Symmetry-Assisted Synthesis of C_2-Symmetric *trans*-α,α′-Bis(hydroxymethyl)pyrrolidine and -piperidine Derivatives via Double Sharpless Asymmetric Dihydroxylation of α,ω-Terminal Dienes†

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A new strategy has been developed for the synthesis of C_2-symmetric *trans*-α,α′-bis(hydroxymethyl)pyrrolidine and piperidine derivatives **1**−**3** starting from symmetric α,ω-terminal dienes **4**−**6**. The double-asymmetric dihydroxylation (AD) reaction of **4**−**6** gave C_2-symmetric tetrols, which were converted in a four-step sequence to C_2-symmetric azacycloalkanes **17**, **9**, and **22**, respectively. These azacycloalkanes were transformed into **1**−**3** in high enantiomeric excess (82% → 98%ee). The double AD reaction proved to cause enantiomeric enhancement, even though the asymmetric induction for the first AD reaction is moderate. In addition, it was observed that the chromatography on silica gel of several C_2-symmetric azacycloalkanes (**17**, **20**, and **22**) of varying ee's resulted in marked enantiomeric fractionation.

Introduction

The growing importance of asymmetric syntheses, especially those involving C_2-symmetric molecules as chiral directors, provides an impetus for the preparation of such compounds.[1] It is expected that if each step of the sequential asymmetric reaction of the achiral, symmetrically bifunctionalized substrates using efficient chiral reagents or catalysts occurred independently under one-pot conditions, the overall reaction could be performed with good overall asymmetric induction, providing C_2-symmetric molecules in very high diastereo- and enantiomeric excess (de and ee).[2] Thus, even though the asymmetric induction for each step is moderate, the second step would convert the minor enantiomer, formed in the initial step, into a meso compound. Therefore, the enantiomeric purity of the products would be enhanced via the double-asymmetric process at the expense of the formation of meso byproducts. The principle is found in the Sharpless epoxidation of bis-allylic alcohols,[3] the reduction of diketones,[4] the alkylation of dialdehydes or diketones,[5] the hydrosilylation of diketones,[6] the allylboration of dialdehydes[7] into the corresponding C_2-symmetric diols, the oxidation of 1,3-dithiane into C_2-symmetric disulfoxide,[8] and the hydrogenation of dienes.[9] Our interest in this field has been focused on the synthetic application of the double Sharpless asymmetric dihydroxylation (AD) to cause enantiomeric enhancement (or amplification of ee).[10,11] In this paper, we describe a symmetry-aided synthesis of C_2-symmetric *trans*-α,α′-bis(hydroxymethyl)pyrrolidine and piperidine derivatives **1**−**3** (Chart 1) via the double AD of terminal α,ω-dienes. We also report a unique phenomenon where the resolution of enantiomerically enriched C_2-symmetric, *O*-protected *trans*-2,6-bis(hydroxymethyl)pyrrolidine and morpholine derivatives was effected in achiral-phase chromatography.[12]

Chart 1

(2*R*,5*R*)-**1**; n=0, X = CH_2 (2*S*,5*S*)-**1**; n = 0, X = CH_2
(2*R*,6*R*)-**2**; n=1, X = CH_2 (2*S*,6*S*)-**2**; n = 1, X = CH_2
(2R,6*R*)-**3**; n=1, X = O (2*S*,6*S*)-**3**; n = 1, X = O

a; R = TBDMS, b; R = CH_3, c; R = MOM, d; R = TBDPS

Results and Discussion

It has recently been demonstrated that the concept of using C_2-symmetric chiral auxiliary groups such as the

† This paper is dedicated to Professor Henry Rapoport on the occasion of his 79th birthday.

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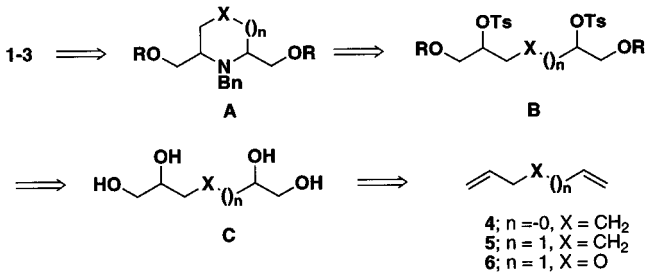
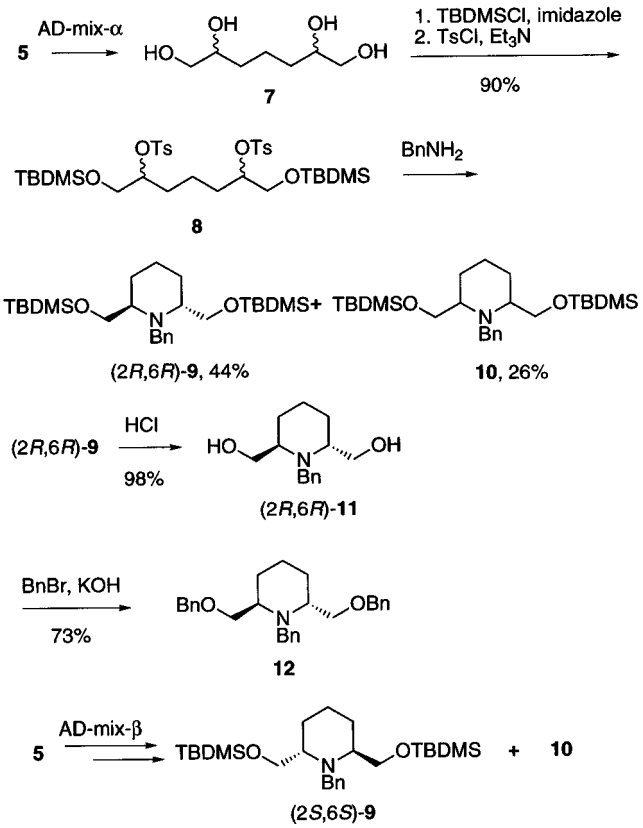
Scheme 1



amines (*O*-protected derivatives of *trans*-α,α′-bis(hydroxymethyl)azacycloalkanes) and their enantiomers, as mediators of stereochemical information, is particularly viable.[13] Accordingly, much attention is focused on the asymmetric synthesis of *trans*-2,5-bis(hydroxymethyl)pyrrolidine (**1**) since the pioneering work by Katsuki on its preparation via chemical resolution.[14] The synthesis of **1** from D-mannitol,[15] by cyclization of dibromoadipate using optically pure 1-phenylethylamine,[16] or by lipase-mediated kinetic resolution of its racemate[17] has recently been reported. So far, two syntheses of the derivatives of **2** using the chiral epoxide (76% ee)[18] and the homochiral phenethylamine[19] as chiral educts have been reported, whereas the synthesis of **3** has not been reported. In addition, no attention has been paid to their asymmetric synthesis by a catalytic fashion. Our retrosynthetic plan involving C_2-symmetrization of terminal α,ω-dienes via the double AD reaction as a key step is shown in Scheme 1. Rapid access to azacycloalkanes **A** is viewed to be possible by selective protection of the primary hydroxyls and subsequent tosylation of the secondary hydroxyls in tetrols **C**, followed by cyclic amination of the resulting product **B** using benzylamine.

We first investigated the synthesis of **2** based on the above tactics. The AD reaction[20] of 1,6-heptadiene **5** by a standard procedure (*t*-BuOH, water, 0 °C, 24 h) with commercially available AD-mix-α (0.2% osmium, 1% $(DHQ)_2$−PHAL ligand) provided an inseparable mixture of the *dl*- and *meso*-tetrols **7** in 98% yield (Scheme 2). Selective protection of the primary hydroxyls in **7** with *tert*-butyldimethylsilyl chloride followed by tosylation of the secondary hydroxyls gave a diastereomeric mixture of the ditosylates **8** in 90% yield. The mixture of the tosylates was stirred with an excess of benzylamine (30 equiv) at 70 °C for 15 h to effect cyclization, with inversion of the two asymmetric centers, into the desired C_2-symmetric piperidine (2*R*,6*R*)-**9** and the σ-symmetric piperidine **10** in 44% and 26% yields, respectively. Treatment of piperidine (2*R*,6*R*)-**9** with 2% ethanolic HCl provided bis(hydroxymethyl)piperidine [(2*R*,6*R*)-**11**] in

Scheme 2



quantitative yield. At this stage, the ee of (2*R*,6*R*)-**11** was determined by HPLC analysis with a chiral column (Daicel AS) to be 93% ee. Thus, it was confirmed that the enantioselectivity was significantly enhanced as compared with that arising from a single AD reaction (vide infra). The absolute configuration of (2*R*,6*R*)-**11**, though predicted by the Sharpless model, was unequivocally assigned to be 2*R*,6*R* by conversion of **11** to the known compound **12**.[18] On the other hand, by using AD-mix-β ($(DHQD)_2$−PHAL ligand), we obtained the enantiomer of (2*R*,6*R*)-**11** in 93% ee and an overall yield of 21% from **5**.

Since $(DHQ)_2$− or $(DHQD)_2$−PYR ligand generally gives better ee's in the AD reaction of terminal olefins,[21] we obtained the $(DHQ)_2$−PYR ligand-derived C_2-symmetric piperidines (2*R*,6*R*)-**9** and **10** in 21% and 7% yields, respectively, through a four-step procedure from **5**. The $(DHQ)_2$−PYR ligand-derived (2*R*,6*R*)-**9** was converted to (2*R*,6*R*)-**11** with marked improvement of the ee to >98%. In like manner, $(DHQD)_2$−PYR ligand-mediated AD reaction of **5** gave (2*S*,6*S*)-**11** (>98% ee) in an overall yield of 21% as expected.

With both enantiomers of the PYR-ligand-derived C_2-symmetry piperidines **9** and **11** in hand, our attention was centered on their transformation into chiral auxiliaries: *trans*-2,6-bis(*O*-protected hydroxymethyl)piperidines (Scheme 3). At the outset, the $(DHQ)_2$−PYR-derived piperidine (2*R*,6*R*)-**9** was converted by hydrogenolysis (H_2/Pd(OH)$_2$) to the 2,6-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]piperidine [(2*R*,6*R*)-**2a**] in 99% yield. Next, *O*-alkylations (methylation and methoxymethylation) of (2*R*,6*R*)-**11** followed by hydrogenolysis gave

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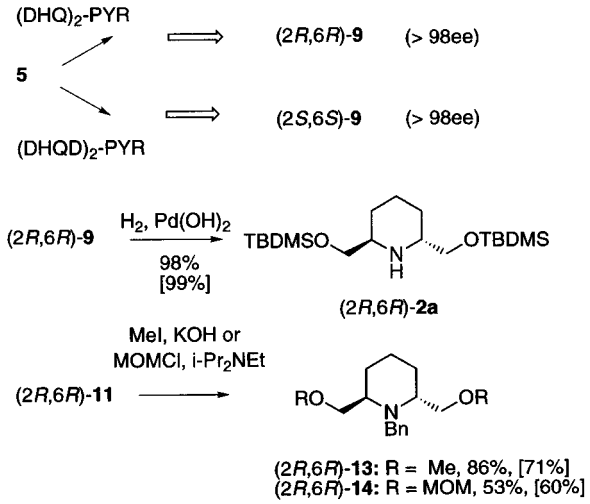
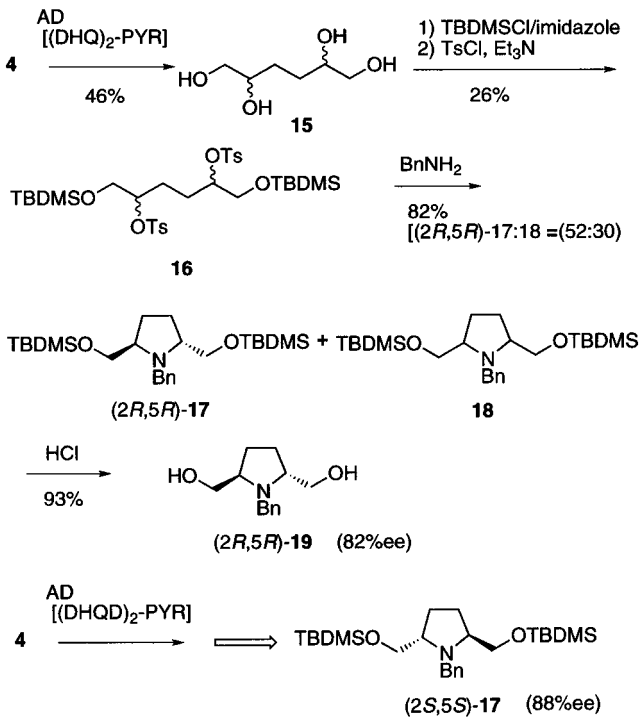
Scheme 3



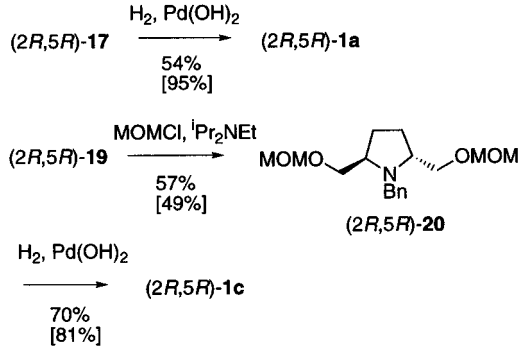
Scheme 4



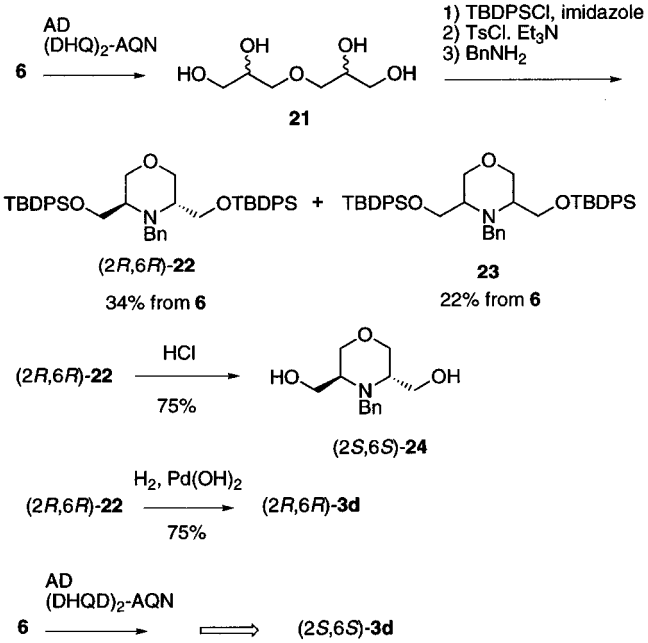
(2*R*,6*R*)-**2b** and (2*R*,6*R*)-**2c** in 73% and 64% yields, respectively. In like manner, we obtained the enantiomers of (2*R*,6*R*)-**2a**−**c** by using the piperidines (2*S*,6*S*)-**9** and (2*S*,6*S*)-**11** from the (DHQD)$_2$−PYR ligand induction, and the yields are shown in brackets.

With the above results in mind, we decided to initiate the synthesis of **1** using the PYR ligand starting from 1,5-hexadiene (**4**). Synthesis of pyrrolidines **19** was carried out by means of a procedure similar to that described for the preparation of **11**. The results are shown in Scheme 4. Unfortunately, ee's of (2*R*,5*R*)-**19** and its enantiomer showed somewhat disappointing values, 82% and 88%, respectively. Similarly, both

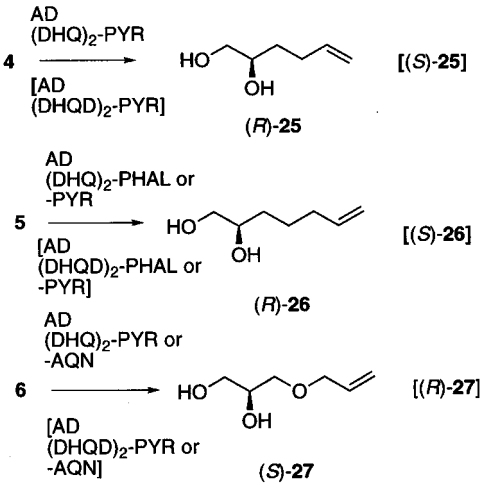
Scheme 5



Scheme 6



Scheme 7



enantiomers of **17** and **19** were transformed into both enantiomers of **1a** and **1c**, respectively (Scheme 5).

Next, the synthesis of the morpholine-type compound **3** was examined. Although the earlier AD reaction for dienes **4** and **5** went to completion in 2 days, a prolonged reaction time (7 days) was required to ensure completion of the AD [(DHQ)$_2$−PYR ligand)] reaction of allyl. Selective silylation using TBDPSCl in place of TBDMSCl and

Table 1. Enantiomeric Excesses for 11, 19, 24, and 25−27

				ee (%)			
entry	substrate	ligand	product	calcd	obsd	product	ee (%)
1	**4**	$(DHQ)_2$−PYR	(2*R*,5*R*)-**19**	94.0	82	(*R*)-**25**	70
2	**4**	$(DHQD)_2$−PYR	(2*S*,5*S*)-**19**	96.6	88	(*S*)-**25**	77
3	**5**	$(DHQ)_2$−PHAL	(2*R*,6*R*)-**11**	98.2	93	(*R*)-**26**	83
4	**5**	$(DHQD)_2$−PHAL	(2*S*,6*S*)-**11**	98.5	93	(*S*)-**26**	84
5	**5**	$(DHQ)_2$−PYR	(2*R*,6*R*)-**11**	98.7	>98	(*R*)-**26**	85
6	**5**	$(DHQD)_2$−PYR	(2*S*,6*S*)-**11**	99.2	>98	(*S*)-**26**	88
7	**6**	$(DHQ)_2$−PYR	(2*S*,6*S*)-**24**	59.4	53	(*S*)-**27**	33
8	**6**	$(DHQD)_2$−PYR	(2*R*,6*R*)-**24**	74.8	59	(*R*)-**27**	45
9	**6**	$(DHQ)_2$−AQN	(2*S*,6*S*)-**24**	98.2	93	(*S*)-**27**	83
10	**6**	$(DHQD)_2$−AQN	(2*R*,6*R*)-**24**	99.3	98	(*R*)-**27**	89

subsequent tosylation gave **21**, which was transformed by aminocyclization into a mixture of chromatographically separable diastereomers (2*R*,6*R*)-**22** and **23** in a 1.1:1 (C_2/meso) ratio. Desilylation of (2*R*,6*R*)-**22** provided (2*S*,6*S*)-**24** in a low ee of 53%.[22] In a similar way using $(DHQD)_2$−PYR ligand, the enantiomer of (2*S*,6*S*)-**24** was produced in 59% ee. Therefore, we began the AD reaction using the recently introduced $(DHQ)_2$− and $(DHQD)_2$−AQN ligands,[23] which showed exceptional face-selectivity with olefins bearing heteroatoms in the allylic position. As expected, the $(DHQ)_2$− and $(DHQD)_2$−AQN ligand-derived **24** were produced in high ee's of 93% and 98%, respectively. It was also found that this AD reaction went to completion in a short reaction time (4 days) compared to the PYR ligand-induced AD reaction. Finally, **22** was converted by hydrogenolysis to **3a**.

To examine the enantiomeric enhancement in the double AD reaction, the single AD reactions of **4**−**6** were carried out to give diols **25** and **26**, respectively. These results are summarized in Table 1. If each step (AD) occurred independently, in the case of entry 1 (the single AD 70%ee), the dual-AD product would be formed in a ratio of approximately 85^2 (7225): 2 × 85 × 15 (2550): 15^2 (225) (*RR*:*RS*:*SS*) and the enantiomeric purity would be enhanced to 94% ee at the expense of the formation of the meso (*RS*) product. The observed value (82% ee) is enhanced as compared with that expected from a single AD. However, it was lower than that calculated. Other examples, with the exception of entries 5 and 6, (Table 1), showed similar results. Accordingly, it was found that substrate control becomes much more important in the second AD reaction. The low ee's of the AD reaction products via **25** may reflect hydrogen bonding between the oxidant and the homoallylic hydroxyl.[24,25] On the other hand, the allyl ether moiety or γ-hydroxyl is fairly problematic.

When a mixture of **17** and **18** was subjected to the chromatographic separation, we were faced with a rare case of fractionation of enantiomers by medium-pressure chromatography on an achiral phase (silica gel). The AD of **1** using the PYR-ligand was carried out several times. However, the product ee values (**17**) from each run gave poor reproducibility. To evaluate this situation, the eluate was collected in three fractions in order of elution: the first, second, and third fractions each contained 50 mL of eluate. The ee values for these fractions were very different (entry 1, Table 2). Other examples are shown in Table 2. It is obvious that ee enhancement occurs in the early fractions while depletion happens in the late fractions. A possible explanation for this enhancement in ee for the first fractions could be found in postulating a stronger associations of the racemic azacycloalkane with the stationary phase. Alternatively, C_2-symmetry derivatives may be associated in the mobile phase, giving rise to diastereomeric entities of different chromatographic mobilities. Indeed, several reports on such phenomena have appeared mostly concerning solid or protic liquid materials.[26] Accordingly, the resolution of enantiomers by achiral-phase chromatography of aprotic oily substances such as **17**, **20**, and **22** are quite intriguing. This method provides a simple procedure to achieve high ee compound (**17** and **22**) from asymmetric synthesis of only modest enantioselectivity.[27]

Table 2. Enantiomeric Deviation in the Fractions of the Medium-Pressure Chromatography[a] for 17, 20, and 22

entry	substrate	ee (%)	eluent[b]	fraction no.	ee[c] (%)	wt (%)
1	(2*R*,5*R*)-**17**	82	50	1	99	38
				2	86	46
				3	33	16
2	(2*S*,5*S*)-**17**	88	50	1	99	44
				2	96	26
				3	67	30
3	(2*R*,5*R*)-**20**	79	15	1	84	37
				2	77	50
				3	73	13
4	(2*S*,5*S*)-**20**	84	15	1	89	21
				2	83	57
				3	80	22
5	(2*R*,5*R*)-**17d**[d]	81	50	1	98	9
				2	91	23
				3	90	39
				4	65	26
				5	15	3
6	(2*S*,5*S*)-**17d**[d]	87	50	1	99	5
				2	96	25
				3	95	30
				4	95	29
				5	77	7
				6	53	4
7	(2*R*,6*R*)-**22**	53	60	1	70	38
				2	53	29
				3	42	33

[a] Silica gel (10 μm)-derived C.I.G. prepacked column (i.d. 22 × 300 nm) purchased from Kusano Kagakukikai Co. was used. The flow rate is 5 mL/min using 10−30 kg/cm^2. [b] A ratio of hexane/ethyl acetate. [c] Ee's were determined after conversion of **17**, **20**, and **22** by hydrolysis to the corresponding diols **19** and **24**. [d] The pyrrolidine **17d** is *N*-benzyl-2,5-bis[[(*tert*-butyldiphenylsilyl)oxy]-methyl]pyrrolidine (see Experimental Section).

In summary, a new strategy for the synthesis of C_2-symmetric *trans*-α,α′-bis(hydroxymethyl)pyrrolidine and

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piperidine derivatives **1**−**3** has been developed based on the double AD reaction of symmetric terminal dienes **4**−**6**, which affects enantiomeric enhancement. A marked behavior of enantiomeric fractionation was observed in the medium-pressure chromatography on silica gel of several C_2-symmetric azacycloalkanes of varying ee's.

Experimental Section

All chiral reagents and ligands were purchased from Aldrich Chemical Co. AD-mix reagents using $K_2OsO_2(OH)_4$ as oxidant and $K_3Fe(CN)_6$ as cooxidant were prepared according to the literature procedure.[21,23] Melting points were determined using a Yanaco micro melting point apparatus and are uncorrected. Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. Infrared spectra (IR) were measured with a Perkin-Elmer 1600 series FTIR spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were recorded either at 300 MHz on a Varian Gemini-300 or 500 MHz on a Varian Unity-500 with $CHCl_3$ (7.26 ppm) as internal standards. Carbon-13 NMR spectra were recorded at 75 or 125 MHz with $CDCl_3$ (77.2 ppm) as an internal standard unless otherwise specified. Fluorine-19 NMR spectra were recorded at 254 MHz on a JEOL 270 GX with $CFCl_3$ (0 ppm) as an internal standard unless otherwise specified. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured on a JEOL JMS D-200 spectrometer. Optical rotations were measured on a JASCO DIP-140 instrument. Column chromatography was performed on silica gel (Fuji-Division BW-200 or Merck 60 (No. 9385)) with a medium-pressure apparatus, and a mixture of ethyl acetate/hexane was used as eluent unless otherwise specified. HPLC was performed with a JASCO Intelligent HPLC pump PU-980 using Daicel Chiralpac AD or AS. The extracts were dried over Na_2SO_4 unless otherwise specified.

Typical Procedure for a Sequence of Asymmetric Dihydroxylation of Dienes, Di-*tert*-butyldimethylsilylation, Ditosylation, and Cyclization. [(2*R*,6*R*)- and (2*R,6*S**)-*N*-Benzyl-2,6-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]piperidines [(2*R*,6*R*)-9] and [(2*R**,6*S**)-10]].** 1,6-Heptadiene (**5**) (2 mL, 14.8 mmol) was added to a mixture of commercially available AD-mix-α [used $(DHQ)_2$−PHAL as ligand] (38.44 g, 29.6 mmol), *t*-BuOH (350 mL), and H_2O (350 mL) at 0 °C. After the reaction mixture was stirred for 24 h at the same temperature, sodium sulfite (24.8 g) was added to the mixture. The mixture was saturated with sodium chloride, stirred for 30 min, filtered through a Celite pad, and washed with 2-propanol (50 mL) three times. The organic layer was separated, and the aqueous layer was extracted with 2-propanol (200 mL) three times. The combined organic layers were dried over K_2CO_3 and evaporated to leave a diastereomeric mixture of tetrol **7** (2.403 g). To a solution of **7** in DMF (26.7 mL) were added imidazole (3.03 g, 44.5 mmol) and *tert*-butyldimethylsilyl chloride (TBDMSCl) (4.81 g, 32.0 mmol). After the mixture was stirred for 12 h, excess water and CH_2Cl_2 were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were washed successively with 20% $KHSO_4$, saturated $NaHCO_3$, and brine, dried, and evaporated. The residue was chromatographed using hexanes−ethyl acetate (3:1) as eluent to give a diastereomeric mixture of the di-TBDMS compounds (3.9 g, 95%) as an oil. Triethylamine (4.31 mL, 24.8 mmol) was added to a solution of di-TBDMS-compounds and *p*-toluenesulfonyl chloride (5.96 g, 24.8 mmol) in CH_2Cl_2 (13.2 mL), and then 4-(dimethylamino)pyridine (DMAP) (243 mg, 1.99 mmol) was added to the mixture. After being stirred for 2 days, the reaction mixture was diluted with ether and filtered through a Celite pad. The filtrate was washed with brine, dried, and evaporated. The residue was chromatographed using hexanes−ethyl acetate (10:1) as eluent to give a diastereomeric mixture of **8** (3.9 g, 95%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.08 (12 H, s), 0.84 (18 H, s), 1.13−1.16 (2 H, m), 1.52−1.64 (4 H, m), 2.45 (6 H, s), 3.54−3.63 (4 H, m), 4.38−4.41 (2 H, m), 7.37 (4 H, d, J = 8.55 Hz), 7.79 (4 H, d, J = 8.12 Hz). A mixture of the oil obtained above (1.552 g, 2.211 mmol) and benzylamine (6.97 mL, 66.34 mmol) was heated at 70 °C for 12 h. Pentane and 2 N NaOH (100 mL) were successively added to the mixture. The organic layer was separated, and the aqueous layer was extracted with pentane three times. The combined organic layers were washed with water, dried, and evaporated. The residue was chromatographed using hexanes−ethyl acetate (40:1−30:1) as eluent to give (2*R**,6*S**)-**10** (269 mg, 26.2%) and (2*R*,6*R*)-**9** (449 mg, 43.8%) as oils. (2*R*,6*R*)-**9**: $[\alpha]^{25}_D$ +10.6° (*c* 1.2, $CHCl_3$); IR (neat) 2928, 2856 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.015 (12 H, d, J = 2.56 Hz), 0.87 (18 H, s), 1.50 (2 H, br d, J = 5.92 Hz), 1.62−1.67 (4 H, m), 2.83 (2 H, br s), 3.61 (2 H, t, J = 2.2 H Hz), 3.71−3.74 (2 H, m), 3.79, 3.92 (each 1 H, ABq, J = 14.7 Hz), 7.28 (1 H, m), 7.29 (2 H, t, J = 6.6 Hz), 7.38 (2 H, d, J = 7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.22, −5.20, 18.47, 19.96, 24.99, 26.13, 53.40, 57.88, 64.09, 126.48, 128.17, 14.99; HRMS calcd for $C_{26}H_{48}NO_2Si_2$ (M^+) 462.3222, found 462.3216.

(2*R*,6*R*)-**9** [used $(DHQ)_2$−PYR as ligand]: $[\alpha]^{25}_D$ +11.1° (*c* 1.6, $CHCl_3$).

10: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.04 (12 H, d, J = 4.7 Hz), 0.85 (18 H, s), 1.36−1.39 (3 H, m), 1.82−1.84 (3 H, m), 2.61−2.62 (2 H, m), 3.29 (2 H, dd, J = 6.09, 7.90 Hz), 3.63 (2 H, dd, J = 10.0, 4.1 Hz), 3.89 (2 H, s), 7.19−7.20 (1 H, m), 7.27−7.30 (2 H, m), 7.36 (2 H, d, 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.45, 18.23, 21.11, 25.90, 27.85, 56.87, 63.39, 66.32, 126.08, 127.25, 127.92, 142.59; HRMS calcd for $C_{26}H_{48}NO_2Si_2$ (M^+) 462.3222, found 462.3216.

(2*S*,6*S*)-9 and (2*S,6*R**)-10.** The AD reaction was performed on 14.8 mmol scale with commercial available AD-mix-β [used $(DHQD)_2$−PHAL as ligand] as described in the typical procedure (vide supra). A diastereomeric mixture of **7** was obtained in 88% yield. A three-step sequence was carried out by a procedure similar to that for the preparation of (2*R*,6*R*)-**9** and **10**. The piperidines (2*S*,6*S*)-**9** and **10** were isolated in 22% and 14% yields, respectively. (2*S*,6*S*)-**9**: $[\alpha]^{25}_D$ −10.3° (*c* 2.11, $CHCl_3$).

(2*S*,6*S*)-9 [used $(DHQD)_2$−PYR as ligand]: $[\alpha]^{25}_D$ −11.5° (*c* 0.8, $CHCl_3$).

(2*R*,6*R*)-*N*-Benzyl-2,6-bis(hydroxymethyl)piperidines [(2*R*,6*R*)-11]. A mixture of (2*R*,6*R*)-**9** (501 mg, 1.08 mmol) and 2% concd HCl in EtOH (11.3 mL) was stirred for 4 h at room temperature. After the solvent was removed by rotary evaporation, 5% HCl (5 mL) was added to the resulting residue. The mixture was washed with ether three times, basified with 2 N NaOH, and extracted with CH_2Cl_2 three times. The extracts were combined, dried over anhyd K_2CO_3, and evaporated to yield (2*R*,6*R*)-**11** (250 mg, 98.4%) as an oil: $[\alpha]^{25}_D$ −47.0° (*c* 1.23, $CHCl_3$); IR (neat) 3418, 3060, 3026, 2925 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31−1.35 (2 H, m), 1.61−1.70 (4 H, m), 3.05−3.10 (2 H, m), 3.44 (2 H, dd, J = 10.7, 5.6 Hz), 3.67, 3.95 (each 1 H, ABq, J = 13.8 Hz), 3.78 (2 H, t, J = 10.7 Hz), 7.26−7.29 (2 H, m), 7.33−7.35 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.81, 21.26, 49.90, 55.92, 61.63, 127.33, 128.54, 128.72, 139.88; HRMS calcd for $C_{14}H_{21}NO_2$ (M^+) 235.1570, found 235.1543. The ee of (2*R*,6*R*)-**11** was determined by HPLC analysis (Daicel Chiralpak AS, 10% *i*-PrOH/hexane, 0.7 mL/min) to be 93%.

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(27) In practice, the pyrrolidine and morpholine derivatives [(2*R*,5*R*)-**17**, (2*S*,5*S*)-**17**, (2*S*,5*S*)-**17d**, (2*R*,6*R*)-**22**, and (2*S*,6*S*)-**22**] in optically pure forms (>98% ee) were isolated by the fractionation phenomenon. Subsequently, (2*R*,5*R*)-**17**, (2*S*,5*S*)-**17**, (2*S*,5*S*)-**17d**, (2*R*,6*R*)-**22**, and (2*S*,6*S*)-**22** were converted into (2*R*,5*R*)-**1a** [$[\alpha]^{25}_D$ +7.4° (*c* 0.83, $CHCl_3$)], (2*S*,5*S*)-**1a** [$[\alpha]^{25}_D$ −7.5° (*c* 0.94, $CHCl_3$)], (2*S*,5*S*)-**1d** [$[\alpha]^{25}_D$ −7.5° (*c* 0.76, EtOH)], (2*R*,6*R*)-**3d** [$[\alpha]^{26}_D$ +10.3° (*c* 0.87, $CHCl_3$)], and (2*S*,6*S*)-**3d** [$[\alpha]^{26}_D$ −10.6° (*c* 0.74, $CHCl_3$)], respectively.

(2*R*,6*R*)-11 [used $(DHQ)_2$−PYR as ligand]: $[\alpha]^{25}_D$ −50.2° (*c* 1.86, $CHCl_3$); (>98% ee).

(2*S*,6*S*)-11. By a procedure similar to that for the preparation of (2*R*,6*R*)-**11**, the hydrolysis of (2*S*,6*S*)-**9** was performed on a 0.448 mmol scale. The diol (2*S*,6*S*)-**11** was obtained in 94% yield: $[\alpha]^{25}_D$ +47.3° (*c* 0.67, $CHCl_3$); 93% ee.

(2*S*,6*S*)-11 [used $(DHQD)_2$−PYR as ligand]: $[\alpha]^{25}_D$ +49.7° (*c* 3.75, $CHCl_3$); (>98% ee).

(2*R*,6*R*)-*N*-Benzyl-2,6-bis(benzyloxymethyl)piperidines [(2*R*,6*R*)-12]. To a stirring suspension of (2*R*,6*R*)-**11** (100 mg, 0.425 mmol), pulverized KOH (95 mg, 1.7 mmol), and molecular sieves 5A (166 mg) in THF (1 mL) was added benzyl bromide (50.6 μL, 0.935 mmol). After the mixture was stirred for 4 h, excess ether was added. The mixture was filtered through a Celite pad, and the filtrate was washed with brine, dried, and evaporated. The residue was chromatographed using hexanes−ethyl acetate (7:1) as eluent to give (2*R*,6*R*)-**12** (120 mg, 73.2%) as an oil: $[\alpha]^{25}_D$ +34.1° (*c* 0.63, $CHCl_3$) [lit.[18a] $[\alpha]_D$ −29.1° (*c* 1.12, $CHCl_3$) for (2*S*,6*S*)-**12**]; IR (neat) 2926 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.53−1.62 (6 H, m), 3.02 (2 H, m), 3.48−3.52 (2 H, m), 3.75, 3.94 (each 1 H, ABq, *J* = 12.2 Hz), 4.43 (4 H, t, *J* = 12.2 Hz), 7.21−7.39 (15 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.70, 25.63, 53.03, 55.31, 70.89, 72.94, 126.34, 127.40, 127.53, 127.57, 127.97, 128.13, 128.25, 138.37, 141.21.

(2*R*,6*R*)-*N*-Benzyl-2,6-bis(methoxymethyl)piperidine [(2*R*,6*R*)-13]. To a stirring suspension of (2*R*,6*R*)-**11** (152 mg, 0.646 mmol), pulverized KOH (181 mg, 3.23 mmol), and molecular sieves 4A (200 mg) in THF (1 mL) was added methyl iodide (0.211 mL, 3.23 mmol). After being stirrrf for 4 h, pulverized KOH (181 mg, 3.23 mmol) and methyl iodide (0.211 mL, 3.23 mmol) were again added to the reaction mixture. After being stirred for 12 h, excess ether was added to the reaction mixture. The mixture was filtered through a Celite pad, and the filtrate was washed with brine, dried, and evaporated. The residue was chromatographed using hexanes−ethyl acetate (10:1) as eluent to yield (2*R*,6*R*)-**13** (127 mg, 85.8%) as an oil: $[\alpha]^{25}_D$ +29.5° (*c* 1.83, $CHCl_3$); IR (neat) 2926, 2871, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.49−1.53 (2 H, m), 1.61−1.64 (4 H, m), 2.97 (2 H, br d, *J* = 5.6 Hz), 3.26 (6 H, s), 3.41−3.44 (2 H, m), 3.52 (2 H, dd, *J* = 9.6, 5.1 Hz), 3.76, 3.93 (each 1 H, ABq, *J* = 14.5 Hz), 7.20−7.23 (1 H, m), 7.28−7.32 (2 H, m), 7.40 (2 H, d, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.98, 25.83, 53.28, 55.45, 58.91, 58.97, 73.77, 126.59, 128.23, 128.34, 141.46; HRMS calcd for $C_{16}H_{25}NO_2$ (M^+) 263.1885, found 263.1887.

(2*S*,6*S*)-13. By a procedure similar to that for the preparation of (2*R*,6*R*)-**13**, the methylation of (2*S*,6*S*)-**11** was performed on a 1.45 mmol scale. The piperidine (2*S*,6*S*)-**13** was isolated in 71% yield: $[\alpha]^{25}_D$ −29.7° (*c* 2.69, $CHCl_3$).

(2*R*,6*R*)-*N*-Benzyl-2,6-bis[(methoxymethoxy)methyl]piperidine [(2*R*,6*R*)-14]. To a solution of (2*R*,6*R*)-**11** (83 mg, 0.395 mmol), *N*,*N*-diisopropylethylamine (0.275 mL, 7.58 mmol), and DMAP (9.67 mg, 0.79 mmol) in CH_2Cl_2 (2 mL) was added chloromethyl methyl ether (0.075 mL, 0.988 mmol). After the mixture was stirred for 12 h, excess ether was added. The mixture was filtered through a Celite pad, and the filtrate was washed with brine, dried, and evaporated. The residue was chromatographed using hexanes−ethyl acetate (10:1) as eluent to give (2*R*,6*R*)-**14** (59 mg, 52.7%) as an oil: $[\alpha]^{25}_D$ +29.3° (*c* 3.37, $CHCl_3$); IR (neat) 2926, 2871, 2809, 1452, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.54−1.56 (2 H, m), 1.65−1.67 (4 H, m), 2.98−3.00 (2 H, m), 3.32 (6 H, s), 3.60 (2 H, dd, *J* = 9.8, 6.8 Hz), 3.68 (2 H, dd, *J* = 9.8, 4.9 Hz), 3.76, 3.96 (each 1 H, ABq, *J* = 14.3 Hz), 4.56 (4 H, s), 7.21−7.28 (1 H, m), 7.28−7.31 (2 H, m), 7.39−7.40 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.83, 25.74, 53.06, 55.26, 55.28, 55.33, 55.42, 68.11, 96.62, 126.69, 128.25, 128.39, 141.03; HRMS calcd for $C_{18}H_{29}NO_2$ (M^+) 323.2096, found 323.2134.

(2*S*,6*S*)-14. By a procedure similar to that for the preparation of (2*R*,6*R*)-**14**, the methoxymethylation of (2*S*,6*S*)-**11** was performed on a 0.394 mmol scale. The piperidine (2*S*,6*S*)-**14** was isolated in 60% yield: $[\alpha]^{25}_D$ −29.6° (*c* 2.92, $CHCl_3$).

Typical Procedure for Hydrogenolysis. [(2*R*,6*R*)-2,6-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]piperidine [(2*R*,-6*R*)-2a]. A suspension of (2*R*,6*R*)-**9** (127 mg, 0.274 mmol) and palladium hydroxide (30 mg) in MeOH (2 mL) under a hydrogen atmosphere was stirred for 4 h. The mixture was filtered through a Celite pad, and the filtrate was evaporated. The residue was chromatographed using hexanes−ethyl acetate (3:1) as eluent to give (2*R*,6*R*)-**2a** (73 mg, 97.9%) as an oil: $[\alpha]^{25}_D$ −18.6° (*c* 0.94, $CHCl_3$); IR (neat) 3340, 2929, 2857, 1256, 1110, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.07 (12 H, s), 0.90 (4 H, m), 1.33−1.37 (2 H, m), 1.49−1.51 (2 H, m), 1.65−1.71 (2 H, br d), 3.00−3.05 (2 H, br d), 3.49 (2 H, dd, *J* = 9.7, 4.5 Hz), 3.65 (2 H, t, *J* = 9.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.48, −5.42, 18.25, 19.66, 25.84, 25.88, 25.91, 26.45, 26.51, 51.89, 64.68, 64.77; HRMS calcd for $C_{19}H_{42}NO_2Si_2$ (M^+ − 1) 372.2752, found 372.2719.

(2*S*,6*S*)-2a. The hydrogenolysis was performed on (2*S*,6*S*)-**9** (0.328 mmol) as described in the typical procedure (vide supra). The piperidine (2*S*,6*S*)-**2a** was isolated in 99% yield: $[\alpha]^{27}_D$ +18.9° (*c* 0.9, $CHCl_3$).

(2*R*,6*R*)-2,6-Bis(methoxymethyl)piperidine [(2*R*,6*R*)-2b]. The hydrogenolysis was performed on (2*R*,6*R*)-**13** (0.49 mmol) as described in the typical procedure (vide supra). The piperidine (2*R*,6*R*)-**2b** was isolated in 84.8% yield: $[\alpha]^{27}_D$ −7.99° (*c* 0.53, $CHCl_3$); IR (neat) 3342, 2927, 1111 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.33−1.41 (2 H, m), 1.48−1.57 (2 H, m), 1.63−1.72 (2 H, m), 2.47−2.56 (1 H, br s), 3.14−3.20 (2 H, br d), 3.30 (2 H, dd, *J* = 8.3, 4.3 Hz), 3.37 (6 H, s), 3.45 (2 H, t, *J* = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.92, 27.06, 50.06, 59.16, 59.21, 74.58; HRMS calcd for $C_9H_{19}NO_2$ (M^+) 173.1414, found 173.1371.

(2*S*,6*S*)-2b. The hydrogenolysis was performed on (2*S*,6*S*)-**13** (0.194 mmol) as described in the typical procedure (vide supra). The piperidine (2*S*,6*S*)-**2b** was isolated in 77% yield: $[\alpha]^{27}_D$ +8.05° (*c* 0.125, $CHCl_3$).

(2*R*,6*R*)-2,6-Bis[(methoxymethoxy)methyl]piperidine [(2*R*,6*R*)-2c]. The hydrogenolysis was performed on (2*R*,6*R*)-**14** (0.28 mmol) as described in the typical procedure (vide supra). The piperidine (2*R*,6*R*)-**2c** was isolated in 90.0% yield: $[\alpha]^{25}_D$ −9.37° (*c* 2.4, $CHCl_3$) [lit.[19] $[\alpha]^{20}_D$ −3.2° (*c* 1.06, $CHCl_3$)]; IR (neat) 3343, 2931, 1111, 1045 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36−1.41 (2 H, m), 1.51−1.56 (2 H, m), 1.65−1.70 (2 H, m), 2.64 (1 H, br s), 3.14−3.19 (2 H, m), 3.36 (6 H, s), 3.43−3.46 (2 H, m), 3.59 (2 H, t, *J* = 9.4 Hz), 4.62−4.65 (4 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.92, 27.21, 50.11, 55.44, 69.76, 96.72; HRMS calcd for $C_{11}H_{23}NO_4$ (M^+) 232.1547, found 232.1544.

(2*S*,6*S*)-2c. The hydrogenolysis was performed on (2*S*,6*S*)-**14** (0.167 mmol) as described in the typical procedure (vide supra). The piperidine (2*S*,6*S*)-**2c** was isolated in 77% yield: $[\alpha]^{27}_D$ +9.58° (*c* 2.12, $CHCl_3$).

(2*R*,5*R*)- and (2*R,5*S**)-*N*-Benzyl-2,5-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]pyrrolidines [(2*R*,5*R*)-17] and [(2*R**,5*S**)-18].** The AD reaction was performed on diene **4** (13.78 mmol) as described in the typical procedure (vide supra) using $(DHQ)_2$−PYR as ligand. A diastereomeric mixture of tetrol **15** was isolated in 45.5% yield. The *tert*-butyldimethylsilylation of **15** (2.06 mmol) [isolated by chromatography using hexanes−ethyl acetae (5:1) as eluent] followed by tosylation was accomplished as described in the typical procedure (vide supra). A diastereomeric mixture of tosylate **16** [isolated by chromatography using hexanes−ethyl acetae (10:1) as eluent] was isolated in 25.8% yield. By a procedure similar to that for the preparation of **9** and **10**, the reaction of **16** (1.79 mmol) with benzylamine (53.7 mmol) gave (2*R**,5*S**)-**18** (30.2%) and (2*R*,5*R*)-**17** (52.2%) [separated by chromatography using hexanes−ethyl acetate (50:1) as eluent] as oils. (2*R*,5*R*)-**17**: $[\alpha]^{25}_D$ +45.4° (*c* 7.8, $CHCl_3$); IR (neat) 2953, 2928, 2885, 2856, 1255, 1095, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.033 (6H, s), −0.030 (6H, s), 0.90 (18 H, s), 1.69−1.71 (2 H, m), 2.00−2.02 (2 H, m), 3.12 (2 H, br d), 3.52 (4 H, d, *J* = 5.1 Hz), 3.93, 4.07 (each 1 H, ABq, *J* = 14.3 Hz), 7.23−7.24 (1 H, m), 7.28−7.30 (2 H, m), 7.31−7.40 (2 H, m) ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.21, 18.41, 26.13, 27.32, 53.04, 62.86, 65.12,

126.66, 128.28, 128.33; HRMS calcd for $C_{25}H_{47}NO_2Si_2$ 449.3145, found 449.3119.

18: IR (neat) 2955, 2928, 2884, 2856, 1255, 1091, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.041 (6H, s), −0.040 (6H, s), 0.85 (18 H, s), 1.60−1.61 (2 H, m), 1.83−1.86 (2 H, m), 2.87−2.88 (2 H, br d), 3.24 (2 H, t, J = 8.8 Hz), 3.37 (2 H, dd, J = 9.8, 4.7 Hz), 3.85 (2 H, s), 7.22−7.24 (1 H, m), 7.28−7.29 (2 H, m), 7.31−7.34 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.22, −5.18, 18.45, 25.99, 26.12, 26.23, 27.63, 60.16, 67.12, 67.34, 126.94, 128.20, 129.29; HRMS calcd for $C_{25}H_{47}NO_2Si_2$ 449.3145, found 449.3113.

(2*S*,6*S*)-17 and (2*S,5*R**)-18.** The AD reaction was performed on diene **4** (33.7 mmol) as described in the typical procedure (vide supra) using $(DHQD)_2$−PYR as ligand. A diastereomeric mixture of tetra-**15** was isolated in 63.6% yield. By a procedure similar to that for the preparation of (2*R*,5*R*)-**17** and (2*R**,5*S**)-**18**, (2*S*,6*S*)-**17** and (2*S**,5*R**)-**18** were obtained in 25% and 5.3% yields, respectively. (2*S*,6*S*)-**17**: $[\alpha]^{25}_D$ −48.1° (*c* 1.78, $CHCl_3$).

(2*R*,5*R*)-*N*-Benzyl-2,5-bis(hydroxymethyl)pyrrolidines [(2*R*,5*R*)-19]. The de-*tert*-butyldimethylsilylation of (2*R*,5*R*)-**17** was performed on a 0.283 mmol scale as described in the typical procedure (vide supra). Diol (2*R*,5*R*)-**19** was isolated in 92.9% yield: $[\alpha]^{25}_D$ +56.6° (*c* 1.69, MeOH) [lit.[16] $[\alpha]^{25}_D$ +49.2° (*c* 0.5, MeOH)]; IR (neat) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.79−1.84 (2 H, m), 1.98−2.06 (4 H, m), 3.18−3.21 (2 H, m), 3.55 (2 H, dd, J = 10.9, 2.8 Hz), 3.63 (2 H, dd, J = 10.9, 4.7 Hz), 3.88 (2 H, s), 7.25−7.27 (1 H, m), 7.27−7.28 (2 H, m), 7.32−7.37 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.17, 51.71, 61.95, 62.17, 76.94, 77.20, 77.45, 127.21, 128.29, 128.64, 139.66. The ee of (2*R*,5*R*)-**19** was determined by HPLC analysis (Daicel Chiralpak AD, 10% *i*-PrOH/hexane, 0.7 mL/min) to be 82%.

(2*S*,5*S*)-19. By a procedure similar to that for the preparation of (2*R*,5*R*)-**19**, the hydrolysis of (2*S*,5*S*)-**17** was performed on a 0.156 mmol scale. The pyrrolidine (2*S*,5*S*)-**19** was obtained in 67% yield: $[\alpha]^{25}_D$ −62.3° (*c* 0.8, MeOH) [lit.[17] $[\alpha]^{25}_D$ −70.3° (*c* 0.5, MeOH)]; 88% ee.

(2*R*,5*R*)-*N*-Benzyl-2,5-bis[(methoxymethoxy)methyl]pyrrolidines [(2*R*,5*R*)-20]. The methoxymethylation of (2*R*,5*R*)-**19** was performed on a 0.648 mmol scale by a procedure similar to that for the preparation of (2*R*,6*R*)-**14**. Compound (2*R*,5*R*)-**20** was isolated in 57.0% yield: $[\alpha]^{25}_D$ +42.8° (*c* 5.19, $CHCl_3$); IR (neat) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.70−1.76 (2 H, m), 2.03−2.08 (2 H, m), 3.20−3.29 (2 H, m), 3.35 (6 H, s), 3.45 (2 H, dd, J = 9.8, 6.1 Hz), 3.51 (2 H, dd, J = 9.8, 4.3 Hz), 3.89, 4.05 (each 1 H, ABq, J = 14.3 Hz), 4.59 (4 H, s), 7.23 (1 H, t, J = 7.3 Hz), 7.28−7.32 (2 H, m), 7.38 (2 H, d, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.61, 52.83, 55.44, 60.60, 69.55, 96.82, 16.69, 128.22, 128.27, 140.62. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. C, 66.08; H, 8.99; N, 4.31.

(2*S*,5*S*)-20. By a procedure similar to that for the preparation of (2*R*,5*R*)-**20**, the methoxymethylation of (2*S*,5*S*)-**19** was performed on a 0.150 mmol scale. The pyrrolidine (2*S*,5*S*)-**20** was obtained in 49% yield: $[\alpha]^{25}_D$ −46.9° (*c* 1.13, $CHCl_3$).

(2*R*,5*R*)-2,5-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-pyrrolidines [(2*R*,5*R*)-1a]. The hydrogenolysis of (2*R*,5*R*)-**17** was performed on a 0.218 mmol scale as described in the typical procedure (vide supra). The pyrrolidine (2*R*,5*R*)-**1a** was isolated in 54% yield: $[\alpha]^{25}_D$ +6.3° (*c* 2.3, $CHCl_3$); IR (neat) 3363, 2955, 2929, 2857, 1472, 1463, 1256, 1094, 837, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.03−0.05 (12 H, m), 0.78−1.03 (18H, m), 1.48−1.55 (2 H, m), 1.87−1.95 (2 H, m), 2.20 (1 H, s), 3.36−3.42 (2 H, m), 3.46−3.63 (4 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.07, −4.98, 18.59, 26.21, 27.48, 27.62, 59.07, 65.06, 65.29, 66.68; HRMS calcd for $C_{18}H_{41}NO_2Si$ 359.2675, found 359.2651.

(2*S*,5*S*)-1a. The hydrogenolysis of (2*S*,5*S*)-**17** was performed on a 0.124 mmol scale as described in the typical procedure (vide supra). The pyrrolidine (2*S*,5*S*)-**1a** was isolated in 95% yield: $[\alpha]^{25}_D$ −6.5° (*c* 1.8, $CHCl_3$).

(2*R*,5*R*)-2,5-Bis[(methoxymethoxy)methyl]pyrrolidines [(2*R*,5*R*)-1c]. The hydrogenolysis of (2*R*,5*R*)-**20** was performed on a 0.343 mmol scale as described in the typical procedure (vide supra). The pyrrolidine (2*R*,5*R*)-**1c** was isolated in 69.6% yield: $[\alpha]^{26}_D$ +4.13° (*c* 2.6, EtOH) [lit.[15] $[\alpha]^{24}_D$ +4.5° (*c* 4.0, EtOH)]; IR (neat) 3346, 2932, 2823, 1215, 1151, 1110, 1044, 918 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (2 H, m), 1.97 (2 H, br s), 3.33−3.38 (6 H, m), 3.48−3.60 (4 H, m), 4.59−4.67 (4 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.12, 55.47, 57.15, 71.37, 96.81; HRMS $C_{10}H_{21}NO_4$ (M^+ − 1) 218.1392, found 218.1397.

(2*S*,5*S*)-1c. The hydrogenolysis of (2*S*,5*S*)-**20** was performed on a 0.068 mmol scale as described in the typical procedure (vide supra). The pyrrolidine (2*S*,5*S*)-**1c** was isolated in 81% yield: $[\alpha]^{25}_D$ −4.2° (*c* 0.72, EtOH) [lit.[15] $[\alpha]^{24}_D$ −4.7° (*c* 4.1, EtOH)].

(2*R*,5*R*)- and (2*R,5*S**)-*N*-Benzyl-2,5-bis[[(*tert*-butyldiphenylsilyl)oxy]methyl]pyrrolidines [(2*R*,5*R*)-17d] and [(2*R**,5*S**)-18d].** To a solution of (2*R*,5*R*)-**15d** (1.16 g, 7.43 mmol) in DMF (12.3 mL) were added imidazole (1.14 g, 16.63 mmol) and *tert*-butyldiphenysilyl chloride (TBDPSCl). After the mixture was stirred for 12 h, excess water and CH_2Cl_2 were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were successively washed with 20% $KHSO_4$, saturated $NaHCO_3$, and brine. The organic layer was dried and evaporated. The residue was chromatographed using hexanes−ethyl acetate (5:1) as eluent to give a diastereomeric mixture of (2*R*,5*R*)-**16d** (2.23 g, 47.9%) as an oil. By a procedure similar to that for the preparation of **9** and **10**, (2*R*,5*R*)-**16d** (2.23 g, 3.56 mmol) was converted in a two-step sequence [(1) *p*-toluenesulfonyl chloride (1.59 g, 8.9 mmol), triethylamine (1.20 mL, 8.9 mmol), DMAP (84.5 mg, 0.71 mmol) in CH_2Cl_2 (4.6 mL); (2) benzylamine (9.1 mL, 1.68 mmol)] to (2*R*,5*R*)-**17d** (1.15 g, 59.4%) and (2*R**,5*S**)-**18d** (0.584 g, 30.1%) as an oils. (2*R*,5*R*)-**17d**: $[\alpha]^{25}_D$ +36.8 (*c* 1.035, $CHCl_3$); IR (neat) 3071, 2930, 1472, 1428, 1112, 823, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (18 H, s), 1.83−1.87 (2 H, m), 2.08−2.13 (2 H, m), 3.22−3.23 (2 H, d, J = 4.9 Hz), 3.58−3.62 (4 H, m), 3.77, 3.97 (each 1 H, ABq, J = 14.5 Hz), 7.16−7.23 (8 H, m), 7.38−7.49 (12 H, m), 7.66−7.73 (5 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.37, 27.08, 27.40, 52.70, 62.65, 65.76, 126.47, 127.78, 127.80, 128.14, 128.21, 129.75, 133.95, 134.00, 135.80, 135.88, 140.94; HRMS calcd for $C_{45}H_{55}NO_2Si_2$ (M^+) 698.1082, found 698.1063.

18d: IR (neat) 3070, 2930, 2857, 1472, 1428, 1389, 1112, 824, 739, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (18 H, s), 1.65−1.70 (2 H, m), 1.86−1.90 (2 H, m), 2.98−3.01 (2 H, m), 3.31−3.34 (2 H, dd, J = 9.8, 7.7 Hz), 3.45−3.48 (2 H, m), 3.78 (2 H, s), 7.16 (5 H, s), 7.28−7.43 (12 H, m), 7.58−7.62 (8 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.39, 27.02, 27.78, 59.57, 66.60, 67.97, 126.77, 127.71, 128.09, 129.24, 129.59, 134.11, 135.72, 135.74, 140.36; HRMS calcd for $C_{45}H_{55}NO_2Si_2$ (M^+) 698.1082, found 698.1111.

(2*S*,5*S*)-17d and (2*S,5*R**)-18d.** By a procedure similar to that for the preparation of (2*R*,5*R*)-**17d** and (2*R**,5*S**)-**18d**, the pyrrolidines (2*S*,5*S*)-**17d** and (2*S**,5*R**)-**18d** were obtained in 19% and 6.9% yields, respectively, from (2*S*,5*S*)-**15d** (9.34 mmol). (2*S*,5*S*)-**17d**: $[\alpha]^{25}_D$ −40.1 (*c* 1.035, $CHCl_3$).

(2*S*,5*S*)-1d. The hydrogenolysis of (2*S*,5*S*)-**17d** was performed on a 0.058 mmol scale as described in the typical procedure (vide supra). The pyrrolidine (2*S*,5*S*)-**1d** was isolated in 96% yield: $[\alpha]^{25}_D$ −6.8° (*c* 1.41, EtOH); IR (neat) 3342, 2930, 2857, 1427, 1111, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (18H, s), 1.47−1.48 (2 H, m), 1.84−1.86 (2 H, m), 3.34−3.41 (1 H, m), 3.47−3.53 (2 H, m), 3.56 (2 H, d, J = 6.6 Hz), 3.64−3.70 (1 H, m), 7.39−7.49 (12 H, m), 7.67−7.71 (8 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.37, 19.45, 27.00, 27.05, 27.12, 27.36, 58.86, 60.62, 66.66, 67.37, 72.95, 127.84, 127.92, 127.93, 129.78, 129.95, 133.33, 133.87, 135.76, 135.82; HRMS calcd for $C_{38}H_{49}NO_2Si_2$ (M^+) 607.3302, found 607.3275.

(2*R*,6*R*)- and (2*R,6*S**)-*N*-Benzyl-2,6-bis[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-oxapiperidines [(2*R*,6*R*)-22] and [(2*R**,6*S**)-23].** The AD reaction was performed on the allyl ether **6** (7 mmol) as described in the typical procedure (vide supra) using $(DHQ)_2$−AQN as ligand. By a procedure similar to that for the preparation of **9** and **10**, a diastereomeric mixture of tetrol **21** (7 mmol) was converted in a three-step sequence [(1) imidazole (1.05 g, 15.4 mmol), TBDPSCl (3.45

mL, 13.3 mmol), DMF (11.6 mL); (2) *p*-toluenesulfonyl chloride (2.50 g, 14 mmol), triethylamine (2.27 mL, 14 mmol), DMAP (167 mg, 1.40 mmol) in CH_2Cl_2 (8 mL); (3) benzylamine (22.9 mL, 210 mmol)/90 °C] to (2*R*,6*R*)-**22** (1.68 g, 33.6%) and (2*R**,6*S**)-**23** (1.12 g, 22.4%) as oils. (2*R*,6*R*)-**22**: $[\alpha]^{27}_D$ +43.11° (*c* 3.96, $CHCl_3$); IR (neat) 2856, 1654, 1458, 1426, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (18 H, s), 2.81−2.84 (2 H, m), 3.44−3.81 (10 H, m), 7.13−7.23 (5 H, m), 7.31−7.43 (2H, m), 7.55−7.62 (8 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.32, 26.98, 54.50, 57.43, 61.07, 69.07, 126.78, 127.86, 128.10, 128.28, 129.83, 133.56, 133.61, 135.73, 140.32; HRMS calcd for $C_{45}H_{55}NO_3Si_2$ (M^+) 713.3720, found 713.3751.

23: IR (neat) 2856, 1654, 1459, 1427, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.99 (18 H, s), 2.70−2.73 (2 H, m), 3.34−3.98 (10 H, m), 7.02−7.05 (2 H, m), 7.14−7.26 (3 H, m), 7.28−7.43 (12 H, m), 7.52−7.54 (8 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.30, 26.97, 57.20, 60.87, 63.56, 69.83, 126.60, 127.57, 128.21, 129.78, 129.83, 133.52, 135.69, 140.77; HRMS calcd for $C_{45}H_{55}NO_3Si_2$ (M^+) 713.3720, found 713.3735.

(2*S*,6*S*)-22 and (2*S,6*R**)-23.** The AD reaction was performed on the allyl ether **6** (7 mmol) as described in the typical procedure (vide supra) using $(DHQD)_2$−AQN as ligand. By a procedure similar to that for the preparation of (2*R*,6*R*)-**22** and (2*R**,6*S**)-**23**, (2*S*,6*S*)-**22** and (2*S**,6*R**)-**23** were obtained in 38% and 23% yields, respectively. (2*S*,6*S*)-**22**: $[\alpha]^{26}_D$ −48.1° (*c* 3.96, $CHCl_3$).

(2*S*,6*S*)-*N*-Benzyl-2,6-bis(hydroxymethyl)-3-oxapiperidines [(2*S*,6*S*)-24]. A mixture of (2*R*,6*R*)-**22** (120 mg, 0.168 mmol) and concd HCl (0.99 mL) in THF (2.3 mL) was heated at 50 °C for 20 h. After the solvent was removed by rotary evaporation, the resulting aqueous residue was washed with ethyl acetate three times, basified with 2 N NaOH, and extracted with CH_2Cl_2 three times. The extracts were dried over anhyd K_2CO_3 and evaporated to yield (2*S*,6*S*)-**24** (30 mg, 75%) as an oil: $[\alpha]^{25}_D$ −37.04° (*c* 0.855, $CHCl_3$); IR (neat) 3364, 2856, 1454, 1126, 1044, 738, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.94−3.00 (2 H, m), 3.57−4.06 (12 H, m), 7.24−7.37 (5 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.06, 55.98, 59.69, 68.34, 127.61, 128.46, 128.93, 138.62; HRMS calcd for $C_{13}H_{19}NO_3$ 23.1365, found 237.1366. The ee of (2*S*,6*S*)-**24** was determined by HPLC analysis (Daicel Chiralpak AS, 10% *i*-PrOH/hexane, 0.5 mL/min) to be 93%.

(2*R*,6*R*)-24. By a procedure similar to that for the preparation of (2*S*,6*S*)-**24**, the hydrolysis of (2*S*,6*S*)-**22** was performed on a 0.182 mmol scale. The diol (2*R*,6*R*)-**24** was obtained in 81% yield: $[\alpha]^{25}_D$ +37.26° (*c* 0.73, $CHCl_3$); 98% ee.

(2*R*,6*R*)-*N*-2,6-Bis[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-oxapiperidines [(2*R*,6*R*)-3d]. A suspension of (2*R*,6*R*)-**22** (238 mg, 0.333 mmol) and palladium hydroxide (70 mg) in ethyl acetate (4.8 mL) under a hydrogen atmosphere was stirred for 48 h. The mixture was filtered through a Celite pad, and the filtrate was evaporated. The residue was chromatographed using hexanes−ethyl acetate (10:1) as eluent to give (2*R*,6*R*)-**3d** (156 mg, 75%) as an oil: $[\alpha]^{25}_D$ +10.1° (*c* 1.74, $CHCl_3$); IR (neat) 2856, 1654, 1427, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (18 H, s), 3.09−3.13 (2 H, m), 3.42 (2 H, dd, *J* = 5.5, 11.5 Hz), 3.58 (2 H, dd, *J* = 5.5, 9.9 Hz), 3.70−3.76 (4 H, m), 7.34−7.45 (12 H, m), 7.64−7.70 (8 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.41, 27.07, 51.87, 64.06, 68.85, 127.92, 129.91, 133.55, 135.72; HRMS calcd for $C_{38}H_{49}NO_3Si_2$ 623.3251, found 623.3276.

(2*S*,6*S*)-3d. The hydrogenolysis of (2*S*,6*S*)-**22** was performed on a 0.35 mmol scale as described in the typical procedure (vide supra). The morphorine (2*S*,6*S*)-**3d** was isolated in 63% yield: $[\alpha]^{25}_D$ +10.0° (*c* 2.39, $CHCl_3$).

(*S*)-5-Hexene-1,2-diol [(*S*)-25]. 1,5-Hexadiene **4** (0.5 mL, 4.2 mmol) was added to a mixture of AD-mix-α [$(DHQ)_2$−PYR ligand] (4.35 g, 9.2 mmol), *t*-BuOH (16.0 mL), and H_2O (16.0 mL) at 0 °C. After the reaction mixture was stirred for 24 h at the same temperature, sodium sulfite (4.89 g) was added to the mixture. The mixture was filtered through a Celite pad and combined, and the filtrate was extracted with ethyl acetate three times. The extracts were washed with brine, dried, and evaporated. The residue was chromatographed using hexanes−ethyl acetate (1:1) as eluent to give (*S*)-**25** (205 mg, 42%) as an oil: $[\alpha]^{25}_D$ −0.44° (*c* 3.1, $CHCl_3$); IR (neat) 3358, 2976, 1641, 1448, 1066, 996 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50−1.60 (2 H, m), 2.11−2.27 (2 H, m), 2.71−2.79 (2 H, br d), 3.43−3.48 (1 H, m), 3.64−3.75 (2 H, m), 4.98−5.08 (2 H, m), 5.80−5.88 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.92, 32.19, 66.74, 71.85, 115.16, 138.21; HRMS calcd for $C_6H_{12}O_2$ 116.0837, found 116.0850.

The ee of (*S*)-**25** was conveniently determined, by ^1H NMR analysis ($CDCl_3$, 500 MHz) of the corresponding bis-Mosher ester [2.3 equiv of (*R*)-MTPA-Cl, 3 equiv of DMAP, THF, 25 °C, 6 h], to be 70%.

(*R*)-25: $[\alpha]^{25}_D$ +0.49° (*c* 3.2, $CHCl_3$), 65%; 77% ee.

(*S*)-5-Heptene-1,2-diol [(*S*)-26]. The AD reaction of **5** was performed on a 0.73 mmol scale as described in the typical procedure (vide supra) using $(DHQ)_2$−PYR as ligand. The diol (*S*)-**26** was isolated in 81% yield: $[\alpha]^{26}_D$ −0.41° (*c* 1.9, EtOH); IR (neat) 3385, 2934, 1067, 911 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.54−1.64 (2 H, m), 1.81−1.91 (2 H, br s), 2.14−2.18 (2 H, m), 4.53 (1 H, dd, *J* = 9.0, 12.0 Hz), 4.67 (1 H, dd, *J* = 9.0, 12.0 Hz), 5.00−5.08 (2 H, m), 5.56−5.60 (1 H, m), 5.76−5.84 (1 H, m), 7.27−8.44 (8 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.73, 32.34, 33.55, 66.63, 72.09, 114.7, 138.3; HRMS calcd for $C_7H_{14}O_2$ 130.0994, found 130.0970. The ee of (*S*)-**26** was determined, by ^1H NMR analysis ($CDCl_3$, 500 MHz) of the corresponding bis-Mosher ester, to be 85%.

(*R*)-26: $[\alpha]^{25}_D$ +0.66° (*c* 2.9, $CHCl_3$), 81%; 88% ee.

(*R*)-3-(2-Propenyloxy)propane-1,2-diol [(*R*)-27]. The AD reaction of **6** was performed on a 1.64 mmol scale as described in the typical procedure (vide supra) using $(DHQ)_2$−AQN as ligand. The diol (*R*)-**27** was isolated in 76% yield: $[\alpha]^{28}_D$ −1.576° (*c* 1.6, $CHCl_3$); IR (neat) 3385, 2926, 1420, 1044, 928 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.09 (1 H, br s), 3.45−3.50 (2 H, m), 3.50−3.60 (1 H, m), 3.66−3.68 (1 H, m), 3.80 (1 H, br s), 3.85−3.87 (1 H, m), 4.00 (2H, d, *J* = 1.1 Hz), 5.18−5.29 (2 H, m), 5.85−5.93 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.07, 70.96, 71.60, 72.48, 117.55, 134.29; HRMS calcd for $C_6H_{12}O_3$ 132.0787, found 132.0782. The ee of (*R*)-**27** was determined, by ^1H NMR analysis ($CDCl_3$, 500 MHz) of the corresponding bis-Mosher ester, to be 83%.

(*S*)-27: $[\alpha]^{26}_D$ +1.887° (*c* 1.7, $CHCl_3$); 96%; 89% ee.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all compounds with high-resolution mass spectra (46 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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