone (16) To a solution of (±)-**4** (0.069 g, 0.54 mmol) in tetrahydrofuran (THF) (3 mL) at 0°C were added $Hg(OCOCF_3)_2$ (0.69 g, 1.62 mmol) and 70% $HClO_4$ solution (0.15 mL, 0.97 mmol), and the reaction mixture was stirred for 2 h at 0°C. To the reaction mixture were added 7% $NaHCO_3$ solution (7 mL) and $NaBH_4$ (0.06 g, 1.59 mmol) at 0°C, and the reaction mixture was stirred for 1 h. The reaction mixture was filtered and the filtrate was acidified with AcOH. The reaction mixture was condensed to afford a residue, which was chromatographed on silica gel (25 g, *n*-hexane–AcOEt=1 : 1) to give (±)-**16** (0.020 g, 26%) as a colorless oil. (±)-**16**: IR (neat): 1732, 3444 cm^{-1}; ^{1}H-NMR (CD_3OD) δ: 1.22 (3H, d, *J*=6 Hz), 2.34 (1H, dd, *J*=18, 2 Hz), 2.89 (1H, dd, *J*=18, 8 Hz), 3.89 (1H, qd, *J*=6, 4 Hz), 4.18 (1H, dd, *J*=4, 2 Hz), 4.50 (1H, dt, *J*=8, 2, 2 Hz). ^{13}C-NMR (CD_3OD) δ: 178.33 (s), 93.27 (d), 67.89 (d), 67.63 (d), 39.27 (t), 19.02 (q). *Anal.* Calcd for $C_6H_{10}O_4 \cdot 0.25H_2O$: C, 47.84; H, 7.03. Found: C, 47.56; H, 7.08. MS (FAB) *m/z*: 147 (M^++1).

Conversion of (±)-(3*S′*,4*R′*,5*R′*)-10 to (±)-(3*S′*,4*R′*,5*R′*)-16 To a solution of (±)-**10** (0.166 g, 0.96 mmol) in THF (4 mL) was added 1 M H_2SO_4 solution (2.5 mL) and the reaction mixture was stirred for 2 h at 80°C. The reaction mixture was diluted with 7% $NaHCO_3$ solution (7 mL) and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and evaporated to afford a residue which was chromatographed on silica gel (20 g, *n*-hexane–AcOEt=1 : 2) to give (±)-**16** (0.117 g, 83%) as a colorless oil. ^{1}H- and ^{13}C-NMR data of (±)-**12** were identical with those of the previous (±)-**16**.

(±)-(3*S′*,4*R′*,5*R′*)-5-Hydroxy-3-methoxyhexano-4-lactone (18) To a solution of (±)-**4** (0.081 g, 0.63 mmol) in MeOH (5 mL) was added $Hg(OCOCF_3)_2$ (0.82 g, 1.92 mmol) and the reaction mixture was stirred for 2 h at rt. To the reaction mixture were added 7% $NaHCO_3$ solution (7 mL) and $NaBH_4$ (0.07 g, 1.85 mmol) at 0°C, and the reaction mixture was stirred for 1 h. The reaction mixture was worked up in the same way of (±)-**12** to give (±)-**18** (0.033 g, 32%) as a colorless oil. (±)-**18**: IR (neat): 1775, 3448 cm^{-1}; ^{1}H-NMR δ: 1.24 (3H, d, *J*=6 Hz), 2.50 (1H, dd, *J*=18, 2 Hz), 2.82 (1H, dd, *J*=18, 7 Hz), 3.30 (3H, s), 4.04 (1H, qd, *J*=6, 4 Hz), 4.12 (1H, dt, *J*=7, 3 Hz), 4.26 (1H, dd, *J*=4, 3 Hz). ^{13}C-NMR δ: 175.85 (s), 88.56 (d), 75.76 (d), 66.74 (d), 56.51 (q), 35.40 (t), 18.34 (q). *Anal.* Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.51; H, 7.29. MS (FAB) *m/z*: 161 (M^++1).

Conversion of (±)-(3*S′*,4*R′*,5*R′*)-18 to (±)-(3*S′*,4*R′*,5*R′*)-16 To a mixture of $AlCl_3$ (0.120 g, 0.9 mmol) in EtSH (2 mL, 0.03 mmol) was added a solution of (±)-**18** (0.047 g, 0.29 mmol) in EtSH (1 mL) at 0°C and the reaction mixture was stirred for 4 h at rt. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and evaporated to afford a residue which was chromatographed on silica gel (10 g) to give a 3 : 2 mixture

of (±)-**19a**,**b** (0.017 g, 31%) as a colorless oil from *n*-hexane–AcOEt=2 : 1 elution, recovery of (±)-**18** (0.020 g, 42%) from *n*-hexane–AcOEt=1 : 1 elution and (±)-**16** (0.006 g, 13%) from *n*-hexane–AcOEt=1 : 3 elution. ^{1}H- and ^{13}C-NMR data of (±)-**16** were identical with those of the previous (±)-**16**. (±)-**19a**,**b**: IR (neat): 1732, 3414 cm^{-1}; *Anal.* Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.42. Found: C, 50.26; H, 7.35. MS (FAB) *m/z*: 191 (M^++1). ^{1}H-NMR of each isomer was analyzed based on the proton–proton decoupling (homo decoupling) analysis technique. **19a**, ^{1}H-NMR (CD_3OD) δ: 1.21 (3H, d, *J*=6 Hz), 1.28 (3H, d, *J*=7 Hz), 2.44 (1H, dd, *J*=18, 4 Hz), 2.50–2.74 (2H, m), 3.09–3.19 (1H, m), 3.68 (1H, ddd, *J*=9, 4, 4 Hz), 3.94 (1H, qd, *J*=6, 4 Hz), 4.22 (1H, dd, *J*=7, 3 Hz). **19b**, ^{1}H-NMR (CD_3OD) δ: 1.25 (3H, d, *J*=7 Hz), 1.40 (3H, d, *J*=6 Hz), 2.50–2.74 (2H, m), 3.05–3.18 (3H, m), 3.35 (1H, dd, *J*=9, 7 Hz), 4.19 (1H, qd, *J*=6, 5 Hz).

Synthesis of L-Oleandrose (6) i) To a mixture of (4*R*,5*S*)-**3** (0.866 g, 3.97 mmol) and molecular sieve (MS) 3A (1.0 g) in MeOH (20 mL) was added Amberlyst A-26 (hydroxide form) (0.6 g) and the reaction mixture was stirred for 3 h at rt. The reaction mixture was filtered and the filtrate was condensed to give a crude oil. To a solution of the above oil in THF (20 mL) was added aqueous 2 M NaOH (6 mL) and the reaction mixture was stirred for 1 h at rt. The reaction mixture was acidified with aqueous 2 M HCl and condensed to give a crude product, which was diluted with AcOEt. The AcOEt layer was filtered and the filtrate was condensed to give a crude oil, which was chromatographed on silica gel (30 g) to give (−)-(3*S*,4*R*,5*S*)-**20** (0.284 g, 28%) as a colorless oil from *n*-hexane–AcOEt=5 : 1 eluent and (−)-(3*R*,4*R*,5*S*)-**21** (0.453 g, 45%) as a colorless oil from *n*-hexane–AcOEt=2 : 1 eluent. (−)-(3*S*,4*R*,5*S*)-**20**: $[\alpha]_D^{22}$ −111.5 (*c*=1.73, $CHCl_3$), IR (neat): 1758 cm^{-1}; ^{1}H-NMR δ: 1.41 (3H, d, *J*=6 Hz), 2.74 (1H, ddd, *J*=16, 4, 1 Hz), 2.79 (1H, dd, *J*=16, 5 Hz), 3.36 (3H, s), 3.39 (1H, ddd, *J*=8, 3, 1 Hz), 3.74 (1H, dd, *J*=8, 4 Hz), 4.19 (1H, qd, *J*=6, 4 Hz), 4.58, 4.72 (each 1H, d, *J*=12 Hz), 7.28–7.38 (5H, m). *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.98; H, 7.41. MS (FAB) *m/z*: 251 (M^++1). (−)-(3*R*,4*R*,5*S*)-**21**: $[\alpha]_D^{24}$ −71.9 (*c*=1.5, $CHCl_3$), IR (neat): 1733 cm^{-1}; ^{1}H-NMR δ: 1.37 (3H, d, *J*=6 Hz), 2.58 (1H, dd, *J*=18, 4 Hz), 2.90 (1H, dd, *J*=18, 5.6 Hz), 3.41 (3H, s), 3.46 (1H, dd, *J*=7, 2 Hz), 3.75 (1H, ddd, *J*=5.8, 4, 2 Hz), 4.70 (1H, qd, *J*=7, 6 Hz), 4.61, 4.72 (each 1H, d, *J*=12 Hz), 7.26–7.38 (5H, m). *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.89; H, 7.31. MS (FAB) *m/z*: 251 (M^++1).

ii) To a solution of (−)-(3*S*,4*R*,5*S*)-**20** (0.246 g, 0.98 mmol) in toluene (12 mL) was added 1 M Dibal-H toluene solution (2 mL, 2 mmol) under argon atmosphere at −20°C and the reaction mixture was stirred for 1 h at −20°C. The reaction mixture was diluted with 2 M HCl solution (2 mL) and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (10 g, *n*-hexane–AcOEt=2 : 1) to give a 1.8 : 1 mixture of α- and β-epimers of (−)-(3*S*,4*R*,5*S*)-**22** (0.226 g, 91%) as a colorless oil. (−)-(3*S*,4*R*,5*S*)-**22**: IR (neat): 3440 cm^{-1}; $[\alpha]_D^{23}$ −72.5 (*c*=0.55, $CHCl_3$), *Anal.* Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.57; H, 8.25. MS (FAB) *m/z*: 253 (M^++1). ^{1}H-NMR of each epimer was analyzed based on NOE and proton–proton decoupling (homo decoupling) analysis technique. α-Epimer: ^{1}H-NMR δ: 1.25 (3H, d, *J*=6 Hz), 1.54 (1H, ddd, *J*=14, 14, 3 Hz), 2.27 (1H, ddd, *J*=14, 5, 2 Hz), 3.02 (1H, dd, *J*=10, 9 Hz), 3.44 (3H, s), 3.72 (1H, ddd, *J*=14, 9, 5 Hz), 3.94 (1H, qd, *J*=10, 6 Hz), 4.63, 4.89 (each 1H, d, *J*=11 Hz), 5.31 (1H, br s), 7.23–7.40 (5H, m). β-Epimer: ^{1}H-NMR δ: 1.30 (3H, d, *J*=6 Hz), 1.43 (1H, ddd, *J*=12, 12, 10 Hz), 2.40 (1H, ddd, *J*=12, 5, 2 Hz), 3.00 (1H, dd, *J*=6, 3 Hz), 3.33–3.43 (2H, m), 3.42 (3H, s), 4.62, 4.88 (each 1H, d, *J*=11 Hz), 5.05 (1H, br s), 7.23–7.40 (5H, m).

iii) A mixture of (−)-(3*S*,4*R*,5*S*)-**22** (1.8 : 1 mixture of α- and β-epimers) (0.207 g, 0.82 mmol) and 20% $Pd(OH)_2$–C (0.16 g) in AcOEt (20 mL) was subjected to a catalytic hydrogenation under ordinary pressure for 12 h at rt. The reaction mixture was filtered and the filtrate was condensed to give a crude oil, which was chromatographed on silica gel (10 g, *n*-hexane–AcOEt=1 : 2) to give a 1.7 : 1 mixture of α- and β-L-oleandrose (**6**) (0.153 g, 95%) as a colorless oil. L-Oleandrose (**6**): IR (neat): 3443 cm^{-1}; $[\alpha]_D^{23}$ +10.0 (*c*=0.51, H_2O), *Anal.* Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.58; H, 8.98. MS (FAB) *m/z*: 145 (M^++1−H_2O). ^{1}H-NMR of each epimer was analyzed based on NOE and proton–proton decoupling (homo decoupling) analysis technique. α-Pyranose (**6**): ^{1}H-NMR δ: 1.26 (3H, d, *J*=6 Hz), 1.47 (1H, ddd, *J*=14, 12, 4 Hz), 2.28 (1H, ddd, *J*=14, 4.4, 1.6 Hz), 3.13 (1H, dd, *J*=9, 9 Hz), 3.37 (3H, s), 3.55 (1H, ddd, *J*=14, 9, 5 Hz), 3.91 (1H, qd, *J*=9, 6 Hz), 5.32 (1H, br s, *J*=3 Hz). ^{13}C-NMR δ: 91.89 (d), 77.85 (d), 76.10 (d), 67.65 (d), 56.45 (q), 34.15 (t), 18.00 (q). β-Pyranose (**6**): ^{1}H-NMR δ: 1.32 (3H, d, *J*=6 Hz), 1.35–1.37 (1H, m), 2.39 (1H, ddd, *J*=12, 4, 2 Hz), 3.08–3.44 (3H, m), 3.35 (3H, s), 4.79 (1H, dd, *J*=10, 2 Hz). ^{13}C-NMR δ: 93.90 (d), 80.50 (d), 75.15 (d), 71.75 (d), 56.38 (q), 36.50 (t), 17.95 (q).

Synthesis of L-Cymarose (7) i) To a solution of (−)-(3*R*,4*R*,5*S*)-**21** (0.313 g, 1.25 mmol) in toluene (13 mL) was added 1 M Dibal-H toluene solution (2.5 mL, 2.5 mmol) under argon atmosphere at −20°C and the reaction mixture was stirred for 1 h at −20°C. The reaction mixture was diluted with 2 M HCl solution (2.5 mL) and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (15 g, *n*-hexane–AcOEt=2 : 1) to give a 3.1 : 1 mixture of α- and β-epimers of (−)-(3*R*,4*R*,5*S*)-**23** (0.308 g, 98%) as a colorless oil. (−)-(3*R*,4*R*,5*S*)-**23**: IR (neat): 3420 cm^{-1}; $[\alpha]_D^{24}$ −87.7 (*c*=1.46, $CHCl_3$), *Anal.* Calcd for $C_{14}H_{20}O_4 \cdot 0.25H_2O$: C, 65.42; H, 7.98. Found: C, 65.22; H, 7.94. MS (FAB) *m/z*: 253 (M^++1). ^{1}H-NMR of each epimer was analyzed based on NOE and proton–proton decoupling (homo decoupling) analysis technique. α-Epimer: ^{1}H-NMR δ: 1.29 (3H, d, *J*=6 Hz), 1.70 (1H, ddd, *J*=14, 6, 2 Hz), 2.19 (1H, ddd, *J*=14, 4, 1.8 Hz), 3.10 (1H, dd, *J*=10, 3 Hz), 3.52 (3H, s), 3.83 (1H, br s), 4.21 (1H, qd, *J*=10, 6 Hz), 4.55, 4.65 (each 1H, d, *J*=12 Hz), 5.17 (1H, br s), 7.24–7.40 (5H, m). β-Epimer: ^{1}H-NMR δ: 1.26 (3H, d, *J*=6 Hz), 1.42 (1H, ddd, *J*=14, 10, 2 Hz), 2.27 (1H, ddd, *J*=14, 4, 2 Hz), 3.10 (1H, dd, *J*=10, 3 Hz), 3.42 (3H, s), 3.72 (1H, br s), 3.96 (1H, qd, *J*=10, 6 Hz), 4.51, 4.63 (each 1H, d, *J*=12 Hz), 5.05 (1H, br s), 7.24–7.40 (5H, m).

ii) A mixture of (−)-(3*R*,4*R*,5*S*)-**23** (3.1 : 1 mixture of α- and β-epimers) (0.142 g, 0.56 mmol) and 20% $Pd(OH)_2$-C (0.16 g) in AcOEt (20 mL) was subjected to a catalytic hydrogenation under ordinary pressure for 12 h at rt. The reaction mixture was filtered and the filtrate was condensed to give a crude oil, which was chromatographed on silica gel (10 g) to give (3*R*,4*R*,5*S*)-**24** (0.007 g, 8%) as a colorless oil from *n*-hexane–AcOEt=1 : 1 eluent and a 3 : 2 mixture of pyranose type and

furanose type of L-cymarose (**7**) (0.079 g, 87%) as a colorless oil from *n*-hexane–AcOEt=1 : 2 eluent. (3*R*,4*R*,5*S*)-**24**: IR (neat): 3450 cm^{-1}; *Anal.* Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.23; H, 9.73. MS (FAB) *m*/*z*: 147 (M^++1). ^{1}H-NMR δ: 1.18 (3H, d, *J*=6 Hz), 1.80–1.97 (2H, m), 2.22 (1H, br s), 3.29 (3H, s), 3.58 (1H, dd, *J*=4, 4 Hz), 3.78–3.98 (3H, m). ^{13}C-NMR δ: 88.09 (d), 80.85 (d), 67.50 (d), 67.35 (t), 56.80 (q), 32.65 (t), 18.60 (q). L-Cymarose (**7**) IR (neat): 3418 cm^{-1}; $[\alpha]_D^{23}$ −51.6 (*c*=0.42, H_2O), *Anal.* Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.54; H, 8.87. MS (FAB) *m*/*z*: 145 (M^++1−H_2O). ^{1}H-NMR of each epimer was analyzed based on NOE and proton–proton decoupling (homo decoupling) analysis technique. α-Pyranose (**7**): ^{1}H-NMR δ: 1.17 (3H, d, *J*=6 Hz), 1.73 (1H, ddd, *J*=15, 4, 3 Hz), 2.02–2.17 (1H, m), 3.32 (3H, s), 3.33–3.43 (1H, m), 3.57–3.66 (1H, m), 3.89–3.90 (1H, m), 5.06 (1H, br s). β-Pyranose (**7**): ^{1}H-NMR δ: 1.25 (3H, d, *J*=6 Hz), 1.49 (1H, ddd, *J*=14, 10, 3 Hz), 2.26 (1H, ddd, *J*=14, 4, 2 Hz), 3.19 (1H, ddd, *J*=10, 10, 3 Hz), 3.39 (3H, s), 3.57–3.66 (1H, m), 3.86–3.98 (1H, m), 4.97 (1H, dd, *J*=10, 2 Hz). A mixture of furanose (**7**): ^{1}H-NMR δ: 1.19, 1.25 (each 3H, d, *J*=6 Hz), 1.98, 2.30 (each 1H, ddd, *J*=15, 4, 3 Hz and ddd, *J*=14, 4, 2 Hz), 2.18, 2.30 (each 1H, ddd, *J*=14, 7, 2 Hz and ddd, *J*=14, 4, 2 Hz), 3.26, 3.49 (each 3H, s), 4.04, 4.13 (each 1H, dd, *J*=4, 2 Hz and ddd, *J*=8, 5, 4 Hz), 5.44, 5.56 (each 1H, d, *J*=5 Hz and dd, *J*=6, 2.8 Hz).

Conversion of (3*R*,4*R*,5*S*)-23 to (3*S*,4*R*,5*S*)-22 To a solution of a mixture of (−)-(3*R*,4*R*,5*S*)-**23** (3.1 : 1 mixture of α- and β-epimers) (0.035 g, 0.14 mmol) in MeOH (2 mL) was added Amberlyst A-26 (hydroxide form) (0.1 g) and the reaction mixture was stirred for 2 h at 35°C. The reaction mixture was filtered and the filtrate was condensed to give a crude oil, which was chromatographed on silica gel (10 g, *n*-hexane–AcOEt=2 : 1) to give a 1.7 : 1 mixture of α- and β-epimers of (3*S*,4*R*,5*S*)-**22** (0.019 g, 55%) as a colorless oil and starting (3*R*,4*R*,5*S*)-**23** (0.007 g, 21%) as a colorless oil. ^{1}H-NMR data of both compounds were identical with those of the previous (3*S*,4*R*,5*S*)-**22** and (3*R*,4*R*,5*S*)-**23**, respectively.

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