

ASYMMETRIC HORNER-WADSWORTH-EMMONS REACTION
UTILIZING ISOMANNIDE AND ISOSORBIDE DERIVATIVES AS
CHIRAL AUXILIARIES

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Abstract – The diastereoselective Horner-Wadsworth-Emmons reaction of chiral
phosphonates with $\square$ -symmetric 4-*tert*-butylcyclohexanone and 4-
phenylcyclohexanone was investigated by employing isomannide and isosorbide
derivatives as chiral auxiliaries. $\square$ -Fluoro- $\square$, $\square$ -unsaturated esters with an axis of
chirality were obtained in diastereomer ratio up to 14 : 86 (*aR* : *aS*).

INTRODUCTION

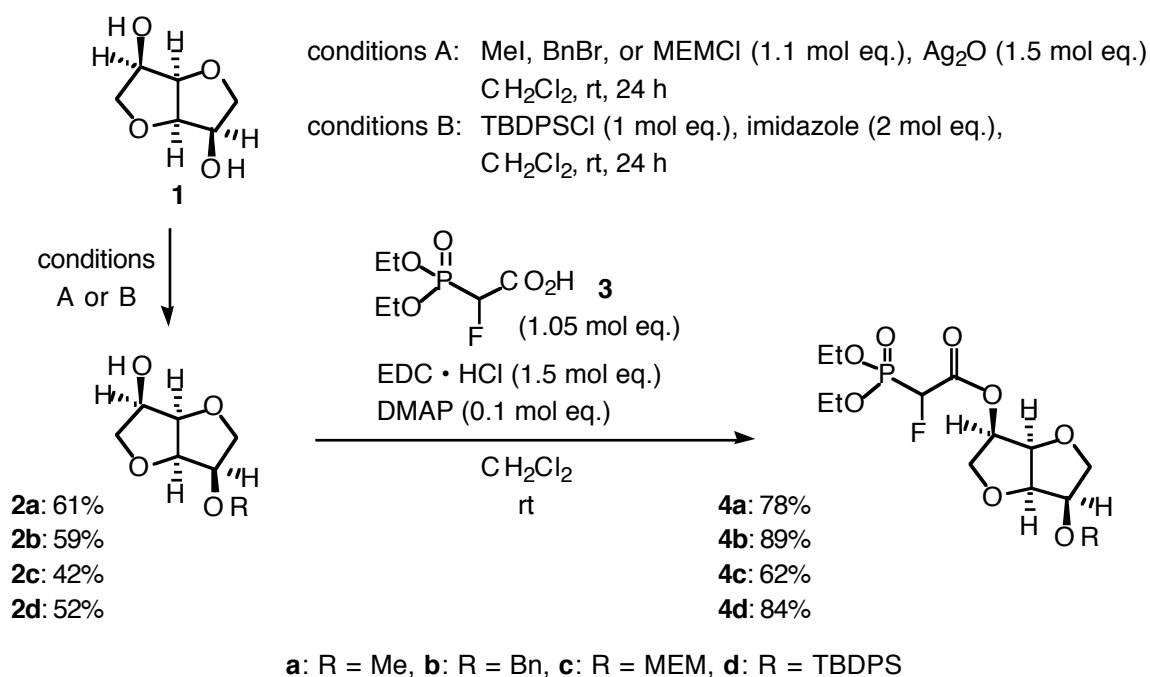
Isomannide [1,4:3,6-dianhydro-D-mannitol (**1**)], derived from D-mannitol by dehydration as a by-product of the starch industry, is an attractive chiral molecule for its C_2 symmetric property and functional groups possessing an oxygen atom.¹ Generally, the presence of the C_2 symmetric axis within a chiral auxiliary molecule can serve to reduce the number of possible competing transition states in an organic reaction.² Thus, chiral diol (**1**) is a promising chiral auxiliary in asymmetric synthesis. To our knowledge, several reports on derivatives of **1** as chiral auxiliaries for asymmetric synthesis have appeared.³ Our ongoing efforts have been directed toward the development of a stereoselective Horner-Wadsworth-Emmons (HWE) reaction with an achiral or a chiral phosphonate.^{4,5} In particular, fluoroolefins attracted our attentions because they have the property of amide isosteres.⁶ Herein, we report the use of monoalkylated and monosilylated derivatives (**2a-d**) of chiral diol (**1**) as chiral auxiliaries in the diastereoselective HWE reactions of chiral phosphonates (**4a-d**) with $\square$ -symmetric 4-*tert*-butylcyclohexanone (**8**) or 4-phenylcyclohexanone (**9**) for the preparation of $\square$ -fluoro- $\square$, $\square$ -

[†] Dedicated to Professor Yuichi Kanaoka on the occasion of his 75th birthday.

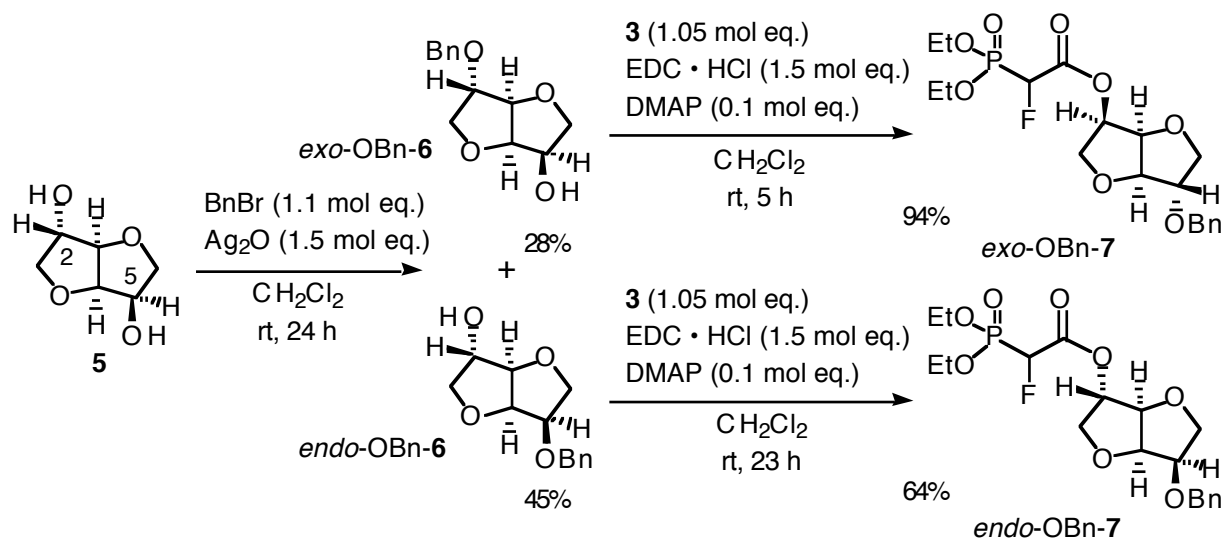
unsaturated esters (**10a-d**) or (**11a,b**) possessing an axis of chirality. Diastereoselective HWE reactions of chiral phosphonates (**7**) derived from *O*-benzylisorbides (**6**) as chiral auxiliaries were also investigated.

RESULTS AND DISCUSSION

Monoalkylation of isomannide (**1**) with silver(I) oxide (1.5 mol eq.) and alkyl halides (1.1 mol eq.) in CH₂Cl₂ afforded alcohols (**2a-c**) in 42-61% yields, as shown in Scheme 1.⁷ Introduction of a *tert*-butyldiphenylsilyl (TBDPS) group onto **1** utilizing *tert*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole gave alcohol (**2d**) in 52% yield. Condensation of 2-fluoro-2-phosphonoacetic acid (**3**)⁸ with chiral alcohols (**2a-d**) accompanied by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl) in the presence of 4-(dimethylamino)pyridine (DMAP) in CH₂Cl₂ provided chiral phosphonates (**4a-d**) as diastereomeric mixtures in 62-89% yields. On the other hand, monobenylation of isosorbide [1,4:3,6-dianhydro-D-sorbitol (**5**)] with silver(I) oxide and benzyl bromide in CH₂Cl₂ afforded 2- and 5-*O*-benzylisorbides (*exo*- and *endo*-OBn-**6**) in 28 and 45% yields, respectively, as shown in Scheme 2.^{9,10} X-Ray crystallographic analysis of *endo*-OBn-**6** was performed in order to determine the structure of *exo*- or *endo*-*O*-benzylisorbides (**6**) (Figure 1). Condensation between **3** and **6** employing EDC•HCl and DMAP in CH₂Cl₂ gave chiral phosphonates *exo*- and *endo*-OBn-**7** in 94 and 64% yields, respectively.



Scheme 1



Scheme 2

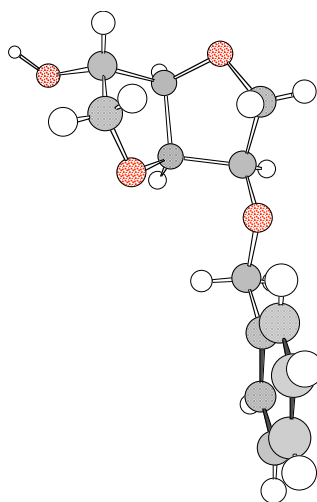
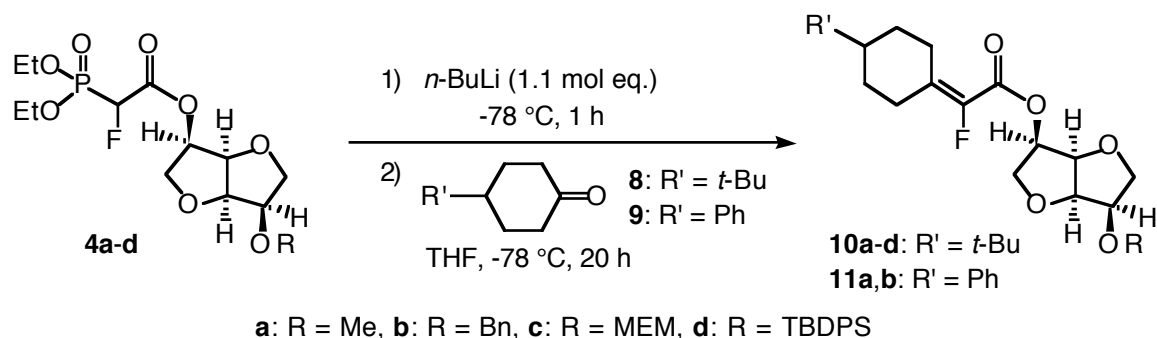


Figure 1. Computer-generated Drawing Derived from X-Ray Coordinates of *endo*-OBn-6

Diastereoselective HWE reactions of chiral phosphonates (**4a-d**) with $\square$ -symmetric prochiral cyclic ketone (**8**) or (**9**) were examined, as shown in Scheme 3. A 14 : 86 (*aR* : *aS*) diastereomer ratio of $\square$ -fluoro- $\square$, $\square$ -unsaturated ester (**10b**) was obtained by the reaction of **4b** with **8** employing BuLi in THF at -78 °C for 20 h (Table 1, Entry 3). All the reactions of chiral phosphonates (**4a-d**) with ketone (**8**) or (**9**) gave good diastereoselectivities in a range of *aR* : *aS* ratios of 19 : 81 - 14 : 86, except in the case of phosphonate (**4b**) with ketone (**9**), as indicated in Table 1. In the case of chiral phosphonate (*exo*-OBn-7) bearing 2-*O*-benzylisosorbide (*exo*-OBn-6), which possesses a stereochemistry similar to that of **4** in the neighborhood of the ester bond, the HWE reaction with **8** is more stereoselective (*aR* : *aS* = 15 : 85) than that of *endo*-OBn-7 (*aR** : *aS** = 44 : 56), as shown in Scheme 4.



Scheme 3

Table 1. Diastereoselective Horner-Wadsworth-Emmons Reactions of **4a-d** with Ketone (**8**) or (**9**)^{a)}

Entry	Phosphonate	Ketone	Yield (%) ^{b)}	Fluoroolefin (a <i>R</i> : a <i>S</i>) ^{c)}
1	4a	8	94	10a (19 : 81)
2	4a	9	95	11a (17 : 83)
3	4b	8	93	10b (14 : 86)
4	4b	9	99	11b (33 : 67)
5	4c	8	83	10c (18 : 82)
6	4d	8	94	10d (16 : 84)

a) Conditions: **4a-d** / *n*-BuLi / **8** or **9** (1.1 : 1.1 : 1).

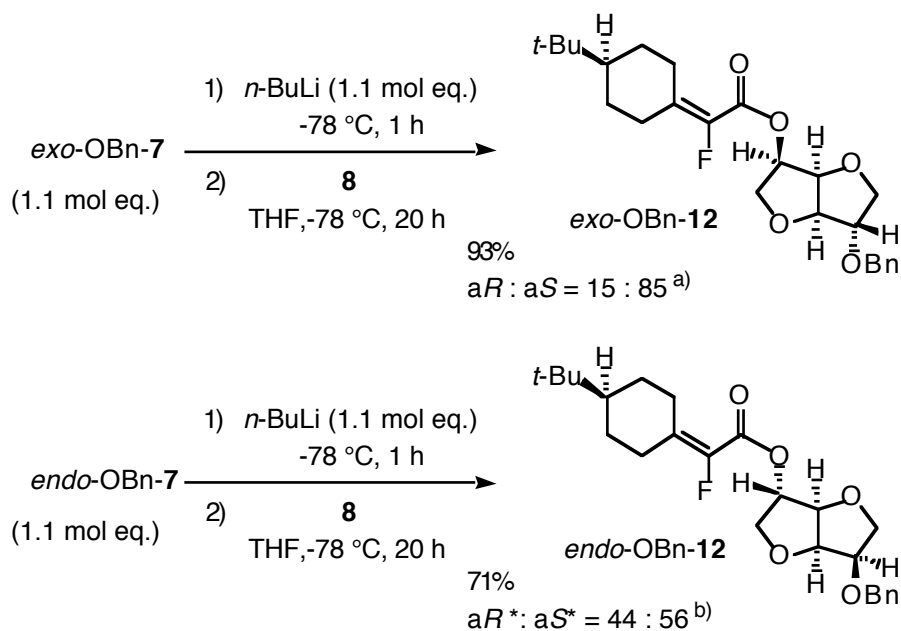
b) Isolated yields.

c) Determined by HPLC (CHIRALCEL OD, hexane - propan-2-ol) analysis.

The absolute configurations of the corresponding major diastereomers of **10a-d**, **11a,b**, and **12**, respectively, were confirmed to be (a*S*)-**10a-d**, (a*S*)-**11a,b**, and (a*S*)-**12** by X-Ray crystallographic analyses (Figure 2) and chemical correlations to primary alcohols (**13**) and (**14**) (Scheme 5). That is to say, reduction of **10b-d**, **11b**, and **12** utilizing DIBAL in CH₂Cl₂ to primary alcohols (**13**) and (**14**), and comparison of their retention times in the chiral-stationary-phase HPLC analysis (Daicel CHIRALCEL OD, hexane/propan-2-ol) with those of the compounds derived from diastereomerically pure esters [(a*S*)-**10a**] and [(a*S*)-**11a**], determined the absolute configuration of α -fluoro- β , γ -unsaturated esters (**10b-d**, **11b**, and **12**).

In conclusion, we have demonstrated the utility of alcohols (**2a-d**) derived from isomannide (**1**) and *exo*-OBn-**6** derived from isosorbide (**5**) as chiral auxiliaries in the asymmetric HWE reaction. Current

efforts are focused on the utility of these chiral alcohols as chiral sources in enantioselective HWE reactions.



a) Determined by HPLC (CHIRALCEL OJ, hexane - ethanol) analysis.

b) Determined by HPLC (CHIRALCEL OD, hexane - propan-2-ol) analysis.

Scheme 4

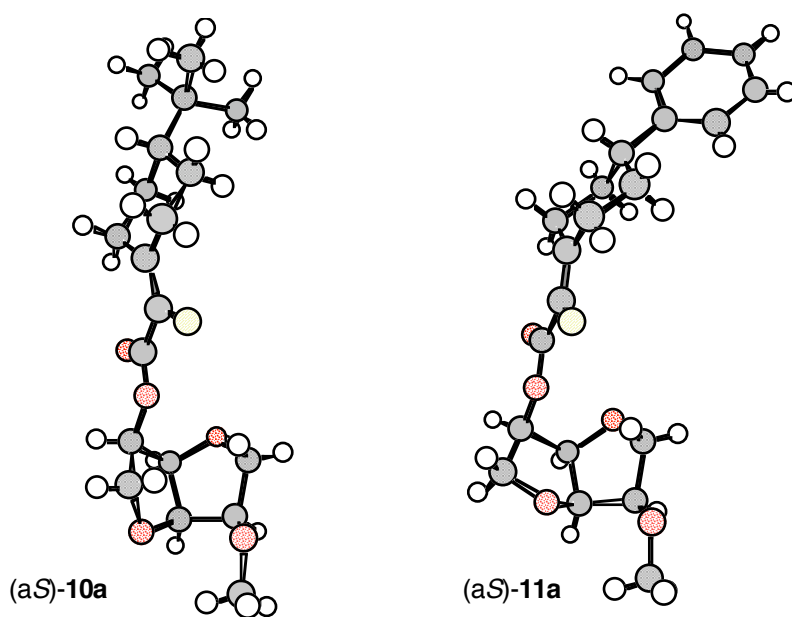
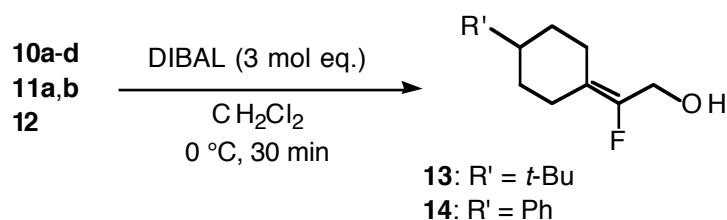


Figure 2. Computer-generated Drawing Derived from X-Ray Coordinates of (aS)-10a and (aS)-11a



Scheme 5

EXPERIMENTAL

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were obtained using a Perkin-Elmer 1720 or JASCO FT/IR-420 IR Fourier transform spectrophotometer. ^1H -NMR (400 MHz) spectra were recorded on a JEOL JNM-AL400 spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane (TMS) as an internal standard. EI-MS spectra were recorded on a JEOL JMS SX-102A spectrometer. Elementary combustion analyses were performed using a Yanaco CHN CORDER MT-5. All reactions were monitored by TLC employing 0.25 mm silica gel plates (Merck 5715; 60 F_{254}). Preparative TLC (PTLC) was performed on 0.5 mm silica gel plates (Merck 5744; 60 F_{254}). Column chromatography was carried out on silica gel [Katayama Chemical K070; 70-300 mesh, Kanto Chemical N60 (spherical, neutral); 63-210 μm , Merck 9385; 230-400 mesh]. The usual workup refers to washing an organic portion with brine, drying it over anhydrous MgSO_4 , filtration, and concentration *in vacuo*. THF was distilled from sodium benzophenone ketyl under N_2 . CH_2Cl_2 was distilled from CaH_2 . All other solvents were distilled prior to use. All reagents were used as purchased.

Typical Procedure for the monoalkylation of isomannide (**1**) and isosorbide (**5**)

To a suspension of isomannide (10.0 g, 68.4 mmol) and Ag_2O (23.8 g, 102.6 mmol) in CH_2Cl_2 (200 mL) was added benzyl bromide (8.95 mL, 75.2 mmol) at rt under nitrogen. After being stirred at rt for 24 h under nitrogen, the reaction mixture was filtered through celite. The resulting solution was evaporated *in vacuo* to afford a crude product, which was purified by column chromatography on silica gel [hexane - acetone (1 : 3)] to afford 1,4:3,6-dianhydro-2-*O*-benzyl-D-mannitol (**2b**) (9.61g, 59%) as colorless needles. mp $85\text{--}86^\circ\text{C}$ (MeOH): $[\alpha]_{\text{D}}^{24} +142^\circ$ (c 1.00, MeOH); ^1H -NMR (400 MHz, CDCl_3) δ 2.82 (1H,

d, $J=8.8$ Hz), 3.67-3.77 (2H, m), 3.95-4.05 (2H, m), 4.05-4.12 (1H, m), 4.24-4.32 (1H, m), 4.46-4.52 (1H, m), 4.53-4.57 (1H, m), 4.57 (1H, d, $J=11.8$ Hz), 4.78 (1H, d, $J=11.8$ Hz), 7.29-7.41 (5H, m); IR (KBr) 3405, 2864, 1424 cm^{-1} ; EI-MS calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4$ MW 236.1049, found m/z 236.1034 (M^+); Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4$: C, 66.08; H, 6.82. Found: C, 65.73; H, 6.75.

1,4:3,6-Dianhydro-2-*O*-methyl-D-mannitol (2a) colorless column: mp 70-71 °C (CHCl_3): $[\alpha]_{\text{D}}^{24} +165^\circ$ (c 1.00, MeOH); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 2.82 (1H, d, $J=8.5$ Hz), 3.49 (3H, s), 3.65-3.75 (2H, m), 3.92-4.03 (2H, m), 4.09 (1H, dd, $J=6.4, 8.5$ Hz), 4.24-4.33 (1H, m), 4.50-4.55 (1H, m), 4.55-4.60 (1H, m); IR (KBr) 3411, 2952, 2869, 1418 cm^{-1} ; EI-MS calcd for $\text{C}_7\text{H}_{12}\text{O}_4$ MW 160.0735, found m/z 160.0762 (M^+); Anal. Calcd for $\text{C}_7\text{H}_{12}\text{O}_4$: C, 52.49; H, 7.55. Found: C, 52.26; H, 7.40.

1,4:3,6-Dianhydro-2-*O*-methoxyethoxymethyl-D-mannitol (2c) colorless oil: $[\alpha]_{\text{D}}^{24} +133^\circ$ (c 1.00, MeOH); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 2.76 (1H, d, $J=8.3$ Hz), 3.39 (3H, s), 3.51-3.61 (2H, m), 3.62-3.78 (4H, m), 3.98 (1H, dd, $J=6.1, 9.2$ Hz), 4.13 (1H, dd, $J=7.1, 8.3$ Hz), 4.23-4.36 (2H, m), 4.49 (1H, t, $J=4.6$ Hz), 4.54 (1H, t, $J=4.4$ Hz), 4.83 (2H, q, $J=6.8$ Hz); IR (neat) 3454, 2882, 1455, 1404, 847, 821 cm^{-1} ; EI-MS calcd for $\text{C}_{10}\text{H}_{18}\text{O}_6$ MW 234.1103, found m/z 234.1070 (M^+); Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_6$: C, 51.27; H, 7.75. Found: C, 50.80; H, 7.51.

1,4:3,6-Dianhydro-2-*O*-benzyl-D-sorbitol (*exo*-OBn-6) colorless plates: mp 100-100.5 °C (CHCl_3 - *n*-hexane), $[\alpha]_{\text{D}}^{24} +48.3^\circ$ (c 1.00, MeOH); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 2.64 (1H, d, $J=7.1$ Hz), 3.56 (1H, dd, $J=5.7, 9.4$ Hz), 3.82-4.93 (2H, m), 4.05-4.15 (2H, m), 4.24-4.32 (1H, m), 4.52 (1H, d, $J=4.4$ Hz), 4.58 (1H, d, $J=12.0$ Hz), 4.60 (1H, d, $J=12.0$ Hz), 4.65 (1H, dd, $J=4.4, 5.1$ Hz), 7.27-7.38 (5H, m); IR (KBr) 3420, 2907, 2871, 1427 cm^{-1} ; EI-MS calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4$ MW 236.1049, found m/z 236.1042 (M^+); Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4$: C, 66.09; H, 6.83. Found: C, 65.86; H, 6.88.

1,4:3,6-Dianhydro-5-*O*-benzyl-D-sorbitol (*endo*-OBn-6) colorless plates. mp 62-62.5 °C (Et_2O): $[\alpha]_{\text{D}}^{24} +103^\circ$ (c 1.00, MeOH); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.75 (1H, d, $J=5.1$ Hz), 3.62 (1H, dd, $J=7.9, 8.7$ Hz), 3.86 (1H, dd, $J=6.7, 8.7$ Hz), 3.96 (1H, d, $J=10.3$ Hz), 4.01 (1H, dd, $J=3.4, 10.3$ Hz), 4.04-4.10 (1H, m), 4.29-4.34 (1H, m), 4.42 (1H, d, $J=4.2$ Hz), 4.57 (1H, d, $J=11.7$ Hz), 4.78 (1H, d, $J=11.7$ Hz), 4.65 (1H, dd, $J=4.2, 4.6$ Hz), 7.27-7.39 (5H, m); IR (KBr) 3449, 2938, 2924, 1371 cm^{-1} ; EI-MS calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4$ MW 236.1049, found m/z 236.1034 (M^+); Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4$: C, 66.09; H, 6.83. Found: C, 66.03; H, 6.94.

1,4:3,6-Dianhydro-2-*O*-(*tert*-butyldiphenylsilyl)-D-mannitol (**2d**)

To a solution of isomannide (5.0 g, 34.2 mmol) and imidazole (4.7 g, 68.4 mmol) in CH₂Cl₂ (120 mL) was added *tert*-butyldiphenylsilyl chloride (TBDPSCl) (8.9 mL, 34.2 mmol) at 0 °C under nitrogen. After being stirred at rt for 1 day under nitrogen, the reaction mixture was treated with an aqueous solution saturated with NH₄Cl and then extracted with CHCl₃ (50 mL x 3). The extract was subjected to the usual workup to give an oily residue, which was purified by silica gel column chromatography [hexane / AcOEt (1 : 1)] to afford **2d** (6.54 g, 52%) as colorless oil. $[\alpha]_D^{24} +75.3^\circ$ (*c* 1.00, MeOH); ¹H-NMR (400 MHz, CDCl₃) δ 1.09 (9H, s), 2.91 (1H, d, *J*=8.8 Hz), 3.81-3.60 (3H, m), 4.02 (1H, dd, *J*=6.1, 9.4 Hz), 4.17-4.28 (3H, m), 4.32-4.40 (1H, m), 7.49-7.33 (6H, m), 7.78-7.63 (4H, m); IR (neat) 3446, 2952, 2857, 1472, 1427, 1391, 1112, 1062, 703 cm⁻¹; EI-MS calcd for C₂₂H₂₈O₄Si M⁺ - *t*-Bu 327.1053, found *m/z* 327.1025 (M⁺ - *t*-Bu); Anal. Calcd for C₂₂H₂₈O₄Si: C, 68.72; H, 7.34. Found: C, 68.41; H, 7.33.

Typical Procedure for the esterification of 2-fluoro-2-phosphonoacetic acid (**3**)

To a solution of carboxylic acid (**3**) (53.3 mg, 0.249 mmol) in CH₂Cl₂ (2 mL) was added 4-(dimethylamino)pyridine (DMAP) (2.9 mg, 0.024 mmol) and alcohol (**2b**) (56.0 g, 0.237 mmol) at rt under nitrogen. After stirring at 0 °C for 5 min, EDC•HCl (68.2 mg, 0.356 mmol) was added at 0 °C under nitrogen. After stirring for 2 h at rt, the reaction mixture was treated with saturated solution of NH₄Cl and then extracted with CHCl₃ (50 mL x 3). The extract was subjected to the usual workup to give an oily residue, which was purified by PTLC [hexane / AcOEt (1 : 3)] to afford a diastereomeric mixture of 1,4:3,6-dianhydro-2-*O*-benzyl-5-*O*-(2-diethylphosphono-2-fluoro)acetyl-D-mannitol (**4b**) (91.0 mg, 89%) as colorless oil. ¹H-NMR (400 MHz, CDCl₃) δ 1.32-1.41 (6H, m), 3.60-3.70 (1H, m), 3.90-3.96 (3H, m), 3.97-4.12 (3H, m), 4.21-4.32 (4H, m), 4.49-4.54 (1H, m), 4.54-4.60 (1H, m), 4.71-4.78 (2H, m), 5.22-5.28 (1H, m), 5.26 (1H, dd, ²*J*_{HP}=12.7 Hz, ²*J*_{HF}=46.9 Hz), 7.28-7.40 (5H, m); EI-MS calcd for C₁₉H₂₆O₈FP MW 432.1349, found *m/z* 432.1360 (M⁺); Anal. Calcd for C₁₉H₂₆O₈FP: C, 52.78; H, 6.06. Found: C, 52.75; H, 6.10.

Typical Procedure for the HWE reaction with *n*-BuLi

To a solution of phosphonate (**4b**) (308 mg, 0.71 mmol) in THF (3 mL) was added BuLi (1.52 mol/L in hexane, 467 μ L, 0.71 mmol) at -78 °C under argon. After stirring at -78 °C for 1 h, a solution of 4-*tert*-butylcyclohexanone (100 mg, 0.65 mmol) in THF (2 mL) was slowly added at -78 °C under argon. After stirring for 20 h at -78 °C, the reaction mixture was treated with 5% HCl and then extracted with ether (50 mL x 3). The extract was subjected to the usual workup to give an oily residue, which was

purified by silica gel column chromatography [hexane / AcOEt (4 : 1)] to afford a diastereomeric mixture (*aR* : *aS* = 14 : 86) of 1,4:3,6-dianhydro-2-*O*-benzyl-5-*O*-[2-(4-*tert*-butylcyclohexylidene)-2-fluoroacetyl]-D-mannitol (**10b**) (259 mg, 93%) as colorless oil.

(*aS*)-1,4:3,6-Dianhydro-5-*O*-[2-(4-*tert*-butylcyclohexylidene)-2-fluoroacetyl]-2-*O*-methyl-D-

mannitol [(*aS*)-10a] colorless needles: mp 78-78.5 °C (Et₂O): $[\alpha]_D^{24} +139^\circ$ (*c* 1.00, CHCl₃); ¹H-NMR (400 MHz, CDCl₃) δ 0.86 (9H, s), 1.03-1.30 (3H, m), 1.70-2.06 (4H, m), 3.00 (1H, d, *J*=13.4 Hz), 3.49 (3H, s), 3.56-3.71 (2H, m), 3.88-4.00 (1H, m), 4.00-4.16 (3H, m), 4.56 (1H, t, *J*=4.9 Hz), 4.81 (1H, t, *J*=5.1 Hz), 5.22 (1H, q, *J*=5.9 Hz); IR (KBr) 2946, 2888, 1730, 1668, 1467, 1442 cm⁻¹; EI-MS calcd for C₁₉H₂₉O₅F MW 356.1999, found *m/z* 356.2025 (M⁺); Anal. Calcd for C₁₉H₂₉O₅F: C, 64.03; H, 8.20. Found: C, 63.87; H, 8.11.

(*aS*)-1,4:3,6-Dianhydro-2-*O*-methy-5-*O*-[2-(phenylcyclohexylidene)-2-fluoroacetyl]-D-mannitol

[(*aS*)-11a] colorless plates: mp 29.5-30 °C (MeOH): $[\alpha]_D^{24} +114^\circ$ (*c* 1.00, CHCl₃); ¹H-NMR (400 MHz, CDCl₃) δ 1.50-1.72 (2H, m), 1.86-2.20 (4H, m), 2.68-2.82 (1H, m), 3.10 (1H, d, *J*=13.7 Hz), 3.49 (3H, s), 3.61-3.79 (2H, m), 3.89-4.00 (1H, m), 4.00-4.14 (3H, m), 4.56 (1H, t, *J*=4.8 Hz), 4.83 (1H, t, *J*=5.3 Hz), 5.24 (1H, q, *J*=5.6 Hz), 7.11-7.36 (5H, m); IR (KBr) 2934, 2879, 1725, 1655, 1493, 1449 cm⁻¹; EI-MS calcd for C₂₁H₂₅O₅F MW 376.1686, found *m/z* 376.1687 (M⁺); Anal. Calcd for C₂₁H₂₅O₅F•1/2MeOH: C, 65.27; H, 6.88. Found: C, 65.33; H, 6.91.

X-Ray Studies

Crystallographic data for *endo*-OBn-6, (*aS*)-**10a**, and (*aS*)-**11a** are summarized in Table 2. All measurements were made on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo-K α radiation. The data were processed using the PROCESS-AUTO program package. The linear absorption coefficient, μ , for Mo-K α radiation is 1.0 cm⁻¹. A symmetry-related absorption correction using the program ABSCOR was applied.¹¹ The data were corrected for Lorentz and polarization effects. Structures were solved by directed methods and expanded using Fourier techniques.^{12,13} The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. Neutral atom scattering factors were taken from Cromer and Waber.¹⁴ The values for the mass attenuation coefficients are those of Creagh and Hubbel.¹⁵ All calculations were performed using the teXsan crystallographic software package.¹⁶

Table 2. Summary of X-Ray Crystallographic Analyses of *endo*-OBn-6, (a*S*)-10a, and (a*S*)-11a

	<i>endo</i> -OBn-6	(a <i>S</i>)-10a	(a <i>S</i>)-11a
Empirical formula	C ₁₃ H ₁₆ O ₄	C ₁₉ H ₂₉ O ₅ F	C _{21.50} H _{27.40} O _{5.70} F
Formula weight	236.27	356.43	396.05
Crystal description	colorless plates	colorless needles	colorless plates
Crystal system	monoclinic	monoclinic	monoclinic
Space group	<i>P</i> 2 ₁	<i>P</i> 2 ₁	<i>C</i> 2
Lattice parameters			
a (Å)	9.8410(8)	11.261(1)	15.1818(9)
b (Å)	5.9742(5)	6.2628(7)	6.1809(3)
c (Å)	10.4744(5)	13.613(2)	41.780(2)
β (°)	113.036(3)	111.518(6)	96.630(1)
Volume (Å ³)	566.71(7)	893.1(2)	3894.3(3)
Z value	2	2	8
<i>D</i> _{calcd} (g/cm ³)	1.384	1.325	1.351
Residuals: <i>R</i> , <i>R</i> _w	0.090, 0.140	0.077, 0.116	0.100, 0.224
GOF indicator	1.18	1.00	1.13
<i>p</i> -factor	0.1030	0.0620	0.1180

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