Stereodivergent Synthesis of Optically Active α-Hydroxy Acids via Diastereoselective Reduction of α-Keto Esters Derived from L-Quebrachitol

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Reduction of an α-keto ester derived from chiral cyclitol, readily available from L-quebrachitol, with K-Selectride proceeded via re-face attack of the ketone with high diastereoselectivity to obtain the α-hydroxy ester in 92% de. On the other hand, reduction of the α-keto ester with K-Selectride in the presence of 18-Crown-6 took place via *si*-face attack of the ketone to furnish the corresponding α-hydroxy ester in 92% de. Thus both enantiomers of mandelic acid were obtained in optically pure form.

Optically pure α-hydroxy acid derivatives are important and versatile synthetic intermediates for the construction of chiral organic molecules.[1] Stereoselective synthesis of these derivatives has attracted much attention.[2]

Diastereoselective reduction of α-keto acid derivatives is one of the most reliable methods for the construction of α-hydroxy acid derivatives. Although highly diastereoselective reduction of α-keto amides has been reported,[3] reduction of chiral α-keto esters resulted in moderate diastereoselectivity[4] except for a few examples.[5]

Although L-quebrachitol (1L-(−)-2-*O*-methyl-*chiro*-inositol), which is a naturally-occurring chiral cyclitol that is obtained from an exudate of the rubber tree,[6] is currently widely used as a chiral source for the synthesis of optically active natural products,[7] it has not been employed as a chiral source for asymmetric reactions.[8]

In connection with our continuing interest in L-quebrahcitol,[9] we reported that chiral alcohol **3**, derived from L-quebrachitol, is an efficient chiral auxiliary; addition of organometallics to an α-keto ester afforded the α-hydroxy ester[10] and [2+3] cycloaddition of nitrile oxide to acrylic ester afforded 2-isoxazolines with high diastereoselectivity.[11] In this article we wish to describe the highly diastereoselective reduction of α-keto ester **5a** with potassium tri-*s*-butylhydroborate (K-Selectride) to afford the α-hydroxy ester and the dramatic changeover in diasteroselectivity by addition of 18-Crown-6.[12]

Results and Discussion

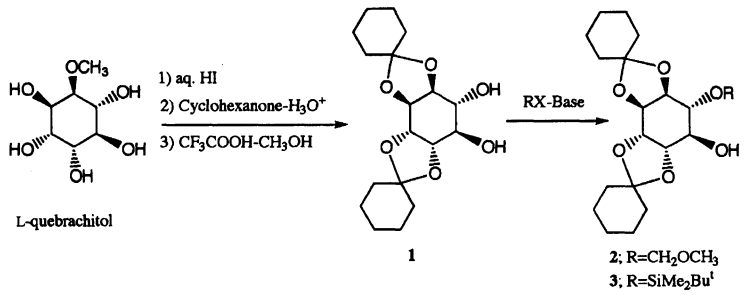
Chiral auxiliaries **2** and **3** were readily prepared from L-quebrachitol via 1L-1,2:5,6-di-*O*-cyclohexylidene-*chiro*-inositol (**1**)[13] as shown in Scheme 1. Treatment of the alcohols with benzoylformic acid chloride[14] afforded the corresponding α-keto acid esters **4a** and **5a** quantitatively (Scheme 2).

Initially, we studied the reduction of α-keto ester **4a**, bearing a methoxymethyl group, as a model compound. The results are shown in Table 1. The diastereometic excess was determined by 270 MHz ^{1}H NMR analysis and the absolute stereochemistry was determined by optical rotation of mandelic acid obtained by hydrolysis. While $NaBH_4$, diisobutylaluminum hydride, $Na[AlH_2(OCH_2CH_2OCH_3)_2]$, $LiBH_4$, and $Li[BEt_3H]$ did not show conceivable diastereoselectivity, reduction with a sterically demanding reducing reagent, K-Selectride, in THF afforded α-hydroxy ester **4b** in good diastereoselectivity (72% de) (Entry 6). This result encouraged us to focus on Selectride as a reducing reagent.

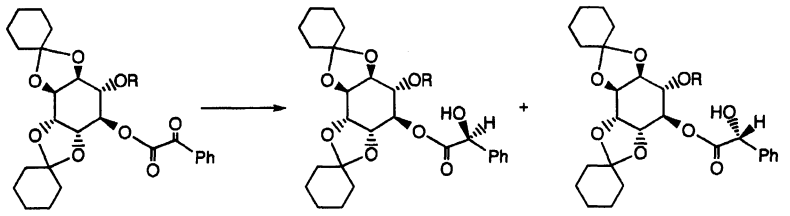
Solvent effects on the reduction of **4a** with K-Selectride were studied and the results are shown in Table 2. Reduction of **4a** with K-Selectride in either Et_2O or toluene afforded predominently 2*S* isomer **4b** in 94% de (Entries 2 and 3). Single recrystallization of the alcohol afforded diastereomerically pure **4b**. Although reduction with lithium tri-*s*-butylhydroborate (L-Selectride) in THF showed no selectivity, reduction in Et_2O gave **4b** in 52% de (Entry 6). It should be noted that addition of 18-Crown-6 resulted in a dramatic changeover in diastereoselection; reduction of **4a** with K-Selectride in the presence of 18-Crown-6 afforded 2*R* isomer **4c** in 80% de. Reduction with L-Selectride in the presence of hexamethylphosphoric triamide (HMPA) also furnished **4c** predominantly.

Next we investigated the reduction of α-keto ester **5a**, bearing a bulky *t*-butyldimethylsilyl group vicinal to the α-ketoacyloxy group, in the hope of improving the diastereoselectivity. The results are shown in Table 3. Reduction of **5a** with K-Selectride in THF or Et_2O proceeded highly diastereoselectively, affording predominantly 2*S*-isomer **5b** in 92 and 96% de, respectively (Entries 1 and 2). Interestingly, addition of 18-Crown-6 entirely changed the sense of diastereoselection; reduction of **5a** with K-Selectride in the presence of 18-Crown-6 in THF gave principally 2*R* isomer **5c** in 92% de (Entry 4). L-Selectride in Et_2O also showed high diastereoselectivity (Entry 8). Addition of either HMPA or *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) led to the preferential formation of **5c**.

Ready separation of **5b** and **5c** by column chromatography on SiO_2 gave the diastereomerically pure compounds. Because hydrolysis of the α-hydroxy ester proceeded smoothly to afford mandelic acid without racemization, the present method allowed us to obtain both enantiomers of mandelic acid in optically pure form. Furthermore, chiral auxiliaries **3** and **4** were readily re-



Scheme 1.



Scheme 2.

Table 1. Results of the Reduction of **4a**

Entry	Reductant	Equiv	Solvent	Temp/°C	Yield/%	**4b** : **4c**
1	$NaBH_4$	1.0	Ethanol	0	44	60 : 40
2	*i*-Bu_2AlH	1.0	Toluene	−72	46	50 : 50
3	Red-Al[a)]	1.0	Toluene	−72	15	33 : 67
4	$LiBH_4$	1.0	THF	−72	83	52 : 48
5	$Li[BEt_3H]$	1.0	THF	−72	93	45 : 55
6	K-Selectride	1.2	THF	−72	85	86 : 14

a) Red-Al: $Na[AlH_2(OCH_2CH_2OCH_3)_2]$.

Table 2. Results of the Reduction of **4a** with Selectride[a)]

Entry	Reducing agent[b)] (equiv)	Solvent	Additive[c)]	Yield/%	**4b** : **4c**
1	K (1.2)	THF	—	85	86 : 14
2	K (1.2)	Et_2O	—	78	97 : 3
3	K (1.0)	Toluene	—	51	97 : 3
4	K (1.7)	THF	18-Crown-6	78	10 : 90
5	L (1.0)	THF	—	71	52 : 48
6	L (1.4)	Et_2O	—	86	76 : 24
7	L (1.4)	Et_2O	HMPA	78	12 : 88

a) The reaction was carried out at −78 °C. b) K; K-Selectride, L; L-Selectride. c) 1.4—1.5 equivalent of additives are employed.

covered quantitatively and could be used repeatedly.

From the synthetic point of view, it is very important to develop methods that provide both enantiomers in high optical purity starting from a single substrate. Although many stereodivergent reactions that fall into the category have been developed recently,[15)] the present reaction is unique because both diastereomers were obtained by means of a single reagent and the proper choice of an additive.

We studied the effect of the amount of K-Selectride and 18-Crown-6 on the diastereoselectivity. The results of the reduction of **5a** with K-Selectride in THF at −78 °C are shown in Fig. 1. Diastereoselectivity showed a linear correlation to the amount of 18-Crown-6. This result clearly implies that K-Selectride forms a stable 1 : 1 complex with 18-Crown-6 instantneously and the rate

Table 3. Results of the Reduction of **5a** with Selectride[a)]

Entry	Reducing agent[b)](equiv)	Solvent	Additive[c)]	Yield/%	**5b** : **5c**
1	K (1.2)	THF	—	75	96 : 4
2	K (1.1)	Et_2O	—	54	98 : 2
3	K (1.0)	Toluene	—	82	87 : 13
4	K (1.2)	THF	18-Crown-6	66	4 : 96
5	K (1.2)	Et_2O	18-Crown-6	66	41 : 59
6	K (1.2)	Toluene	18-Crown-6	65	48 : 52
7	L (1.3)	THF	—	77	59 : 41
8	L (1.0)	Et_2O	—	60	98 : 2
9	L (1.3)	THF	12-Crown-4	71	29 : 71
10	L (1.3)	THF	HMPA	68	9 : 91
11	L (1.3)	Et_2O	TMEDA	71	9 : 91

a) The reaction was carried out at −78 °C. b) K; K-Selectride, L; L-Selectride. c) 1.3—1.6 Equivalent of additives were employed.

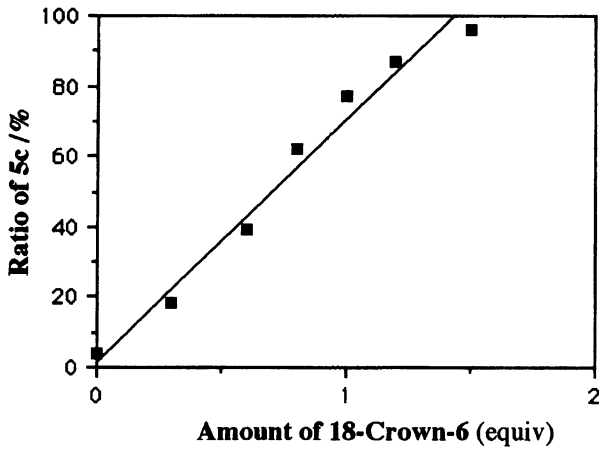


Fig. 1.

of reduction with K-Selectride is approximately identical to that of the reduction with the 1 : 1 complex of K-Selectride and 18-Crown-6.

Next, the effect of the neighboring substituents was studied and the results of the reduction of **6a**, **7a**, **8a**, and **9a** are shown in Table 4 together with those of **4a** and **5a**. Reduction of **5a**, **6a**, **7a**, and **8a** with K-Selectride led to the preferential formation of the corresponding 2*S* isomers. In Et_2O, particularly, the 2*S* isomer was obtained with excellent diastereoselectivity. On the other hand, reduction with K-Selectride in the presence of 18-Crown-6 in Et_2O showed no selectivity, but in THF afforded the corresponding 2*R* isomers exclusively. It is noteworthy that not only the $SiMe_2Bu^t$ substituent but also MON, benzyl, MTM, and even the propyl group worked efficiently as chirality-controlling elements. Methyl ether was not highly effective as a stereo-controlling element.

The stereoselection may be explained as follows (Fig. 2). Selectrides and an α-keto ester form a rigid 5-membered chelated complex (**10**) in Et_2O, thus the α-keto ester is fixed in the *s-cis* conformation. Because the *si*-face of the ketone is blocked by bulky substituents such as *t*-butyldimethylsilyl ether, the hydride attacks the *re*-face of the ketone to produce predominantly the 2*S* isomer.[16] This chelation is stronger in Et_2O than in THF. In contrast, in the presence of 18-Crown-6 or HMPA, which traps metal cations efficiently, formation of the 5-membered chelated complex is less favored and the *s-trans* isomer predominates, and hence the complex hydride attacks the *si*-face of the carbonyl group of **11** to give the 2*R* isomer favorably. Selectrides are classified as a reagent of choice in non-chelation controlled reductions. The present results, however, suggest that the chelation of the metal cation, Li^+ or K^+, plays a crucial role in the diastereoselection in Selectrides reduction.[17]

These results led us to conclude that chiral cyclitols **2** and **3** have proven to be efficient chiral auxiliaries, and that both diastereomers of α-hydroxy esters were obtained highly stereoselectively by the use of K-Selectride as the sole reducing agent either with or without 18-Crown-6. This constitutes the first diastereoselective reduction, which affords both diastereomers from a single metal hydride by the proper choice of additives.

Experimental

The melting points were recorded on a Yamato melting point apparatus and are uncorrected. NMR spectra were observed with a JEOL GSX-270 spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a Hitachi EPI G-3 spectrometer. Specific rotations were recorded with a Union PM-101 digital polarimeter. Purification of products was performed by column chromatography on silica gel (Wako gel C-300) or preparative TLC on silica gel (Wako gel B-5F). K-Selectride and L-Selectride were purchased from Aldrich as 1.0 mol solutions in THF.

1L-1,2:3,4:5,6-Tri-*O*-cyclohexylidene-*chiro*-inositol. 1L-*chiro*-Inositol[7a] (9.61 g, 53.3 mmol), cyclohexanone (22.1 ml, 0.213 mol), and concd H_2SO_4 (2 ml) were heated to reflux for 8 h employing a Dean–Stark separator in a mixture of DMF (30 ml) and benzene (75 ml) to remove H_2O continuously. Benzene was removed in vacuo and ice cold water (50 ml) was added to the remaining solution. The aqueous layer was extracted with ethyl acetate and the combined or-

Table 4. Results of the Reduction of α-Keto Esters with K-Selectride[a)]

Entry	Substrate	R	2S : 2R in THF		2S : 2R in Et_2O	
			—	18-Crown-6	—	18-Crown-6
1	**4a**	CH_2OCH_3	86 : 14	10 : 90	97 : 3	23 : 77
2	**5a**	$SiMe_2Bu^t$	96 : 4	4 : 96	98 : 2	41 : 59
3	**6a**	CH_2Ph	94 : 6	15 : 85	94 : 6	78 : 22
4	**7a**	CH_2SCH_3	80 : 20	9 : 91	94 : 6	39 : 61
5	**8a**	$CH_2CH_2CH_3$	91 : 7	21 : 79	96 : 4	79 : 21
6	**9a**	CH_3	77 : 23	24 : 76	81 : 19	76 : 24

a) Reactions were carried out at −70——78 °C.

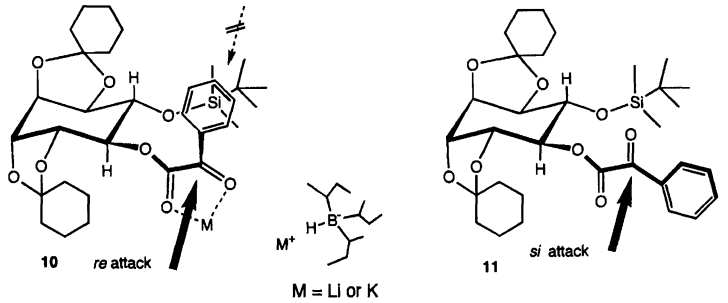


Fig. 2.

ganic layers were successively washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to leave crystals, which were washed with small amount of Et_2O to give 1L-1,2:3,4:5,6-tri-*O*-cyclohexylidene-*chiro*-inositol as colorless crystals (18 g) in an 80% yield. Mp 187—189 °C (MeOH), (lit, 191—192 °C);[13] ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.20—1.96 (30H, m, $(CH_2)_5\times3$), 3.55—3.68 (2H, H-3,4), and 4.26—4.45 (4H, m, H-1,2,5,6); IR (Nujol) 1100 and 1030 cm^{-1}; $[\alpha]_D^{21}$ +19° (*c* 1.1, $CHCl_3$).

1L-1,2:5,6-Di-*O*-cyclohexylidene-*chiro*-inositol (1). To a solution of 1L-1,2:3,4:5,6-tri-*O*-cyclohexylidene-*chiro*-inositol (926 mg, 2.19 mmol) in a mixture of CH_2Cl_2 (4 ml) and CH_3OH (2 ml) was added trifluoroacetic acid (2 ml) at 0 °C. After being stirred at room temperature for 30 min, the reaction mixture was diluted with CH_2Cl_2, quenched by addition of aq 5% $NaHCO_3$ solution and adjusted to pH 7. The solid thus formed was collected by filtration and washed with Et_2O to afford **1** (723 mg) as a crystalline solid in a 97.0% yield. Mp 207—209 °C (CH_3OH) (lit, 209—210 °C);[13] ^{1}H NMR (270 MHz, $CDCl_3$–CD_3OD, v/v=10/1) δ=1.30—1.75 (20H, m, $(CH_2)_{10}$), 2.50 (2H, brs, OH), 3.43—3.53 (2H, m, H-3,4), 4.07—4.22 (2H, m, H-2,5), and 4.31—4.38 (2H, m, H-1,6); IR (Nujol) 3470, 3300, and 1080 cm^{-1}; $[\alpha]_D^{24}$ −24° (*c* 1.1, $CHCl_3$); (lit, $[\alpha]_D^{27}$ −16° (*c* 1.4, $CHCl_3$)).[13] Found: C, 63.39; H, 8.22%. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29%.

1L-1,2:5,6-Di-*O*-cyclohexylidene-3-*O*-methoxymethyl-*chiro*-inositol (2). To a solution of **1** (526 mg, 1.55 mmol) and *N*,*N*-diisopropylethylamine (0.81 ml, 4.6 mmol) in THF (10 ml) was added chloromethyl methyl ether (0.53 ml, 6.95 mmol) at room temperature. After being stirred at 60 °C for 1 h, the reaction mixture was quenched by addition of 5% $KHSO_4$ solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were successively washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to leave crude material, which was purified by column chromatography (SiO_2, ethyl acetate : hexane=1 : 3) to afford **2** (463 mg) as amorphous solids in a 77.7% yield. ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.43—1.72 (20H, m, $(CH_2)_{10}$), 3.46 (3H, s, OCH_3), 3.52—3.62 (2H, m, H-3,4), 4.31—4.35 (2H, m, H-1,6), and 4.82—4.91 (2H, ABq, *J*=6.4 Hz, CH_2); IR ($CHCl_3$) 3500, 2950, 1440, 1200, 1160, and 1100 cm^{-1}; $[\alpha]_D^{21}$ +18.9° (*c* 1.11, $CHCl_3$). Found: C, 62.47; H, 8.33%. Calcd for $C_{20}H_{31}O_7$: C, 62.48; H, 8.39%.

A typical procedure for the acylation of a chiral alcohol with benzoylformic acid chloride[14] is described for the synthesis of **4a**.

1L-3-*O*-Benzoylformyl-1,2:5,6-di-*O*-cyclohexylidene-4-*O*-methoxymethyl-*chiro*-inositol (4a). To a solution of **2** (2.60 g, 6.76 mmol), triethylamine (1.13 ml, 8.10 mmol), and a catalytic amount of 4-dimethylaminopyridine in CH_2Cl_2 (20 ml) was added benzoylformic acid chloride (1.25 g, 7.44 mmol) at 0 °C. After being stirred at room temperature for 0.5 h, the reaction mixture was quenched by addition of 5% $KHSO_4$ solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were successively washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to leave crude material, which was purified by column chromatography (SiO_2, ethyl acetate : hexane=1 : 10) to afford **4a** (6.76 g) in a 96.6% yield. ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.26—1.84 (20H, m, $(CH_2)_{10}$), 3.36 (3H, s, OCH_3), 3.76 (1H, dd, $J_{3,4}$=11.6 Hz, $J_{4,5}$=8.2 Hz H-4), 4.30—4.36 (2H, m, H-2,5), 4.52—4.54 (2H, m, H-1,6), 4.70 and 4.92 (2H, ABq, *J*=6.7 Hz, CH_2), 5.26 (1H, dd, $J_{2,3}$=8.9 Hz, $J_{3,4}$=11.6 Hz, H-3), 7.48—7.55 (2H, m, aromatic), 7.63—7.70 (1H, m, aromatic), and 8.01—8.10 (2H, m, aromatic); IR ($CHCl_3$) 3000, 2930, 1740, 1680, and 1200 cm^{-1}; $[\alpha]_D^{20}$ −65.6° (*c* 1.19, $CHCl_3$).

1L-1,2:5,6-Di-*O*-cyclohexylidene-3-*O*-[(2*S*)-2-hydroxy-2-phenylacetyl]-4-*O*-methoxymethyl-*chiro*-inositol (4b). To a solution of **4a** (211 mg, 0.409 mmol) in Et_2O (1.0 ml) was added K-Selectride (0.694 ml, 0.694

mmol) at −78 °C. After being stirred at that temperature for 0.5 h, the reaction mixture was quenched by addition of 5% $KHSO_4$ solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were successively washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to leave crude material, which was purified by column chromatography (SiO_2, ethyl acetate : hexane=1 : 5) to afford the corresponding alcohol as a mixture of diastereomers (**4b** : **4c**=96 : 4) in an 83% yield. The mixture was recrystallized from a mixture of hexane and ethyl acetate to afford diastereomerically pure **4b**. Mp 144—145 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.38—1.74 (20H, m, $(CH_2)_{10}$), 3.04 (3H, s, OCH_3), 3.24 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{4,5}$=7.6 Hz, H-4), 3.60 (1H, d, J=5.2 Hz, OH), 3.65, 3.89 (2H, ABq, J=6.7 Hz, CH_2), 4.16 (1H, dd, $J_{4,5}$=7.6 Hz, $J_{5,6}$=5.2 Hz, H-5), 4.21 (1H, dd, $J_{1,2}$=5.2 Hz, $J_{2,3}$=8.5 Hz, H-2), 4.38—4.47 (2H, m, H-1,6), 5.04 (1H, dd, $J_{2,3}$=8.5 Hz, $J_{3,4}$=11.3 Hz, H-3), 5.23 (1H, d, J=5.2 Hz, PhC<u>H</u>(OH)), and 7.31—7.46 (5H, m, aromatic); IR ($CHCl_3$) 3450, 1730, 1190, 1100, and 1020 cm^{-1}. Found: C, 64.78; H, 7.39%. Calcd for $C_{28}H_{38}O_9$: C, 64.85; H, 7.39%.

1L-1,2 : 5,6-di-*O*-Cyclohexylidene-3-*O*-[(2*S*)-2-hydroxy-2-phenylacetyl]-4-*O*-methoxymethyl-*chiro*-inositol (4c). To a solution of **4a** (54.2 mg, 0.105 mmol) and 18-Crown-6 (55.5 mg, 0.210 mmol) in THF (0.5 ml) was added K-Selectride (0.178 ml, 0.178 mmol) at −78 °C. After being stirred at that temperature for 15 min, the reaction mixture was quenched by addition of 5% $KHSO_4$ solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were successively washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to leave crude material, which was purified by column chromatography (SiO_2, ethyl acetate : hexane=1 : 5) to afford the alcohol as a mixture of diastereomers (**4b** : **4c**=10 : 90) in a 78% yield. ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.22—1.82 (20H, m, $(CH_2)_{10}$), 3.41 (3H, s, OCH_3), 3.50—3.58 (1H, br, OH), 3.68 (1H, dd, $J_{3,4}$=11.4 Hz, $J_{4,5}$=7.8 Hz, H-4), 4.05 (1H, dd, $J_{1,2}$=5.8 Hz, $J_{2,3}$=8.4 Hz, H-2), 4.29 (1H, dd, $J_{5,6}$=5.8 Hz, $J_{4,5}$=7.8 Hz, H-5), 4.41 (1H, dd, $J_{1,6}$=2.8 Hz, $J_{1,2}$=5.8 Hz, H-1), 4.46 (1H, dd, $J_{1,6}$=2.8 Hz, $J_{5,6}$=5.8 Hz, H-6), 4.67 and 4.87 (2H, ABq, J=7.1 Hz, CH_2), 5.08 (1H, dd, $J_{2,3}$=8.4 Hz, $J_{3,4}$=11.4 Hz, H-3), 5.19—5.28 (1H, br, PhC<u>H</u>(OH)), and 7.32—7.51 (5H, m, aromatic); IR ($CHCl_3$) 3400, 2900, 1720, 1680, 1420, 1340, 1200, 1080, and 900 cm^{-1}.

1L-3-*O*-(*t*-Butyldimethylsilyl)-1,2 : 5,6-di-*O*-cyclohexylidene-*chiro*-inositol (3). To a solution of **1** (2.02 g, 5.92 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.75 ml, 11.8 mmol) in CH_3CN (15 ml) was added a solution of *t*-butylchlorodimethylsilane (1.61 g, 10.7 mmol) in CH_3CN (10 ml) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was quenched by addition of 5% $KHSO_4$ solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were successively washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The solvent was successively evaporated in vacuo to leave crude material, which was purified by column chromatography (SiO_2, ethyl acetate : hexane=1 : 20) to afford **3** (2.39 g) as amorphous solids in an 88.8% yield. ^{1}H NMR (270 MHz, $CDCl_3$) δ=0.15 (3H, s, CH_3), 0.19 (3H, s, CH_3), 0.93 (9H, s, $(CH_3)_3$), 1.38—1.69 (20H, m, $(CH_2)_{10}$), 2.62 (1H, s, OH), 3.52 (2H, m, H-3, 5), 4.07 (1H, m, H-4), and 4.15—4.27 (3H, m, H-1,2,5); IR (Nujol) 3550, 2960, 2400, 1440, 1360, 1200, 1090, and 920 cm^{-1}; $[\alpha]_D^{24}$ +15° (c 2.4, $CHCl_3$). Found: C, 63.89; H, 9.45%. Calcd for $C_{24}H_{42}O_6Si$: C, 63.40; H, 9.31%.

1L-4-*O*-Benzoylformyl-3-*O*-(*t*-butyldimethylsilyl)-1,2 : 5,6-di-*O*-cyclohexylidene-*chiro*-inositol (5a). This was obtained from **3** in a 97% yield. ^{1}H NMR (270 MHz, $CDCl_3$) δ=0.05 (3H, s, CH_3), 0.13 (3H, s, CH_3), 0.87 (9H, s, $(CH_3)_3$), 1.41—1.84 (20H, m, $(CH_2)_{10}$), 3.71 (1H, dd, $J_{3,4}$=11.1 Hz, $J_{2,3}$=7.0 Hz, H-3), 4.22 (1H, dd, $J_{2,1}$=6.1 Hz, $J_{2,3}$=7.0 Hz, H-2), 4.30 (1H, dd, $J_{5,6}$=6.0 Hz, $J_{4,5}$=8.6 Hz, H-5), 4.46 (1H, dd, $J_{1,6}$=3.4 Hz, $J_{2,1}$=6.1 Hz, H-1), 4.50 (1H, dd, $J_{5,6}$=6.0 Hz, $J_{1,6}$=3.4 Hz, H-6), 5.23 (1H, dd, $J_{3,4}$=11.1 Hz, $J_{4,5}$=8.6 Hz, H-4), 7.47—7.53 (2H, m, aromatic), 7.62—7.68 (1H, m, aromatic), and 8.10—8.14 (2H, m, aromatic); IR ($CHCl_3$) 2900, 1730, 1680, 1440, 1340, 1080, and 1040 cm^{-1}; $[\alpha]_D^{24}$ −47° (c 2.8, $CHCl_3$). Found: C, 65.30; H, 7.69%. Calcd for $C_{32}H_{46}O_8Si$: C, 65.50; H, 7.90%.

1L-3-*O*-(*t*-Butyldimethylsilyl)-1,2 : 5,6-di-*O*-cyclohexylidene-4-*O*-[(2*S*)-2-hydroxy-2-phenylacetyl]-*chiro*-inositol (5b). To a solution of **5a** (56 mg, 0.095 mmol) in THF (0.5 ml) was added K-Selectride (0.114 ml, 0.114 mmol) at −78 °C. After being stirred at that temperature for 10 min, the reaction was quenched by addition of 5% $KHSO_4$ solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were successively washed with brine, sat. $NaHCO_3$, and brine, and concentrated to afford an oil. Purification of the crude material with SiO_2 column chromatography (hexane : ethyl acetate=7 : 1) afforded the alcohol as a mixture of diastereomers (**5b** : **5c**=96 : 4) in a 75% yield, which was further purified by thin-layer chromatography to afford diastereomerically pure **5b**. R_f 0.30 (hexane : ethyl acetate=9 : 1); ^{1}H NMR (270 MHz, $CDCl_3$) δ=−0.31 (3H, s, CH_3), −0.03 (3H, s, CH_3), 0.73 (9H, s, $(CH_3)_3$), 1.36—1.65 (20H, m, $(CH_2)_{10}$), 3.32 (1H, d, J=4.9 Hz, OH), 3.62 (1H, dd, $J_{3,4}$=11.2 Hz, H-3), 4.14 (1H, dd, $J_{2,1}$=6.6 Hz, $J_{2,3}$=6.6 Hz, H-2), 4.23 (1H, dd, $J_{5,6}$=5.8 Hz, $J_{4,5}$=8.6 Hz, H-5), 4.36—4.43 (2H, m, H-1,6), 5.00 (1H, dd, $J_{3,4}$=11.2 Hz, $J_{4,5}$=8.6 Hz, H-4), 5.25 (1H, d, J=4.9 Hz, PhC<u>H</u>(OH)), and 7.29—7.50 (5H, m, aromatic); IR ($CHCl_3$) 3500, 2900, 1720, 1440, 1360, 1200, 1080, 1040, and 920 cm^{-1}; $[\alpha]_D^{23}$ −15° (c 0.4, $CHCl_3$). Found: C, 65.27; H, 8.23%. Calcd for $C_{32}H_{48}O_8Si$: C, 65.28; H, 8.22%.

1L-3-*O*-(*t*-Butyldimethylsilyl)-1,2 : 5,6-di-*O*-cyclohexylidene-4-*O*-[(2*R*)-2-hydroxy-2-phenylacetyl]-*chiro*-inositol (5c). To a solution of **5a** (53 mg, 0.091 mmol) and 18-Crown-6 (35.8 mg, 0.136 mmol) in THF (0.5 ml) was added K-Selectride (0.108 ml, 0.108 mmol) at −78 °C. After being stirred at that temperature for 10 min, the reaction was quenched by addition of 5% $KHSO_4$ solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were successively washed with brine, sat. $NaHCO_3$, and brine, and concentrated to afford an oil. Purification of the crude material with SiO_2 column chromatography (hexane : ethyl acetate=7 : 1) afforded the alcohol as a mixture of diastereomers (**5b** : **5c**=4 : 96) in a 66% yield, which was further purified by thin-layer chromatography to afford diastereomerically pure **5c**. R_f 0.33 (hexane : ethyl acetate=9 : 1); ^{1}H NMR (270 MHz, $CDCl_3$) δ=0.09 (3H, s, CH_3), 0.14 (3H, s, CH_3), 0.90 (9H, s, $(CH_3)_3$),

1.30—1.64 (20H, m, $(CH_2)_{10}$), 3.44 (1H, d, J=6.1 Hz, OH), 3.59 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{2,3}$=7.0 Hz, H-3), 3.90 (1H, dd, $J_{5,6}$=6.4 Hz, $J_{4,5}$=8.3 Hz, H-5), 4.15 (1H, t, $J_{2,3}$=$J_{2,1}$=7.0 Hz, H-2), 4.27 (1H, dd, $J_{5,6}$=6.4 Hz, $J_{1,6}$=4.0 Hz, H-6), 4.37 (1H, dd, $J_{1,6}$=4.0 Hz, $J_{2,1}$=7.0 Hz, H-1), 5.03 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{4,5}$=8.3 Hz, H-4), 5.16 (1H, d, J=6.1 Hz, PhC<u>H</u>(OH)), and 7.28—7.46 (5H, m, aromatic); IR ($CHCl_3$) 3500, 1740, and 1080 cm^{-1}; $[\alpha]_D^{23}$ −68° (*c* 1.0, $CHCl_3$). Found: C, 65.00; H, 8.17%. Calcd for $C_{32}H_{48}O_8Si$: C, 65.28; H, 8.22%.

1L-3-*O*-Benzyl-1,2 : 5,6-di-*O*-cyclohexylidene-*chiro*-inositol. Monobenzylation of **1** was best carried out according to the method of Paulsen.[7e] To a suspension of **1** (968 mg, 2.84 mmol), *n*-Bu_4NI (21 mg, 0.057 mmol), and benzyl bromide (0.513 mmol, 4.31 mmol) in CH_2Cl_2 (25 ml) was added 20% NaOH solution at room temperature and the mixture was stirred at 45 °C for 3 h. After addition of CH_2Cl_2 to the reaction mixture, the organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford crude material, which was purified by column chromatography (SiO_2, ethyl acetate : hexane=1 : 6) to afford 1L-3-*O*-benzyl-1,2 : 5,6-di-*O*-cyclohexylidene-*chiro*-inositol as crystalline solids (2.39 g) in an 89% yield. Mp 60.5—62.0 °C (hexane–Et_2O); ^1H NMR (270 MHz, $CDCl_3$) δ=1.30—1.75 (10H, m, $(CH_2)_{10}$), 2.80 (1H, brs, OH), 3.41 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{4,5}$=6.0 Hz, H-4), 3.63 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{2,3}$=7.0 Hz, H-3), 4.15—4.33 (4H, m, H-1,2,5,6), 4.65 and 4.98(2H, ABq, J=11.3 Hz, CH_2), and 7.25—7.40 (5H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ=137.75, 128.46, 128.11, 127.92, 110.57, 110.39, 79.48, 78.62, 77.94, 76.87, 76.36, 72.97, 71.56, 37.62, 37.49, 34.49, 34.40, 24.99, 24.05, 23.89, 23.70, and 23.49; $[\alpha]_D^{24}$ +30 ° (*c* 1.0, $CHCl_3$).

1L-3-*O*-Benzoylformyl-4-*O*-benzyl-1,2 : 5,6-di-*O*-cyclohexylidene-*chiro*-inositol (6a). This was obtained from 1L-3-*O*-benzyl-1,2 : 5,6-di-*O*-cyclohexylidene-*chiro*-inositol in a 100% yield. ^1H NMR (270 MHz, $CDCl_3$) δ=1.28—1.87 (20H, m, $(CH_2)_{10}$), 3.57 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{4,5}$=7.3 Hz, H-4), 4.33 (1H, dd, $J_{3,2}$=8.5 Hz, $J_{2,1}$=5.8 Hz, H-2), 4.42 (1H, dd, $J_{5,6}$=6.1 Hz, $J_{4,5}$=7.3 Hz, H-5), 4.48 (1H, dd, $J_{1,6}$=2.7 Hz, $J_{2,1}$=5.8 Hz, H-1), 4.53 (1H, dd, $J_{1,6}$=2.7 Hz, $J_{5,6}$=6.1 Hz, H-6), 4.69 and 4.92 (2H, ABq, J=11.6 Hz, CH_2Ph), 5.32 (1H, dd, $J_{3,2}$=8.5 Hz, $J_{3,4}$=11.3 Hz, H-3), 7.18—7.43 (7H, m, aromatic), 7.55—7.64 (1H, m, aromatic), and 7.95—8.06 (2H, m, aromatic); IR ($CHCl_3$) 2930, 2850, 1740, 1680, 1590, 1440, 1360, 1270, 1170, 1090, 1040, 990, and 920 cm^{-1}. Found: C, 70.60; H, 6.72%. Calcd for $C_{33}H_{38}O_8$: C, 70.44; H, 6.81%.

1L-4-*O*-Benzyl-1,2 : 5,6-di-*O*-cyclohexylidene-3-*O*-(2-hydroxy-2-phenylacetyl)benzoylformyl-*chiro*-inositol (6b and 6c). ^1H NMR (270 MHz, $CDCl_3$) δ=1.21—1.79 (21H, m, $(CH_2)_{10}$+OH), 3.25 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{4,5}$=7.3 Hz, H-4(*S*)), 3.40 (1H, brs, OH), 3.45 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{4,5}$=7.3 Hz, H-4(*R*)), 3.91 and 4.33 (2H, ABq, J=12.2 Hz, CH_2Ph (*S*)), 3.97 (1H, dd, $J_{3,2}$=8.2 Hz, $J_{2,1}$=6.1 Hz, H-2(*S*)), 4.23 (1H, dd, $J_{3,2}$=8.2 Hz, $J_{2,1}$=6.1 Hz, H-2(*R*)), 4.26 (1H, dd, $J_{4,5}$=7.3 Hz, $J_{5,6}$=6.1 Hz, H-5), 4.39 (1H, dd, $J_{1,6}$=3.1 Hz, $J_{2,1}$=6.1 Hz, H-1), 4.42 (1H, dd, $J_{1,6}$=3.1 Hz, $J_{5,6}$=6.1 Hz, H-6), 4.64 and 4.87 (2H, ABq, J=12.2 Hz, $PhCH_2$(*R*)), 5.12 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{3,2}$=8.2 Hz, H-3), 5.25 (1H, s, PhC<u>H</u>(OH)), 6.87—6.98 (2H, m, aromatic), 7.10—7.46 (6H, m, aromatic), and 7.27—7.43 (2H, m, aromatic); IR ($CHCl_3$) 3550, 3000, 2950, 2860, 1740, 1490, 1440, 1360, 1330, 1230, 1170, 1090, 1070, 1050, 990, 920, and 840 cm^{-1}. Found: C, 70.06; H, 7.30%. Calcd for $C_{33}H_{40}O_8$: C, 70.19; H, 7.14%.

1L-1,2 : 5,6-Di-*O*-cyclohexylidene-3-*O*-methylthiomethyl-*chiro*-inositol. To a solution of **1** (351 mg, 1.03 mmol) in *N*,*N*-dimethylformamide (10 ml) was added sodium hydride (54 mg, 1.35 mmol), followed by chloromethyl methyl sulfide (0.175 ml, 2.09 mmol) at 0 °C. After being stirred at room temperature for 10 h, the reaction mixture was quenched by addition of 5% $KHSO_4$ solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were successively washed with sat. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to leave crude material, which was purified by column chromatography (SiO_2, ethyl acetate : hexane=1 : 5) to afford 1L-1,2 : 5,6-di-*O*-cyclohexylidene-3-*O*-methylthiomethyl-*chiro*-inositiol (186 mg) in a 45% yield. ^1H NMR (270 MHz, $CDCl_3$) δ=1.21—1.78 (21H, m, $(CH_2)_{10}$+OH), 2.21(3H, s, SCH_3), 3.58 (1H, dd, J=11.3 and 7.6 Hz), 3.69 (1H, dd, J=11.3 and 7.3 Hz), 4.17—4.22 (2H, m, H-2,5), 4.31—4.35 (2H, m, H-1,6), and 4.92 and 4.96 (2H, ABq, J=11.6 Hz, OCH_2S); IR ($CHCl_3$) 3600, 3020, 2950, 2860, 1500, 1470, 1420, 1360, 1330, 1270, 1160, 1090, 1040, 960, 920, 870, 840, and 720 cm^{-1}; $[\alpha]_D^{22}$ −69° (*c* 1.0, $CHCl_3$). Found : C, 59.78; H, 8.10%. Calcd for $C_{20}H_{32}O_6S$: C, 59.98; H, 8.05%.

1L-4-*O*-Benzoylformyl-1,2 : 5,6-di-*O*-cyclohexylidene-3-*O*-methylthiomethyl-*chiro*-inositol (7a). This was prepared from 1L-1,2 : 5,6-di-*O*-cyclohexylidene-3-*O*-methylthiomethyl-*chiro*-inositol in a 97% yield. ^1H NMR (270 MHz, $CDCl_3$) δ=1.29—1.88 (20H, m, $(CH_2)_{10}$), 2.09 (3H, s, CH_3S), 3.40 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{3,2}$=7.9 Hz, H-3), 4.29—4.38 (2H, m, H-2,5), 4.52—4.56 (2H, m, H-1, 6), 4.84 and 5.00 (2H, ABq, J=11.6 Hz, OCH_2S), 5.27 (1H, dd, $J_{4,5}$=8.5 Hz, $J_{3,4}$=11.3 Hz, H-4), 7.45—7.58 (2H, m, aromatic), 7.60—7.71 (1H, m, aromatic), and 8.01—8.13 (2H, m, aromatic); IR (Nujol) 3070, 2850, 1730, 1680, 1590, 1570, 1440, 1360, 1270, 1240, 1220, 1170, 1090, 1000, 970, 920, 900, 840, 820, 770, and 730 cm^{-1}. Found: C, 63.20; H, 6.80%. Calcd for $C_{28}H_{36}O_8S$: C, 63.14; H, 6.81%.

1L-Benzoylformyl-1,2 : 5,6-di-*O*-cyclohexylidene-4-*O*-(2-hydroxy-2-phenylacetyl)-3-*O*-methylthiomethyl-*chiro*-inositol (7b and 7c). ^1H NMR (270 MHz, $CDCl_3$) δ=1.20—1.80 (21H, m, $(CH_2)_{10}$+OH), 1.79 (3H, s, CH_3S(*S*)), 2.14 (3H, s, CH_3S(*R*)), 3.58 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{3,2}$=7.9 Hz, H-3(*S*)), 3.83 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{3,2}$=7.6 Hz, H-3(*R*)), 3.79 and 4.10 (2H, ABq, J=11.3 Hz, OCH_2S(*R*)), 4.03 (1H, dd, $J_{4,5}$=8.6 Hz, $J_{5,6}$=5.8 Hz, H-5(*R*)), 4.16 (1H, dd, $J_{1,2}$=5.5 Hz, $J_{3,2}$=7.9 Hz, H-2(*S*)), 4.22 (1H, dd, $J_{4,5}$=8.9 Hz, $J_{5,6}$=5.2 Hz, H-5(*S*)), 4.27 (1H, dd, $J_{1,2}$=6.1 Hz, $J_{3,2}$=7.6 Hz, H-2(*R*)), 4.33—4.50 (2H, m, H-1,6), 4.79 and 4.92 (2H, ABq, J=11.3 Hz, OCH_2S(*S*)), 5.04 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{4,5}$=8.7 Hz, H-4), 5.18 (1H, s, PhC<u>H</u>(OH)(*R*)), 5.22 (1H, s, PhC<u>H</u>(OH)(*S*)), and 7.26—7.50 (5H, m, aromatic); IR ($CHCl_3$) 3700, 3630, 2950, 2400, 1740, 1500, 1470, 1420, 1090, 1040, 920, 870, and 720 cm^{-1}. Found: C, 62.52; H, 7.10%. Calcd for $C_{28}H_{38}O_8S$: C, 62.90; H, 7.16%.

1L-1,2 : 5,6-Di-*O*-cyclohexylidene-3-*O*-propyl-*chiro*-inositol. To a solution of **1** (778 mg, 2.29 mmol) and *n*-Bu_4NI (42 mg, 0.11 mmol) in *N*,*N*-dimethylformamide

(15 ml) was added sodium hydride (111 mg, 2.78 mmol), followed by 1-iodopropane (0.446 ml, 4.57 mmol) at 0 °C. After being stirred at room temperature for 8 h, the reaction mixture was quenched by addition of 5% $KHSO_4$ solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were successively washed with sat. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to leave crude material, which was purified by column chromatography (SiO_2, ethyl acetate : hexane=1 : 5) to afford 1L-1,2 : 5,6-di-*O*-cyclohexylidene-3-*O*-propyl-*chiro*-inositol as a crystalline solid (532 mg) in a 60.8% yield. Mp 118—119 °C (Et_2O–hexane); ^1H NMR (270 MHz, $CDCl_3$) δ=0.95 (3H, t, J=7.5 Hz, CH_3), 1.27—1.78 (22H, m, $(CH_2)_{10}+CH_2$), 2.71—2.95 (1H, br, OH), 3.24 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{2,3}$=6.7 Hz, H-3), 3.44—3.60 (2H, m, OCH_2O), 3.87 (1H, dt, $J_{3,4}=J_{4,OH}$=11.3 Hz, $J_{4,5}$=9.5 Hz, H-4), 4.13—4.29 (4H, m, H-1,2,5,6); IR ($CHCl_3$) 3630, 3030, 2940, 2400, 1500, 1470, 1410, 1090, 1040, and 920 cm^{-1}; $[\alpha]_D^{20}$ +29° (*c* 1.0, $CHCl_3$). Found: C, 65.50; H, 9.28%. Calcd for $C_{21}H_{34}O_6$: C, 65.94; H, 8.96%.

1L-3-*O*-Benzoylformyl-1,2 : 5,6-di-*O*-cyclohexylidene-4-*O*-propyl-*chiro*-inositol (8a). This was prepared from 1L-1,2 : 5,6-di-*O*-cyclohexylidene-3-*O*-propyl-*chiro*-inositol in a 100% yield. ^1H NMR (270 MHz, $CDCl_3$) δ=0.88 (3H, t, J=7.0 Hz, CH_3), 1.28—1.85 (22H, m, $(CH_2)_{10}+CH_2$), 3.40 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{4,5}$=7.6 Hz, H-4), 3.52 (1H, dt, J=9.2 and 6.7 Hz, OCH_2), 3.78 (1H, dt, J=9.2 and 6.7 Hz, OCH_2), 4.30 (1H, dd, $J_{5,6}$=6.1 Hz, $J_{4,5}$=7.6 Hz, H-5), 4.32 (1H, dd, $J_{1,2}$=5.8 Hz, $J_{2,3}$=7.3 Hz, H-2), 4.48 (1H, dd, $J_{1,2}$=5.8 Hz, $J_{1,6}$=2.8 Hz, H-1), 4.50 (1H, dd, $J_{5,6}$=6.1 Hz, $J_{1,6}$=2.8 Hz, H-6), 5.24 (1H, dd, $J_{2,3}$=7.3 Hz, $J_{3,4}$=11.3 Hz, H-3), 7.44—7.55 (2H, m, aromatic), 7.60—7.70 (1H, m, aromatic), and 8.03—8.12 (2H, m, aromatic); IR (Nujol) 2950, 2860, 1740, 1680, 1590, 1440, 1360, 1280, 1170, 1100, 1000, and 930 cm^{-1}; $[\alpha]_D^{22}$ −73° (*c* 1.0, $CHCl_3$). Found: C, 67.60; H, 7.64%. Calcd for $C_{29}H_{38}O_8$: C, 67.69; H, 7.44%.

1L-1,2 : 5,6-Di-*O*-cyclohexylidene-3-*O*-(2-hydroxy-2-phenylacetyl)-4-*O*-propyl-*chiro*-inositol (8b and 8c). ^1H NMR (270 MHz, $CDCl_3$) δ=0.60 (3H, t, J=7.2 Hz, $CH_3(S)$), 0.89 (3H, t, J=7.2 Hz, $CH_3(R)$), 0.94—1.20 (2H, m, CH_2), 1.24—1.78 (22H, m, $(CH_2)_{10}+CH_2$), 2.26—2.58 (1H, brs, OH), 2.58—2.73 (1H, m, $OCH_2(S)$), 3.07 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{4,5}$=7.6 Hz, H-4(*S*)), 3.12—3.24 (1H, m, $OCH_2(S)$), 3.29 (1H, dd, $J_{3,4}$=11.5 Hz, $J_{4,5}$=7.5 Hz, H-4(*R*)), 3.37—3.47 (1H, m, $OCH_2(R)$), 3.70—3.80 (1H, m, $OCH_2(R)$), 4.02 (1H, dd, $J_{1,2}$=6.1 Hz, $J_{2,3}$=8.5 Hz, H-2(*R*)), 4.15 (1H, dd, $J_{5,6}$=5.2 Hz, $J_{4,5}$=7.6 Hz, H-5(*S*)), 4.23 (1H, dd, $J_{2,3}$=8.5 Hz, $J_{1,2}$=5.0 Hz, H-2(*S*)), 4.23 (1H, dd, $J_{4,5}$=7.5 Hz, $J_{5,6}$=6.1 Hz, H-5(*R*)), 4.33 (1H, dd, $J_{1,6}$=3.4 Hz, $J_{1,2}$=6.1 Hz, H-1(*R*)), 4.37—4.45 (2H, m, H-1,6(*S*)), 4.40 (1H, dd, $J_{5,6}$=6.1 Hz, $J_{1,6}$=3.4 Hz, H-6(*R*)), 5.00 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{2,3}$=8.5 Hz, H-3(*S*)), 5.02 (1H, dd, $J_{2,3}$=8.5 Hz, $J_{3,4}$=11.5 Hz, H-3(*R*)), 5.19 (1H, s, PhC<u>H</u>(OH)(*S*)), 5.25 (1H, s, PhC<u>H</u>(OH)(*S*)), 7.27—7.40 (3H, m, aromatic), and 7.40—7.51 (2H, m, aromatic); IR (Nujol) 3620, 3000, 2930, 2400, 1730, 1500, 1460, 1410, 1320, 1090, 1040, 920, 870, and 720 cm^{-1}. Found: C, 67.10; H, 7.79%. Calcd for $C_{29}H_{40}O_8$: C, 67.42; H, 7.80%.

1L-1,2 : 5,6-Di-*O*-cyclohexylidene-3-*O*-methyl-*chiro*-inositol. To a solution of **1** (2.01 g, 5.90 mmol) and powdered KOH (671 mg, 12.0 mmol) in a mixture of CH_3CN (50 ml), dimethyl sulfoxide (17 ml), and *N*,*N*-dimethylformamide (2 ml) was added methyl iodide (0.99 ml, 15.9 mmol). After being stirred at room temperature overnight, the reaction mixture was quenched by addition of 5% $KHSO_4$ solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were successively washed with sat. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to leave crude material, which was purified by column chromatography (SiO_2, ethyl acetate : hexane=1 : 3) to afford 1L-1,2 : 5,6-di-*O*-cyclohexylidene-3-*O*-methyl-*chiro*-inositol (1.48 g) as crystalline solids in a 70.7% yield. Mp 110—111 °C (ethyl acetate–hexane); ^1H NMR (270 MHz, $CDCl_3$) δ=1.29—1.76 (20H, m, $(CH_2)_{10}$), 2.76—2.89 (1H, br, OH), 3.16 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{2,3}$=7.3 Hz, H-3), 3.56 (1H, dd, $J_{4,5}$=6.7 Hz, $J_{3,4}$=11.3 Hz, H-4), 3.60 (3H, s, OCH_3), and 4.13—4.30 (4H, m, H-1,2,5,6); IR (Nujol) 3450, 1160, and 1090 cm^{-1}; $[\alpha]_D^{20}$ +34° (*c* 1.0, $CHCl_3$). Found: C, 64.15; H, 8.65%. Calcd for $C_{19}H_{30}O_6$: C, 64.39; H, 8.53%.

1L-3-*O*-Benzoylformyl-1,2 : 5,6-di-*O*-cyclohexylidene-4-*O*-methyl-*chiro*-inositol (9a). This was prepared from 1L-1,2 : 5,6-di-*O*-cyclohexylidene-3-*O*-methyl-*chiro*-inositol in a 97% yield. ^1H NMR (270 MHz, $CDCl_3$) δ=1.26—1.74 (20H, m, $(CH_2)_{10}$), 3.27 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{4,5}$=8.5 Hz, H-4), 3.53 (3H, s, OCH_3), 4.27 (1H, dd, $J_{1,2}$=5.8 Hz, $J_{2,3}$=7.6 Hz, H-2), 4.29 (1H, dd, $J_{5,6}$=5.8 Hz, $J_{4,5}$=8.5 Hz, H-5), 4.43—4.48 (2H, m, H-1,6), 5.19 (1H, dd, $J_{2,3}$=7.6 Hz, $J_{3,4}$=11.3 Hz, H-3), 7.42—7.53 (2H, m, aromatic), 7.57—7.68 (1H, m, aromatic), and 7.98—8.10 (2H, m, aromatic); IR (Nujol) 1750, 1685, 1590, 1270, 1195, 1090, 1000, and 920 cm^{-1}; $[\alpha]_D^{17.5}$ −73° (*c* 1.0, $CHCl_3$). Found: C, 66.51; H, 7.03%. Calcd for $C_{27}H_{34}O_8$: C, 66.65; H, 7.04%.

1L-1,2 : 5,6-di-*O*-Cyclohexylidene-3-*O*-(2-hydroxy-2-phenylacetyl)-4-*O*-methyl-*chiro*-inositol (9b and 9c). ^1H NMR (270 MHz, $CDCl_3$) δ=1.27—1.77 (21H, m, $(CH_2)_{10}$+OH), 2.27 (3H, s, $OCH_3(S)$), 2.87 (1H, dd, $J_{3,4}$=11.3 Hz, $J_{4,5}$=7.6 Hz, H-4), 3.44 (3H, s, $OCH_3(R)$), 3.99 (1H, dd, $J_{5,6}$=5.2 Hz, $J_{4,5}$=7.6 Hz, H-5(*R*)), 4.10 (1H, dd, $J_{5,6}$=5.2 Hz, $J_{4,5}$=7.6 Hz, H-5(*S*)), 4.19 (1H, dd, $J_{1,2}$=5.2 Hz, $J_{2,3}$=8.6 Hz, H-2), 4.26—4.42 (2H, m, H-1,6), 4.94 (1H, dd, $J_{2,3}$=8.6 Hz, $J_{3,4}$=11.3 Hz, H-3), 5.20 (1H, br, PhC<u>H</u>(OH)), and 7.20—7.49 (5H, m, aromatic); IR (neat) 3450, 2930, 2850, 1740, 1440, 1360, 1320, 1270, 1160, 1090, 920, and 840 cm^{-1}. Found: C, 65.10; H, 8.30%. Calcd for $C_{27}H_{36}O_8$: C, 66.38; H, 7.43%.

A typical procedure for the hydrolysis of α-hydroxy esters is described for the hydrolysis of **5c** to (*R*)-mandelic acid.

To a solution of **5c** (63.0 mg, 0.11 mmol) in a mixture of tetrahydrofuran (0.4 ml), methanol (0.1 ml), and H_2O (0.1 ml) was added LiOH (9.0 mg, 0.214 mmol) at 0 °C. After being stirred for 1 h at that temperature, and another 30 min at room temperature, the mixture was quenched by addition of sat. $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with brine and concentrated to obtain **3** (49 mg) in a 100% yield. After the aqueous layer was acidified to pH 1 by addition of 2 mol dm^{-3} HCl, it was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give crude (*R*)-mandelic acid, which was distilled by Kugel Rohr (180 °C, 0.6 mmHg, 1 mmHg=133.322 Pa) to furnish pure (*R*)-mandelic acid (12.9 mg, 79%). $[\alpha]_D^{28}$ −155° (*c* 0.63, H_2O). (lit., *S*-iso-

mer 158° (H_2O))[18] Esterification of the mandelic acid with diazomethane afforded methyl mandelate. The optical purity of the ester was confirmed to be >98% ee by HPLC analysis (column, Daicel Chemical Co., CHIRALCEL OD; eluent, hexane : 2−propanol=50 : 1; flow rate, 1.0 ml min^{-1}; detection, 254-nm light).

Basic hydrolysis of **4b** to (*S*)-mandelic acid, carried out similarly, afforded optically pure (*S*)-mandelic acid. The HPLC analysis of its methyl mandelate showed that the optical purity of the mandelic acid was >98% ee.

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