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Synthesis of Pure Enantiomers of a New Diol Ligand, *trans*-4,5-Bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane

Hidetoshi Yamamoto, Shigeru Kobayashi,† and Shuji Kanemasa*

Institute of Advanced Material Study, Kyushu University, Kasugakoen, Kasuga 816, Japan

†Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasugakoen, Kasuga 816, Japan

Abstract: A new chiral diol, *trans*-4,5-bis(2-hydroxyphenyl)-1,3-dioxolane, was synthesized by the reductive coupling of *O*-benzylated salicylaldehyde with a low-valent titanium reagent followed by acetalization and deprotection. Resolution of the diol was achieved through a sequence of esterification with *O*-methylmandelic acid, chromatographic separation and purification, and methanolysis.

Design and synthesis of new effective chiral catalysts is one of the most essential subjects in the area of asymmetric synthesis. Although a variety of chiral ligands such as diols, diamines, diphosphines and others have been successfully utilized for the structural modification of metal catalysts in asymmetric syntheses,[1] development of new chiral ligands is still strongly desired from the standpoints of high catalytic activity (or reactivity), high stereoselectivity, and efficient catalytic cycle. Establishment of a general rule for highly effective catalytic chiral induction would be a final target.

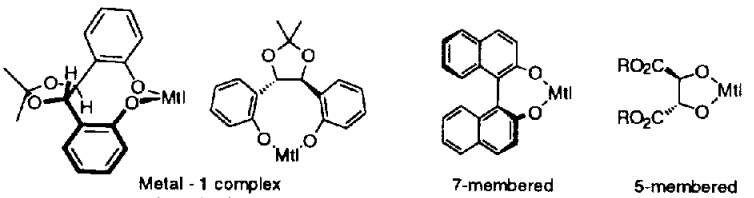


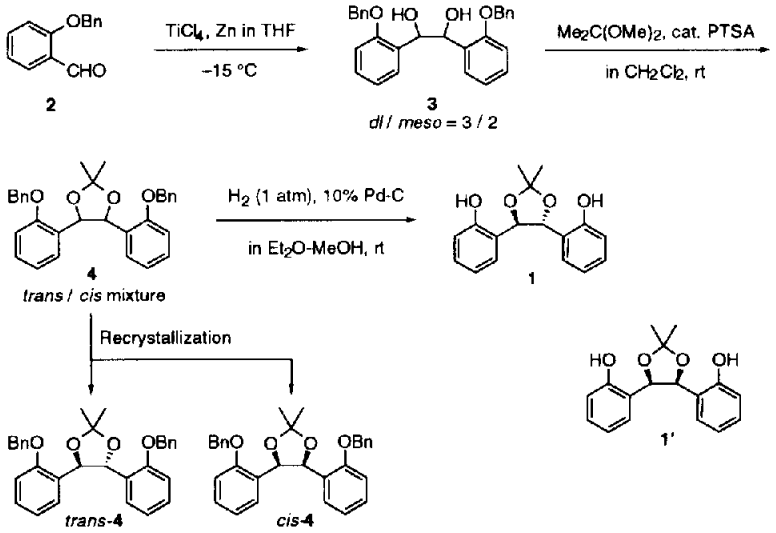
Figure 1.

As a part of our investigations on the new methodology for asymmetric synthesis, a new chiral aromatic diol, *trans*-4,5-bis(2-hydroxyphenyl)-1,3-dioxolane, was chosen. This diol has the following structural features: (1) It has a 1,6-diol structure of the substituted phenol type which forms 9-membered C_2-symmetric metal complexes.[2] (2) The resulting complex catalysts may be able to stabilize a variety of transition state structures due to its structural flexibility and the open space around the metal center. Since the increased flexibility might decrease the thermodynamic stability of the resulting metal complexes, the two *o*-hydroxyphenyl moieties are designed to bind to a five-membered ring trans to each other. (3) The two phenylene planes make

C_2-symmetric shielding walls effective for high chiral inductions in reactions. In the present paper, the synthesis and optical resolution of the title diol is described.

Synthesis of *trans*-4,5-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane **1** is shown in Scheme 1. The first step of the synthesis involves the reductive coupling of the *O*-protected salicylaldehyde **2**. Although a number of reducing reagents[3] have been utilized for the reductive coupling reactions of aldehydes, including Mg/MgI_2,[4] Sm (II),[5] Yb,[6] and Ce/I_2,[7] these reactions offer 1,2-diols with low *dl*/*meso* selectivities. In the present work, a low-valent titanium reagent[8] was employed because of its high reactivity and easy preparation. Thus, *o*-(benzyloxy)benzaldehyde **2**, prepared from salicylaldehyde and benzyl bromide in THF at –15 °C, was treated with the titanium reagent (prepared in situ from titanium tetrachloride and zinc powder) at –15 °C to provide the 1,2-diol **3** as a 3:2 mixture of *dl*- and *meso*-isomers. A lower reaction temperature improved *dl*/*meso* selectivity of the diol, but the yield was lowered.

Separation of the *dl*- and *meso*-isomers of **3** from each other by column chromatography or crystallization was unsuccessful. Accordingly, the diol mixture was transformed, without separation, to acetonide **4** as a mixture of *trans*- and *cis*-isomers. Careful crystallization of the *trans*/*cis*-isomer mixture from diethyl ether - hexane gave two forms of crystals, prisms (*trans*-**4**) and needles (*cis*-**4**). Although hand-picking separation of the two crystalline forms provided pure isomers, this separation procedure is not practical. Hydrogenolysis of the acetal mixture **4** was performed on 10% Pd-C at room temperature in diethyl ether - methanol (2/1 v/v) at the atmospheric pressure of hydrogen. Although two kinds of benzylic carbon - oxygen bonds exist in acetonide **4**, the C(3)-C(4) bonds of the dioxolane ring remained intact and debenzylation was the only reaction observed. However, under more severe conditions, 1,2-bis(2-hydroxyphenyl)ethane was formed as an overreduction product. Separation of the *trans*/*cis* stereoisomers by column chromatography led to the desired *trans*(or *rac*)-4,5-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane *rac*-**1**.

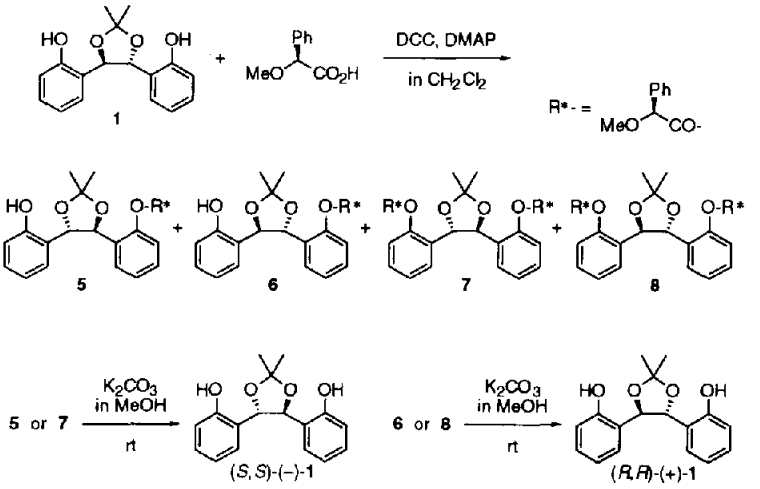


Scheme 1.

Resolution of **1** was achieved *via* esterification[9] with an enantiomerically pure carboxylic acid. Reaction of *rac*-**1** with enantiomerically pure (*S*)-*O*-methylmandelic acid[10] in the presence of dicyclohexylcarbodiimide in

the presence of a catalytic amount of 4-(dimethylamino)pyridine gave two diastereomers of monoesters **5**, **6** along with a small amount of two diastereomers of diesters **7**, **8** (Scheme 2). These four esters **5-8** could be separated and purified through a silica gel column chromatography and crystallization from diethyl ether - hexane. Removal of the chiral auxiliary was performed by transesterification using methanol in the presence of potassium carbonate at room temperature, where no racemization took place. Esters **5** and **7** produced the enantiomer (–)-**1**, while esters **6** and **8** led to the other enantiomer (+)-**1**. The enantiomeric purity of the resulting diols **1** was determined to be perfect by the HPLC analysis using Chiralcel OJ (Daicel, hexane/2-propanol = 1/1 v/v).

The absolute configuration of diols (–)-**1** and (+)-**1** was determined on the basis of the X-ray structural analysis of diester **7**. The X-ray-assigned structure of **7** is shown in Figure 2. The absolute configurations at the C4 and C5 positions of the dioxolane ring were assigned to be 4*S*,5*S* based on the relative stereochemistry to the known configuration of the auxiliary ester. Accordingly, it is concluded that monoester **5** and (–)-**1** have the absolute configuration of 4*S*,5*S* with respect to the stereogenic centers of the dioxolane ring; monoester **6**, diester **8**, and (+)-**1** were determined to be 4*R*,5*R* stereostructures.



Scheme 2.

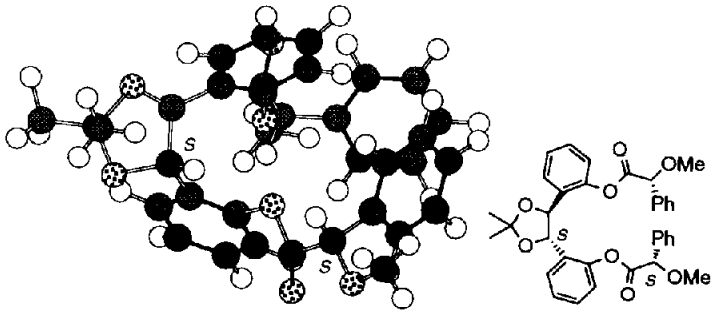


Figure 2. The stereostructure of (4*S*,5*S*)-diester **7** determined by X-ray crystal analysis.

Use of the diol **1** either for the preparation of homochiral metal complexes or as chiral promotor[11,12] is now under investigation in our laboratory. The results will be reported in due time.

Experimental

Reductive Coupling of *o*-(Benzyloxy)benzaldehyde with $TiCl_4$/Zn. To a solution of $TiCl_4$ (4.9 ml, 45 mmol) in dry THF (150 ml) was added Zn powder (5.88 g, 90 mmol) at –15 °C under nitrogen. After stirring for 30 min, *o*-(benzyloxy)benzaldehyde (**2**, 6.36 g, 30 mmol) was added, the mixture was stirred at –15 °C for additional 3.5 h, quenched with 10% aqueous $NaHCO_3$ (300 ml), and extracted with Et_2O (250 ml × 3). The combined extracts were washed with saturated aqueous $NaHCO_3$ (250 ml) and brine (250 ml), dried over anhydrous $MgSO_4$, and evaporated in vacuo to give the crude diol **3** (6.35 g). Crystallization from hexane - CH_2Cl_2 gave 1,2-bis(2-benzyloxyphenyl)-1,2-ethanediol **3** (4.65 g, 73%) as a 3/2 mixture of *dl*/*meso* stereoisomers. Colorless needles; mp 111.5-112.5 °C; IR (KBr) 3421, 3037, 2864, 1600, 1589, 1494, 1540, 1379, 1336, 1293, 1237, 1160, 1106, 1024, 854, 738, 696, 627, 573, and 482 cm^{-1}; ^1H NMR ($CDCl_3$) *dl*-isomer: δ = 3.57 (2H, m, OH), 4.54, 4.69 (each 2H, d, J_{gem} = 11.7 Hz, $PhCH_2$), 5.07 (2H, m, H-1 and H-2), 6.67 (2H, d, J = 8.1 Hz, Ar), 6.83 (2H, m, Ar), and 7.11 - 7.37 (14H, m, Ar). *meso*-isomer: δ = 2.96 (2H, m, OH), 4.69, 4.84 (each 2H, d, J_{gem} = 11.7 Hz, $PhCH_2$), 5.35 (2H, m, H-1 and H-2), 6.76 (2H, d, J = 8.3 Hz, Ar), and 6.86 (2H, m, Ar). The other signals are overlapping with those of *dl*-isomer; ^{13}C NMR ($CDCl_3$) *dl*-isomer: δ = 69.82 ($PhCH_2$), 74.83 (C-1 and C-2), 111.46, 120.70, 127.44, 127.97, 128.46, 128.52, 128.55, 128.55, 136.76, and 156.22 (each Ar). *meso*-isomer: δ = 69.88 ($PhCH_2$), 73.32 (C-1 and C-2), 111.52, 120.70, 127.28, 127.89, 128.30, 128.81, 136.90, and 156.02 (each Ar). The other signals are overlapping with those of *dl*-isomer; Mass (70 eV) *m/z* (rel intensity, %) 214 (13), 213 (44, $M^+/2$), 123 (24), 122 (31), 121 (41), 92 (61), 91 (base peak), 90 (58), 77 (12), and 65 (35). Anal. Found: C, 78.59; H, 6.15%. Calcd for $C_{28}H_{26}O_4$: C, 78.85; H, 6.14%.

Acetalization of 1,2-Bis(2-benzyloxyphenyl)-1,2-ethanediol. The *dl*/*meso* mixture of **3** (3:2, 3.27 g, 7.67 mmol), 2,2-dimethoxypropane (1.42 ml, 11.5 mmol), and a catalytic amount of *p*-TsOH in CH_2Cl_2 (15 ml) was stirred at room temperature for 30 min, quenched with saturated aqueous $NaHCO_3$ (20 ml), and extracted with CH_2Cl_2 (20 ml × 4). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to give a pale yellow viscous oil (3.73 g). The residual oil was chromatographed on silica gel with hexane - Et_2O (7/1 v/v) to yield a mixture of *trans*- and *cis*-4,5-bis(2-benzyloxyphenyl)-2,2-dimethyl-1,3-dioxolane **4** (3:2, 3.46 g, 97%) as colorless solid. This mixture was used for the following reaction without further purification. The samples for analysis were obtained by crystallization from hexane - Et_2O. ***trans*-4,5-Bis(2-benzyloxyphenyl)-2,2-dimethyl-1,3-dioxolane *trans*-4**: Colorless prisms; mp 108.5 °C; IR (KBr) 3043, 2979, 2940, 2896, 1600, 1589, 1493, 1450, 1371, 1315, 1291, 1256, 1220, 1160, 1106, 1040, 1016, 891, 816, 784, 760, 730, 688, 632, and 507 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.63 (6H, s, Me), 4.62, 4.76 (each 2H, d, J_{gem} = 11.9 Hz, $PhCH_2$), 5.41 (2H, s, H-4 and H-5), 6.75 (2H, dd, Ar), 7.12 - 7.25 (8H, m, Ar), and 7.62 (2H, dd, Ar); ^{13}C NMR ($CDCl_3$) δ = 27.23 (Me), 69.80 ($PhCH_2$), 78.63 (C-4 and C-5), 108.46 (C-2), 111.67, 120.99, 126.01, 126.85, 127.42, 127.86, 128.24, 128.79, 136.96, and 156.65 (each Ar); Mass (20 eV) *m/z* (rel intensity, %) 408 (M^+- Me_2CO, 12), 255 (30), 254 (85), 253 (11), 195 (15), 181 (14), 167 (14), 165 (11), 164 (base peak), 162 (80), 152 (11), 145 (21), 121 (33), 120 (11), 105 (24), 90 (14), 77 (89), and 65 (19). Anal. Found: C, 79.82; H, 6.56%. Calcd for $C_{31}H_{30}O_4$: C, 79.80; H, 6.48%. ***cis*-4,5-Bis(2-benzyloxyphenyl)-2,2-dimethyl-1,3-dioxolane *cis*-4**: Colorless needles; mp 118 °C. IR (KBr) 3024, 2986, 2858, 1589, 1493, 1448, 1374, 1317, 1288, 1224, 1154, 1107, 1048, 1000, 910, 872, 850, 736, 694, 549, 581, 515, and 496 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.60, 1.81 (each 3H, s, Me), 4.61, 4.78 (each 2H, d, J_{gem} = 12.6 Hz, $PhCH_2$), 6.07 (2H, s, H-4 and H-5), 6.55 (2H, d, Ar), 6.73 (2H, t, Ar), 7.01 (2H, m, Ar), and 7.20 - 7.36 (12H, m, Ar); ^{13}C NMR ($CDCl_3$) δ = 24.79, 26.88 (each Me), 69.48 ($PhCH_2$), 74.87 (C-4 and C-5), 107.86 (C-2), 110.88, 119.86, 126.55, 126.79, 127.42, 128.03, 128.30, 128.34, 137.42, and 155.63 (each Ar); Mass (20 eV) *m/z* (rel intensity, %) 254 (4), 164 (14), 163 (82), 162 (9), 121 (21), 105 (12), 92 (11), 91 (base peak), 90 (10), 77 (7), and 65 (7). Anal. Found: C, 79.64; H, 6.56%. Calcd for $C_{31}H_{30}O_4$: C, 79.80; H, 6.48%.

Hydrogenolysis of 4,5-Bis(2-benzyloxyphenyl)-2,2-dimethyl-1,3-dioxolane. A suspension of **4** (2.35 g, 5.04 mmol) and 10% Pd-C (Aldrich Co., 0.152 g, 0.144 mmol) in Et_2O - MeOH (2/1 v/v, 22.5 ml) was stirred under hydrogen (1 atm) at room temperature for 20 h. The catalyst was filtered off through a celite column and the filtrate was evaporated in vacuo to give 4,5-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane (**1+1'**, 1.45 g, 100%) as a colorless solid. Each stereoisomer **1** and **1'** was isolated by chromatography on silica gel with hexane - Et_2O (3/1 v/v). ***trans*-4,5-Bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane 1**: Colorless fine powder (hexane-Et_2O); mp 178.5 - 179 °C; IR (KBr) 3312, 2979, 1600, 1500, 1461, 1368, 1342, 1280, 1221, 1157, 1090, 1066, 1016, 984, 944, 888, 856, 742, 632, 496, and 472 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.74 (6H, s, Me), 5.08 (2H, s, H-4 and H-5), 6.53 (2H, dd, *J* = 7.3 and 1.6 Hz, H-6'), 6.73 (2H, dt, *J* = 7.3, 7.3, and 1.1 Hz, H-5'), 6.91 (2H, dd, *J* = 8.1 and 1.1 Hz, H-3'), 7.21 (2H, ddd, *J* = 8.1, 7.3, and 1.6 Hz, H-4'), and 7.79 (2H, s, OH); ^{13}C NMR ($CDCl_3$) δ = 26.88 (Me), 83.73 (C-4 and C-5), 110.23 (C-2), 117.33 (C-3'), 118.07 (C-1'), 119.91 (C-5'), 128.94 and 130.03 (C-4' and C-6'), and 155.63 (C-2'); Mass (70 eV) *m/z* (rel intensity, %) 286 (M^+, 20), 229 (11), 228 (44, M^+-Me_2CO), 212 (69), 209 (75), 200 (28), 199 (87), 183 (55), 182 (42), 166 (21), 165 (17), 163 (87), 153 (42), 152 (48), 151 (10), 150 (17), 149 (base peak), 148 (17), 147 (41), 146 (88), 145 (41), 135 (59), 132 (16), 131 (84), 123 (48), 118 (25), 108 (30), 104 (12), 93 (11), 79 (24), 76 (16), 65 (30), and 51 (37). Anal. Found: C, 71.48; H, 6.43%. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34%. ***cis*-4,5-Bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane 1'**: Colorless prisms (hexane - Et_2O); mp 181 - 181.8 °C; IR (KBr) 3389, 3222, 2992, 1600, 1500, 1461, 1371, 1248, 1216, 1154, 1102, 1056, 997, 947, 874, 830, 795, 757, 706, and 677 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.62,1.84 (each 3H, s, Me), 5.78 (2H, s, H-4 and H-5), 6.47 (2H, dd, *J* = 8.1 and 1.1 Hz, H-3'), 6.62 (2H, s, OH), 6.66 (2H, dt, *J* = 7.6, 7.6, and 1.1 Hz, H-5'), 6.93 (2H, ddd, *J* = 8.1, 7.6, and 1.9 Hz, H-4'), and 7.08 (2H, dd, *J* = 7.6 and 1.9 Hz, H-6'); ^{13}C NMR ($CDCl_3$) δ = 22.88 and 26.35 (Me), 79.82 (C-4 and C-5), 108.98 (C-2), 115.69 (C-3'), 119.65 (C-5'), 121.98 (C-1'), 128.00 and 128.85 (C-4' and C-6'), and 153.77 (C-2'); Mass (70 eV) *m/z* (rel intensity, %) 286 (M^+, 2), 211 (54), 210 (base peak), 209 (27), 199 (13), 183 (15), 181 (22), 163 (49), 146 (14), 122 (19), 120 (90), 107 (32), 106 (63), 104 (55), 77 (42), and 51 (15). Anal. Found: C, 71.48; H, 6.52%. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34%.

Resolution of 1. A mixture of **1** (1 g, 3.49 mmol), (*S*)-*O*-methylmandelic acid (0.696 g, 4.19 mmol), dicyclohexylcarbodiimide (0.864 g, 4.19 mmol), and 4-(dimethylamino)pyridine (0.043 g, 0.35 mmol) in CH_2Cl_2 (17 ml) was stirred at room temperature for 24 h. After dilution with another portion of CH_2Cl_2 (50 ml), the resulting colorless precipitate was filtered off and washed with CH_2Cl_2. The combined filtrate and washings were evaporated in vacuo and the residue was chromatographed on silica gel with hexane - Et_2O (3/2 v/v) followed by crystallization to afford **1** (0.174 g, 17%), 2-[(4*S*,5*S*)-4-(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolan-5-yl]phenyl (*S*)-1-methoxy-1-phenylacetate **5** (0.342 g, 23%), 2-[(4*R*,5*R*)-4-(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolan-5-yl]phenyl (*S*)-1-methoxy-1-phenylacetate **6** (0.322 g, 21%), 2,2'-[(4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl]diphenyl bis[(*S*)-1-methoxy-1-phenylacetate] **7** (0.061 g, 3%), and 2,2'-[(4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl]diphenyl bis[(*S*)-1-methoxy-1-phenylacetate] **8** (0.048 g, 2%). **5**: Colorless solid; softening point <35 °C; $[\alpha]_D^{24}$ = 71.2 (*c* 0.70, $CHCl_3$); IR (KBr) 3380, 2973, 2909, 1768, 1588, 1493, 1450, 1372, 1232, 1216, 1150, 1104, 1050, 987, 816, 755, 696, 504, and 490 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.63, 1.66 (each 3H, s, Me), 3.37 (3H, s, OMe), 4.38 (1H, s, CH), 4.89, 5.05 (each 1H, d, *J* = 8.8 Hz, H-4' and H-5'), 6.61, 6.69, 6.79, 6.94, 7.21 - 7.35, 7.67 (each 1, 1, 1, 1, 8, and 1H, m, Ar), and 7.91 (1H, br. s, OH); ^{13}C NMR ($CDCl_3$) δ = 26.71, 26.95 (Me), 57.33 (OMe), 77.00 (CH), 81.68, 85.25 (C-4 and C-5), 109.77, 117.13, 119.29, 120.12, 121.92, 126.57, 127.12, 127.47, 128.27, 128.40, 128.63, 128.76, 129.28, 129.64, 135.43, 148.24, 155.57 (each Ar), and 168.53 (C=O); Mass (70 eV) *m/z* (rel intensity, %) 377 (18), 376 (22, M^+-Me_2CO), 359 (19), 358 (17), 328 (39), 327 (51), 326 (18), 314 (94), 313 (24), 311 (base peak), 300 (24), 299 (28), 211 (20), 210 (81), 209 (13), 182 (11), 181 (46), 165 (68), 162 (88), 153 (21), 152 (22), 149 (18), 147 (11), 146 (27), 145 (15), 135 (32), 134 (16), 133 (17), 131 (19), 123 (65), 65 (25), and 51 (57). Anal. Found: C, 72.11; H, 6.20%. Calcd for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03%. **6**: Colorless prisms (hexane - Et_2O); mp 133 - 133.5 °C; $[\alpha]_D^{24}$ = 66.3 (*c* 1.03, $CHCl_3$); IR (KBr) 3363, 3000, 2954, 1771, 1600, 1496, 1458, 1376, 1350, 1219, 1146, 1080, 1040, 1006, 980, 900, 864, 819, 755, 700, 646, and 504 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.56, 1.65 (each 3H, s, Me), 3.27 (3H, s, OMe), 4.28 (1H, s, CH), 4.85, 4.93 (each 1H, d, *J* = 8.8

Hz, H-4' and 5'), 6.51, 6.75, 6.94, 7.12 - 7.40, 7.62 (each 1, 1, 1, 9, and 1H, m, Ar), and 8.07 (1H, br. s, OH); ^{13}C NMR ($CDCl_3$) δ = 26.81 (Me), 56.94 (OMe), 76.54 (CH), 81.58, 85.64 (C-4 and C-5), 109.74, 117.06, 118.80, 120.02, 121.69, 126.13, 127.34, 127.44, 127.50, 127.90, 128.85, 128.92, 129.12, 129.64, 135.43, 148.20, 155.46 (each Ar), and 167.75 (C=O); Mass (20 eV) *m/z* (rel intensity, %) 376 (2, M^+-Me_2CO), 314 (12), 313 (69), 312 (base peak), 311 (28), 211 (10), 210 (49), 209 (12), 181 (23), 165 (16), 164 (83), 163 (24), 162 (19), 152 (13), 146 (12), 123 (10), 122 (75), 119 (23), 107 (13), 106 (20), 105 (60), 104 (16), 91 (17), 78 (41), and 77 (59). Anal. Found: C, 71.93; H, 6.31%. Calcd for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03%. **7**: Colorless leaflets (hexane - Et_2O); mp 135 - 136 °C; $[\alpha]_D^{24}$ = 148.7 (*c* 0.73, $CHCl_3$); CD (EtOH) λ_{ext} 228.6 nm (Δε +33.5), 202.8 (–19.2); IR (KBr) 2915, 1768, 1587, 1488, 1448, 1378, 1213, 1141, 1110, 1051, 1026, 986, 888, 813, 755, 744, 715, 696, 568, 488 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.55 (6H, s, Me), 3.28 (6H, s, OMe), 4.20 (2H, s, CH), 4.84 (2H, s, H-4 and H-5), 6.75, 7.20-7.36, and 7.66 (each 2, 14, and 2 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ = 26.98 (Me), 57.21 (OMe), 78.70 (CH), 81.60 (C-4 and C-5), 109.53 (C-2), 121.84, 126.48, 127.07, 127.45, 128.66, 128.81, 129.00, 129.80, 135.36, 148.63 (each Ar), and 168.40 (C=O); Mass (70 eV) *m/z* (rel intensity, %) 313 (21), 312 (22), 164 (26), 163 (base peak), 122 (74), 121 (71), 120 (33), 106 (10), 105 (45), 91 (46), and 77 (51). Anal. Found: C, 72.26; H, 5.96%. Calcd for $C_{35}H_{34}O_8$: C, 72.15; H, 5.88%. **8**: Cololess prisms (hexane - Et_2O); mp 122.5 - 123 °C; $[\alpha]_D^{24}$ = 77.29 (*c* 0.78, $CHCl_3$); CD (EtOH) λ_{ext} 238.4 nm (Δε +7.82), 234.2 (7.38), 214.2 (49.4); IR (KBr) 2900, 1764, 1584, 1486, 1448, 1371, 1349, 1328, 1242, 1210, 1136, 1100, 1053, 984, 888, 808, 760, 750, 739, 693, 565, 504, and 488 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.47 (6H, s, M), 3.28 (6H, s, OMe), 4.20 (2H, s, CH), 4.65 (2H, s, H-4 and H-5), 7.15, 7.24-7.37, and 7.45 (each 2, 14, and 2 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ = 26.93 (Me), 56.99 (OMe), 78.17 (CH), 81.65 (C-4 and C-5), 109.14 (C-2), 121.80, 125.93, 127.66, 127.77, 128.29, 128.81, 128.85, 129.11, 135.47, 148.35 (each Ar), and 168.86 (C=O); Mass (20 eV) *m/z* (rel intensity, %) 313 (41), 312 (base peak), 311 (31), 164 (39), 105 (13), 104 (24), and 91 (11). Anal. Found: C, 72.07; H, 5.87%. Calcd for $C_{35}H_{34}O_8$: C, 72.15; H, 5.88%.

Removal of the Auxiliary from the Esters. As a typical procedure, methanolysis of ester **6** is described below: A mixture of **6** (0.44 g, 1.01 mmol) and K_2CO_3 (0.168 g, 1.22 mmol) in MeOH (10 ml) was stirred at room temperature for 1 h. To the residue were added CH_2Cl_2 (20 ml) and 1N HCl (10 ml), and the resulting mixture was extracted with CH_2Cl_2 (20 ml × 4). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to give a mixture of **1** and methyl *O*-methylmanderate (0.447 g). The pure sample of (4*R*,5*R*)-(+)-**1** was obtained by crystallization from CH_2Cl_2 - hexane (0.183 g, 63%). Silica gel column chromatography of the mother liquor with hexane - Et_2O (3/1 v/v) gave another portion of **1** (46 mg, 16%). $[\alpha]_D^{24}$=37.6 (*c* 0.29, $CHCl_3$). Spectral data of **1** were shown above.

X-Ray Structure Analysis of 7. [13] The single crystal was grown from a hexane - Et_2O solution. A colorless prism of the molecular formula $C_{35}H_{34}O_8$ having approximate dimensions of 0.1 × 0.15 × 0.3 mm was mounted on a glass fiber in a random orientation. Data collection was performed with Cu *K*α radiation (λ = 1.54184 Å) on an Enraf-Nonius FR590 computer controlled kappa axis diffractometer equipped with a graphite crystal, incident beam monochromator. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 16 reflections in the range 21 < θ < 43°, measured by the computer controlled diagonal slit method of centering. The orthorhombic cell parameters and calculated volume are: *a* = 10.401 (3), *b* = 32.287 (6), *c* = 9.539 (2) Å, *V* = 3203 (1)Å^3. For *Z* = 4 and F.W. = 584.67 the calculated density is 1.21 g/cm^3. From the systematic absences of: h00:h = 2n, 0k0:k = 2n, 00l:l = 2n and from subsequent least-squares refinement, the space group was determined to be $P2_12_12_1$. The data were collected at a temperature of 23 ± 1 °C using the ω-2θ scan technique. A total of 3724 reflections were collected, of which 3693 were unique and not systematically absent. A linear decay correction and an empirical absorption correction based on a series of psi-scans were applied to the data. The structure was solved by direct methods (SIR88).[14] Hydrogen atoms were located at calculated positions and were included in the refinement but restrained to ride on the atom to which they are bonded. The structure was refined in full-matrix least-squares. Only the 1451 reflections having intensities greater than 3.0 times their standard deviation were used in the refinements. The final cycle of refinement included 440 variable parameters and converged (largest parameter shift was 0.07 times *vs* esd) with unweighted and weighted agreement factors of R = 0.057 and R_w = 0.068. The standard deviation of an observation of unit weight was 2.06. The highest peak in the final differ-

ence Fourier had a height of 0.19 e/Å^3 and the minimum negative peak had a height of –0.18 e/Å^3. Scattering factors were taken from Cromer and Waber.[15]

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