ENANTIOSELECTIVE [2,3]-WITTIG REARRANGEMENT *VIA* A CHIRAL BORON ESTER ENOLATE

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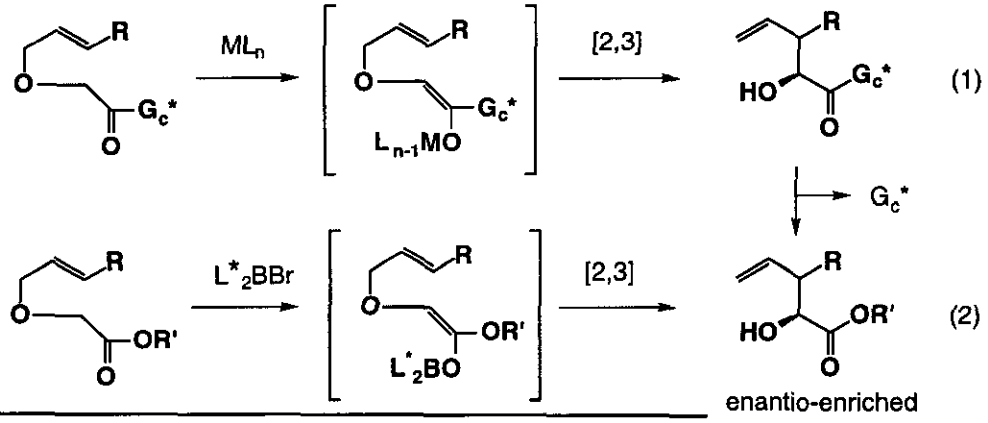
Abstract - The first enantioselective [2,3]-Wittig rearrangement of α-(allyloxy)- acetates is described which involves a chiral boron enolate with a chiral bis-sulfonamide ligand to afford the α-hydroxy-β-alkyl-γ,δ-unsaturated esters in a high enantioselectivity (>95%ee), along with a high *threo* diastereoselectivity.

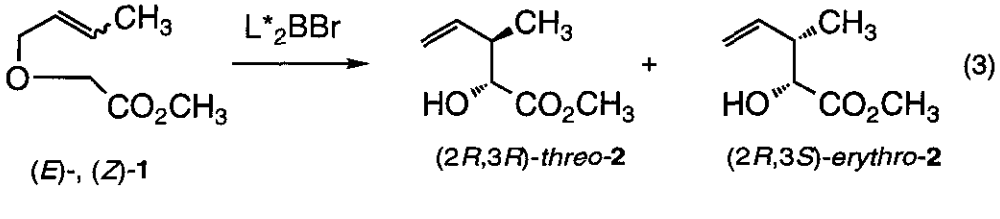
The [2,3]-Wittig sigmatropic rearrangement currently enjoys wide application in organic synthesis.[2] Of special value among many variants is the "enolate [2,3]-Wittig" rearrangement that involves an enolate as the migrating terminus to eventually provide α-hydroxy-β-alkylcarboxylic acid derivatives of biological and synthetic importance.[2] Recently several asymmetric versions of the enolate [2,3]-Wittig process have been developed which involve a chiral enolate terminus generated from optically active substrates or auxiliaries (eq 1).[3] However, no example has been reported of the *enantioselective* version that involves a chiral ligand-bound ester enolate.[4] Herein we wish to report the first example of the enantioselective version of the ester enolate [2,3]-Wittig rearrangement (eq 2).[5] The key to this success is the use of a chiral boron enolate terminus containing a chiral bis-sulfonamide as the controller ligand (L*).



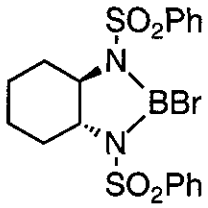
This paper is dedicated to the memory of the late Professor Yoshio Ban

After several attempts,[6] we chose as a chiral ligand on boron chiral bis-sulfonamides, easily prepared from commercially available (1*R*,2*R*)-1,2-diaminocyclohexane[7a] and (1*R*,2*R*)-1,2-diamino-1,2-diphenylethane,[7b] and prepared the chiral boron reagents (**3**) and (**4**) from BBr_3 and the chiral bis-sulfonamides according to the literature procedure.[7c]

First, we studied the rearrangement of (*E*)-**1** using the boron reagents (**3**) and (**4a-c**) (eq 3). Thus, (*E*)-**1** was treated with a slight excess of **3** or **4** in the presence of Et_3N in CH_2Cl_2 at -50 °C to afford a diastereomeric mixture of the enantio-enriched α-hydroxy-β-methyl ester (**2**) in moderate yields. The results are summarized in Table 1 (Entries 1-4).



(*E*)-, (*Z*)-**1** (2*R*,3*R*)-*threo*-**2** (2*R*,3*S*)-*erythro*-**2**



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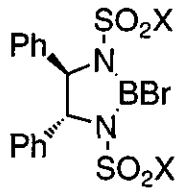


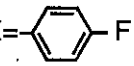
4a ; X= phenyl
4b ; X=CH_3
4c ; X= β-naphthyl
4d ; X= 

Table 1. Eantioselective Rearrangements of (*E*)- or (*Z*)-**1**

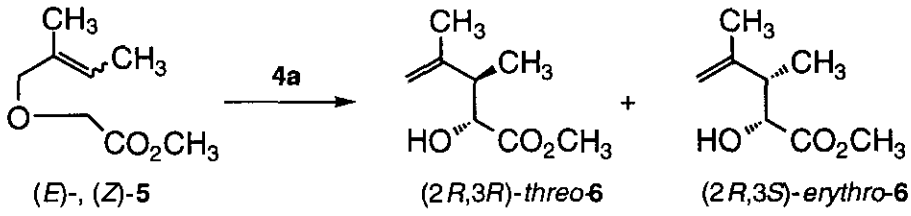
Entry	Substrate	L*2BBr	%Yield	*threo*:*erythro* [a]	%ee [b]	Config.[c]
1	(*E*)-1	**3**	69	68:32	62 (*threo*)	2*R*,3*R*
					40 (*erythro*)	2*R*,3*S*
2	(*E*)-1	**4a**	66	83:17	96 (*threo*)	2*R*,3*R*
					71 (*erythro*)	2*R*,3*S*
3	(*E*)-1	**4b**	57	63:37	90 (*threo*)	2*R*,3*R*
					68 (*erythro*)	2*R*,3*S*
4	(*E*)-1	**4c**	27	66:34	90 (*threo*)	2*R*,3*R*
					55 (*erythro*)	2*R*,3*S*
5	(*Z*)-1	**4a**	56	84:16	94 (*threo*)	2*R*,3*R*
					38 (*erythro*)	2*R*,3*S*

(a) Determined by ^{1}Hnmr analysis. (b) Determined by hplc analysis of the MTPA esters. (c) Assigned by LIS-nmr analysis as described in our previous paper (ref. 3a).

As seen in Table 1, the present rearrangements uniformly exhibit (*R*)-preference at C-2 of **2** and *threo* preference between the two new chiral centers. Interestingly, the yields and the levels of enantio- and diastereoselection vary critically with the structure of chiral ligands. While the use of **3** leads to the modest levels of enantioselectivity (62%ee) and *threo* selectivity (68%), the use of **4a** provides the highest degrees of enantioselectivity (96%ee) and *threo* selectivity (83%). Of particular interest is the relatively high *E*→*threo* selection observed here, which is in sharp contrast to the high *E*→*erythro* selections previously reported for the [2,3]-Wittig rearrangements of (*E*)-**1** involving lithium,[8] zirconium,[9] tin,[10] titanium,[10] and dialkylboron[11] enolates.

Next, we carried out the rearrangement of (*Z*)-**1**. Under the same conditions as described above, (*Z*)-**1** was treated with **4a** to afford a stereoisomeric mixture of **2**, again, in a high enantioselectivity (94%ee) and *threo* selectivity (84%) (Entry 5). These findings indicate that, surprisingly enough, the present rearrangements of (*E*)- and (*Z*)-**1** exhibit the identical senses of both enantio- and diastereoselection regardless of the crotyl geometry.

In order to gain more information about the rather unusual diastereoselection observed above, we also examined the rearrangements of (*E*)- and (*Z*)-**5** which have a β-methyl on the allylic moiety (eq 4). Thus, (*E*)- or (*Z*)-**5** was treated with **4a** under the same conditions as described above. We found that the

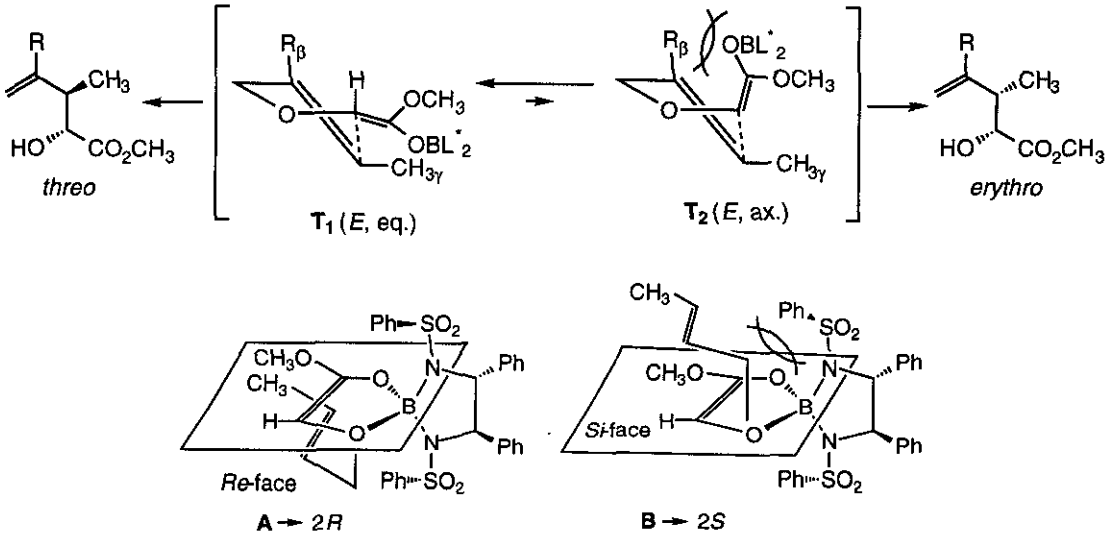


(*E*)-, (*Z*)-**5** (2*R*,3*R*)-*threo*-**6** (2*R*,3*S*)-*erythro*-**6** (4)

rearrangement of (*E*)-**5** afforded *threo*-**6** as the major product (48% yield) in a high diastereo- (96%) and enantioselectivity (94%ee, 2*R*-preference), whereas the rearrangement of (*Z*)-**5** showed the opposite sense of diastereoselection to give *erythro*-**6** (48% yield) in a high diastereo- (95%) and enantioselectivity (94%ee, 2*R*-preference).[12] Interestingly, these observed levels of diastereoselection are significantly higher than those observed with (*E*)- and (*Z*)-**1**, while the enantioselectivities are equally high. Of particular interest is the high *Z*→*erythro* selection observed with (*Z*)-**5**, which is in sharp contrast to the high *Z*→*threo* selection observed with (*Z*)-**1**. These findings indicate that the β-substituent on the allylic moiety might exert a great influence in dictating the sense and degree of diastereoselection.

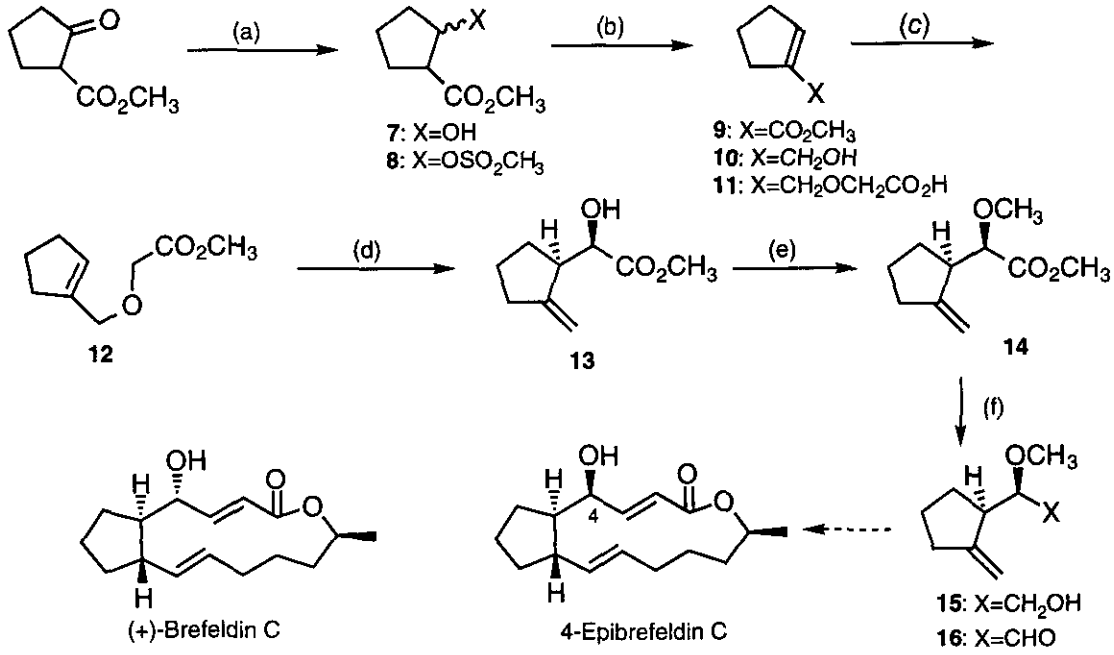
At present we have no definitive explanation to accommodate these stereochemical outcomes owing to the great complexities of this process. Nonetheless, the *E* →*threo* selections are reasonably interpreted as the result that the transition state **T1** is sterically more favorable than **T2**, since the 1,3-diaxial repulsion of the enolate part with R_β (H or CH_3) in **T2** would prevail over the gauche repulsion of the enolate part with the γ–methyl group in **T1**. The equatorial preference for the enolate part in the transition states can also account for the *erythro* selection for (*Z*)-**5**, but not for the unusual *threo* selection for (*Z*)-**1**, of which the origin is still unclear.[13] Furthermore, the observed sense of enantioselection (2*R*) might be interpreted as

follows. The enolization leads to the metal-chelated (*E*)-enolate which undergoes the [2,3]-shift preferentially from the bottom side (*Re*-face) as depicted in formula **A**, where the steric repulsion between the crotyl and phenyl groups would be minimized.



Finally, we turned our attention to the application of this type of enantioselective [2,3]-Wittig variant to the asymmetric synthesis of (epi)brefeldin C intermediate (Scheme 1). Brefeldin C, a fungal metabolite isolated from *Eupenicillium brefeldianum* by Nozoe *et al.*,[14] is known to be a biosynthetic precursor[15] of brefeldin A,[16] a macrolide antibiotic possessing a wide range of biological activity. Two groups have already completed the total synthesis of (+)-brefeldin C.[17] The key to our approach is the level of asymmetric induction, along with a high degree of either *threo* or *erythro* selectivity in the rearrangement of the (1-cyclopentenyl)methyl ether (**12**); the *threo*- and *erythro* selective process lead to (+)-brefeldin C and 4-epibrefeldin C, respectively. The requisite substrate (**12**) was prepared from methyl 2-oxocyclopentanecarboxylate in 41% overall yield *via* the conventional six-step sequence depicted in Scheme 1. The rearrangement of **12** was first carried out using the chiral boron reagent (**4a**). Unfortunately, **13** was obtained in poor yield (7%). After several attempts, we found that the use of the chiral boron reagent (**4d**) derived from the *p*-fluorophenyl-substituted bis-sulfonamide afforded **13** in 54% yield as a single stereoisomer. The enantiomeric purity of **13** was determined to be 98%ee by ^{1}Hnmr analysis of its (*R*)-MTPA ester. The absolute configuration at the hydroxy center of **13** was assigned to be *R* from ^{1}Hnmr analysis of the (*S*)- and (*R*)-MTPA esters by the modified Mosher method.[18] The relative configuration was assigned to *threo* after its conversion to the epibrefeldin C intermediate (**18**). Thus, **13** was transformed into aldehyde (**16**) *via* the three-step sequence: etherification, reduction, and Swern oxidation, and then aldehyde (**16**) was further converted to **18** according to Corey's procedure.[19] Product (**18**) was distinguished by ^{1}Hnmr from the *erythro*-rich authentic sample previously reported from our laboratory,[20] thereby confirming the *threo* stereochemistry. Overall, this rearrangement was found to exhibit an extremely high enantioselectivity (98%ee; 2*R*, 3*R*) and *threo*-selectivity (99%), thus providing a useful tool for asymmetric synthesis of 4-epibrefeldin C.

Scheme 1



(a) (1) $NaBH_4$, (2) MsCl, $(C_2H_5)_3N$; (b) (1)CH_3OK, (2) DIBAL, (3) NaH, $BrCH_2CO_2H$;
(c) CH_2N_2, 41% (6 steps); (d) 4d, $(C_2H_5)_3N$, 54%; (e) CH_3I, Ag_2O, quant.; (f) (1) $LiAlH_4$, quant.
(2) $(COCl)_2$, DMSO, $(i\text{-}C_3H_7)_2NC_2H_5$, 62%, (3) CBr_4, PPh_3, Zn, 53% (4) $n\text{-}C_4H_9Li$, TMSCl, 51%.

In summary, we have developed the first enantioselective version of the ester enolate [2,3]-Wittig rearrangement which involves a chiral ligand-bound boron enolate to provide the α-hydroxy β-methyl ester in a high enantio- and diastereoselectivity. The synthetic potential of this enantioselective variant has been demonstrated by the asymmetric synthesis of 4-epibrefeldin C intermediate. Further efforts are in progress to prove this interesting process and to apply the present methodology to natural product synthesis.

EXPERIMENTAL

Melting points and boiling points are uncorrected. Ir spectra were recorded on JASCO FT/IR-5000 spectrophotometer. ^{1}HNmr spectra were recorded on Varian Gemini-200 (200 MHz), Varian Gemini-300 (300 MHz) spectrometers and ^{13}Cnmr spectra were recorded on Varian Gemini-200, Varian Gemini-300 spectrometers, and chemical shifts were reported in ppm using TMS or $CHCl_3$ as internal standard. High resolution mass spectra were performed on JEOL JMS-505H, AX-500 mass spectrometer. Hplc analyses were run on a Shimazu LC-6A pump equipped with a 4.6 mm x 250 mm ODS L-column and Shimazu SPD-6A as a uv detector (254 nm).

Preparation of Substrates for [2,3]-Wittig Rearrangement.

The (allyloxy)acetic acids, prepared from an allylic alcohol and bromoacetic acid according to the previous report,[21] were treated with CH_3OH in the presence of 1,1'-carbonyldiimidazole in CH_3CN or CH_2N_2 in ether to afford substrates (**1**) and (**5**).

Data for (*E*)-**1**: Ir (neat), 1765, 1674, 1439, 1283, 1211, 1142, 1134, 970 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 1.72 (d, *J* =6.3 Hz, 3H), 3.76 (s, 3H), 4.02 (d, *J* =6.4 Hz, 2H), 4.07 (s, 2H), 5.52~5.64 (m, 1H), 5.68~5.82 (m, 1H); ^{13}Cnmr ($CDCl_3$), δ 18.1, 51.8, 66.8, 72.1, 126.6, 131.1, 171.0; ms (EI), *m/z* 143 (M^+-H, 16), 129 (3), 71 (100), 55 (93), 43 (26).

Data for (*Z*)-**1**: Ir (neat), 1755, 1660, 1440, 1378, 1214, 1137 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 1.67 (d, *J* =6.0 Hz, 3H), 3.76 (s, 3H), 4.08 (s, 2H), 4.16 (d, *J* =6.6 Hz, 2H), 5.52~5.62 (m, 1H), 5.68~5.79 (m, 1H); ^{13}Cnmr ($CDCl_3$), δ 13.2, 51.9, 66.5, 67.0, 125.7, 129.4, 171.0; ms (EI), *m/z* 143 (M^+-H, 3), 129 (4), 71 (100), 55 (96), 43 (27).

Data for (*E*)-**5**: Ir (neat), 1756, 1439, 1383, 1282, 1211, 1134 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 1.62 (d, *J* =6.9 Hz, 3H), 1.65 (s, 3H), 3.74 (s, 3H), 3.94 (s, 2H), 4.01 (s, 2H), 5.50 (q, *J* =6.9 Hz, 1H); ^{13}Cnmr ($CDCl_3$), δ 13.2, 13.5, 51.8, 66.4, 77.6, 124.2, 132.0, 171.1; HRms found *m/z* 158.0949, calcd for $C_8H_{14}O_3$ 158.0943.

Data for (*Z*)-**5**: Ir (neat), 1736, 1650, 1382, 1224, 1131, 1098, 987, 949 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 1.63 (d, *J* =6.9 Hz, 3H), 1.75 (s, 3H), 3.75 (s, 3H), 4.03 (s, 2H), 4.10 (s, 2H), 5.49 (q, *J* =6.9 Hz, 1H); ms (EI), *m/z* 158 (M^+, 1), 144 (4), 116 (21), 87 (41), 71 (32), 58 (36), 43 (100).

Preparation of Bis-sulfonamides.

(1*R*, 2*R*)-1,2-*N*, *N'*-Bis(benzenesulfonylamino)cyclohexane.

To a solution of (1*R*, 2*R*)-1,2-diaminocyclohexane (3.0 g, 26.3 mmol) in CH_2Cl_2 (30 ml) was added Et_3N (8.42 ml, 60.4 mmol) and benzenesulfonyl chloride (10.7 g, 60.4 mmol) at 0 °C. The resulting mixture was stirred for 15 h at room temperature and then quenched by addition of water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed successively with 1*N* HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product. Purification of the crude product by silica gel chromatography gave the title compound (10.4 g, quant.). Ir (KBr), 3280, 3066, 2939, 2862, 1448, 1327, 1161, 1093, 971 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 1.11 (m, 4H), 1.57 (m, 2H), 1.82 (m, 2H), 2.78 (m, 2H), 4.82 (m, 2H), 7.49~7.63 (m, 6H), 7.87 (d, *J*=6.8 Hz, 4H); ^{13}Cnmr ($CDCl_3$), δ 24.2, 33.4, 56.7, 127.2, 129.2, 132.8, 140.1; HRms found *m/z* 395.1106, calcd for $C_{18}H_{23}N_2O_4S_2$ 395.1101.

(1*R*, 2*R*)-1,2-*N*, *N'*-Bis(benzenesulfonylamino)-1,2-diphenylethane.

mp 162~164 °C; ir (KBr), 3292, 1448, 1326, 1163, 1092, 935 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 4.53 (m, 2H), 5.80 (m, 2H), 6.67 (d, *J*=7.3 Hz, 4H), 6.92 (dd, *J*=7.3, 7.3 Hz, 4H), 7.00 (t, *J*=7.3 Hz, 2H), 7.26 (dd, *J*=8.1, 7.3 Hz, 4H), 7.39 (t, *J*=7.3 Hz, 2H), 7.60 (d, *J*=8.1 Hz, 4H); ^{13}Cnmr ($CDCl_3$), δ 62.4, 127.1, 127.6, 127.8, 128.1, 128.7, 132.3, 136.1, 140.0; HRms found *m/z* 493.1252, calcd for $C_{26}H_{25}N_2O_4S_2$ 493.1253.

(1*R*, 2*R*)-1,2-*N*, *N'*-Bis(methanesulfonylamino)-1,2-diphenylethane.
mp 164~170 °C; ir (KBr), 3299, 3032, 1497, 1457, 1319, 1151, 1066, 983 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 2.57 (s, 6H), 4.69 (m, 2H), 5.99 (m, 2H), 7.13 (m, 4H), 7.22 (m, 6H); ^{13}Cnmr (DMSO-d_6), δ 41.0, 62.1, 127.2, 127.4, 128.0, 139.7; ms (EI), *m/z* 368 (M^+, 1), 184 (100), 106 (64), 77 (5)

(1*R*, 2*R*)-1,2-*N*, *N'*-Bis(β-naphtharenesulfonylamino)-1,2-diphenylethane.
mp 227~229 °C; ir (KBr), 3287, 3059, 1504, 1457, 1329, 1160, 1130, 1074, 955, 928 cm^{-1}; ^{1}Hnmr (DMSO-d_6), δ 4.62 (m, 2H), 6.53 (t, *J*=7.2 Hz, 2H), 6.62 (dd, *J*=7.2, 7.2 Hz, 4H), 6.81 (d, *J*=7.2 Hz, 4H), 7.40 (d, *J*=8.8 Hz, 2H), 7.50~7.61 (m, 4H), 7.71 (d, *J*=8.8 Hz, 2H), 7.81~7.87 (m, 4H) 7.91 (s, 2H), 8.45 (m, 2H); ^{13}Cnmr (DMSO-d_6), δ 62.4, 121.8, 126.3, 126.8, 127.0, 127.1, 127.4, 128.1, 128.3, 128.8, 131.2, 133.6, 137.5, 138.1; HRms found *m/z* 593.1566, calcd for $C_{34}H_{29}N_2O_4S_2$ 593.1571.

(1*R*, 2*R*)-1,2-*N*, *N'*-Bis(*p*-fluorobenzenesulfonylamino)-1,2-diphenylethane.
mp 190~192 °C; ir (KBr), 3290, 1591, 1494, 1457, 1332, 1292, 1231, 1153, 1091, 936 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 4.59 (m, 2H), 6.14 (m, 2H), 6.69 (d, *J*=7.3 Hz, 4H), 6.84~6.94 (m, 8H), 7.00 (t, *J*=7.3 Hz, 2H), 7.56 (m, 4H); ^{13}Cnmr ($CDCl_3$), δ 62.5, 115.7, 115.9, 127.6, 127.9, 128.2, 129.7, 129.8, 135.8, 136.1, 163.5, 166.0; HRms found *m/z* 529.1059, calcd for $C_{26}H_{23}N_2O_4F_2S_2$ 529.1069.

A Typical Procedure for the [2,3]-Wittig Rearrangements.
To a solution of **4a** [prepared from (1*R*,2*R*)-1,2-*N*,*N'*-bis(benzenesulfonylamino)-1,2-diphenylethane (0.64 g, 1.3 mmol) and BBr_3 (1M in CH_2Cl_2, 1.3 ml, 1.3 mmol)][7c] in CH_2Cl_2 (3 ml) was added dropwise a solution of (*E*)-**1** (0.144 g, 1 mmol) and Et_3N (0.21 ml, 1.5 mmol) in CH_2Cl_2 (2.5 ml) at -50 °C. The resulting mixture was stirred for 2 h at -50 °C and then quenched by addition of water at -50 °C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product. Purification of the crude product by silica gel chromatography (hexane:ethyl acetate=13:1) gave **2** (0.095 g, 66% yield) (Entry 2).

Methyl 2-hydroxy-3-methyl-4-pentenoate (2).
Ir (neat), 3491, 1740, 1642, 1440, 1265, 1216, 1128, 1078, 998, 920 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 1.16 (d, *J* =7.0 Hz, 3H), 2.57~2.75 (m, 2H), 3.78 (s, 3H), 4.13 (m, 1H), 5.05 (d, *J*=17.2 Hz, 1H), 5.07 (d, *J*=9.7 Hz, 1H), 5.68~5.80 (m, 1H); ^{13}Cnmr ($CDCl_3$), δ 16.2, 41.9, 52.9, 74.5, 116.5, 137.7, 174.6 for *threo*-**2** ; ^{1}Hnmr ($CDCl_3$), δ 1.01 (d, *J* =7.0 Hz, 3H), 2.57~2.75 (m, 2H), 3.80 (s, 3H), 4.18 (m, 1H), 5.09 (d, *J*=9.6 Hz, 1H), 5.12 (d, *J*=17.4 Hz, 1H), 5.77~5.90 (m, 1H); ^{13}Cnmr ($CDCl_3$), δ 13.7, 41.7, 52.4, 74.0, 115.6, 139.3, 174.6 for *erythro*-**2**; HRms found *m/z* 145.0859, calcd for $C_7H_{13}O_3$ 145.0865.

Methyl 2-hydroxy-3,4-dimethyl-4-pentenoate (6).
^{1}HNmr ($CDCl_3$), δ 1.14 (d, *J* =7.1 Hz, 3H), 1.71 (s, 3H), 2.55~2.67 (m, 1H), 2.59 (d, *J* =5.3 Hz, 1H), 3.76 (s, 3H), 4.13 (dd, *J* =5.3, 6.6 Hz, 1H), 4.78 (m, 1H), 4.86 (m, 1H) for *threo*-**6** ; δ 1.01 (d, *J* =7.0 Hz, 3H), 1.80 (s, 3H), 2.55~2.67 (m, 1H), 2.62 (d, *J* =5.8 Hz, 1H), 3.79 (s, 3H), 4.28 (dd, *J* =3.8, 5.8 Hz, 1H), 4.82 (m, 1H), 4.88 (m, 1H) for *erythro*-**6**.

Determination of the Enantiomeric Excess of 2 and 6.

To a solution of product (**2**) or a diastereomeric mixture of (±)-**2** (*threo*:*erythro*=80:20)[22] in pyridine was added (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPACl] at room temperature. After stirring for 1 h at room temperature, the resulting mixture was diluted with ether, and the organic layer was washed successively with 1*N* HCl, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtrated and concentrated under reduced pressure to afford the (*R*)-MTPA esters, which were analyzed by hplc [L-column ODS ; eluent , CH_3CN : H_2O = 2 : 1 (0.01*M* $AcONH_4$) ; flow rate 1.0 ml/min ; detection, 254 nm]. Data for **2:** 2*S*,3*S* isomer, t_R=14.7 min ; 2*S*,3*R* isomer, t_R=15.2 min ; 2*R*,3*R* isomer, t_R=16.0 min ; 2*R*,3*S* isomer, t_R=16.6 min. Data for **6:** 2*S*,3*S* isomer, t_R=18.5 min ; 2*S*,3*R* isomer, t_R=19.2 min ; 2*R*,3*R* isomer, t_R=20.5 min ; 2*R*,3*S* isomer, t_R=21.3 min.

Determination of the Absolute Configuration of 2 and 6.

The absolute configuration for **2** was assigned by LIS-nmr analysis as described in our previous paper.[3c] To a solution of **2** (14.4 mg) in $CDCl_3$ (0.4 ml) was added a 30 w/v% CCl_2FCClF_2 solution of (+)-Eu(DPPM)$_3$ (55 μl). Each of the two singlets due to the methoxy group at δ 3.78 (*threo*) and 3.80 (*erythro*) was separated into the two singlets at δ 4.53 (2*R*, 3*R*-isomer), 4.58 (2*S*, 3*S*-isomer), 4.62 (2*R*, 3*S*-isomer), and 4.69 (2*S*, 3*R*-isomer) (Entry 1). The absolute configuration of **6** was tentatively assigned by hplc similarity of its (*R*)-MTPA ester with that of **2**.

Asymmmetric Synthesis of 4-Epibreferdin C Intermediate.

Methyl 2-hydroxycyclopentanecarboxylate (7).

To a solution of methyl 2-oxocyclopentanecarboxylate (15 g, 102 mmol) in THF/CH_3OH (1:1, 200 ml) was added $NaBH_4$ (1.94 g, 51 mmol) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and then the solvent was cocentrated under reduced pressure. To the residue was added 1*M* KH_2PO_4 (375 ml) and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product. Purification of the crude product by silica gel chromatography (hexane:ethyl acetate=10:1) gave **7** as a diastereomeric mixture (13.5 g, 92% yield). Ir (neat), 3500, 1734, 1203 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 1.55~2.10 (m, 6H), 2.25 (br s, 0.45H), 2.63~2.73 (m, 1H), 3.02 (bs, 0.55H), 3.70 (s, 0.45H), 3.72 (s, 0.55H), 4.37 (m, 0.45H), 4.43 (m, 0.55H); ^{13}Cnmr ($CDCl_3$), δ 22.2, 22.4, 26.4, 27.6, 34.2, 34.5, 49.8, 52.0, 52.8, 74.1, 175.6, 176.1; HRms found *m/z* 145.0831, calcd for $C_7H_{13}O_3$ 145.0865.

Methyl 2-methanesufonyloxycyclopentanecarboxylate (8).

To a solution of **7** (12.62 g, 87.5 mmol) in CH_2Cl_2 (130 ml) was added dropwise methanesulfonyl chloride (8.13 ml, 105 mmol) and Et_3N (14.64 ml, 105 mmol) at 0 °C. The resulting mixture was stirred for 1 h at room temperature and then quenched by addition of water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed successively with 1*N* HCl and saturated aqueous $NaHCO_3$; dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product (**8**) as a diastereomeric mixture (19.2 g, 98% yield). Ir (neat), 2960, 1740, 1357, 1178 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 1.65~2.23 (m, 6H), 2.85~3.02 (m, 1H), 2.97 (s, 0.55H), 3.02 (s,

0.45H), 3.71 (s, 3H), 5.20~5.30 (m, 1H); ^{13}Cnmr ($CDCl_3$), δ 21.3, 22.8, 24.7, 28.0, 33.0, 33.2, 37.8, 38.1, 50.3, 51.8, 52.0, 84.5, 84.7, 171.1, 173.7.

Methyl 1-cyclopentenecarboxylate (9).

To a solution of **8** (10.63 g, 55.9 mmol) in THF/CH_3OH (3:1, 320 ml) was added CH_3OK (9.01 g, 129 mmol) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and then poured to a mixture of 5% aqueous citric acid and ether. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with 1% aquerous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude ester (**9**) (7.05 g, quant.). ^{1}HNmr ($CDCl_3$), δ 1.93 (m, 2H), 2.40~2.60 (m, 4H), 3.70 (s, 3H), 6.75 (m, 1H); ^{13}Cnmr ($CDCl_3$), δ 23.0, 31.3, 33.3, 51.3, 136.4, 144.0, 166.0.

1-Cyclopentenylmethanol (10).

To a solution of **9** (8.07 g, 71.4 mmol) in ether (200 ml) was added dropwise DIBAL (1*M* in hexane, 141 ml, 141 mmol) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and then CH_3OH (9.2ml) and saturated aqueous $NaHCO_3$ were added. After stirring for 15 h at room temperature, the resulting mixture was quenched by addition of 1*N* HCl. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product. Distillation of the crude product gave **10** (5.26 g, 75% yield). bp 88~90 °C (29 mmHg); ir (neat), 3230, 1659 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 1.68 (br s, 1H), 1.84~1.94 (m, 2H), 2.27~2.37 (m, 4H), 4.17 (s, 2H), 6.00 (m, 1H); ^{13}Cnmr ($CDCl_3$), δ 23.3, 32.2, 32.4, 62.1, 125.5, 144.3; HRms found *m/z* 98.0736, calcd for $C_6H_{10}O$ 98.0732.

(1-Cyclopentenyl)methoxyacetic acid (11).

To a suspension of NaH (55% in oil, 3.11 g, 71.4 mmol) in THF (20 ml) was added dropwise a solution of **10** (2.5 g, 25.5 mmol) in THF (25 ml) at 0 °C. The resulting mixture was stirred for 1.5 h at room temperature and then a solution of bromoacetic acid in THF (25ml) was added dropwise at 0 °C. After stirring for 15 h at room temperature, the resulting mixture was poured to ice water and then washed with hexane. After acidification to pH 1 with 6*N* hydrochloric acid, the aqueous layer was saturated with NaCl and then extracted three times with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product. Distillation of the crude product gave **11** (2.3 g, 70% yield). bp 96~104 °C (3 mmHg); ir (neat), 1734, 1429, 1110 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 1.82~1.95 (m, 2H), 2.25~2.38 (m, 4H), 4.09 (s, 2H), 4.15 (s, 2H), , 5.67 (m, 1H), 9.35 (br s, 1H); ^{13}Cnmr ($CDCl_3$), δ 23.2, 32.3, 32.7, 66.3, 70.1, 129.6, 139.3, 175.5; HRms found *m/z* 156.0777, calcd for $C_8H_{12}O_3$ 156.0787.

Methyl (1-cyclopentenyl)methoxyacetate (12).

To a solution of **11** (2.0 g, 13.0 mmol) in ether (20 ml) was added dropwise a solution of CH_2N_2 in ether at room temperature and then the solvent was evaporated under reduced pressure to afford the crude ester

(**12**) (2.09 g, 94% yield). Ir (neat), 1758, 1112 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 1.85~1.95 (m, 2H), 2.29~2.40 (m, 4H), 3.75 (s, 3H), 4.06 (s, 2H), 4.14 (s, 2H), 5.67 (m, 1H); ^{13}Cnmr ($CDCl_3$), δ 23.2, 32.3, 32.7, 51.7, 66.9, 70.1, 129.2, 144.4, 171.1; HRms found *m/z* 170.0944, calcd for $C_9H_{14}O_3$ 170.0943.

(2*R*, 1'*R*)-Methyl 2-hydroxy-2-(2'-methylidene-1'-cyclopentyl)acetate (13).

Treatment of **12** (0.17 g, 1 mmol) with **4d** as described for **1** gave **13** as a single stereoisomer (0.092 g, 54%). Ir (neat), 3316, 2956, 1740, 1655 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 1.45~2.00 (m, 4H), 2.25~2.40 (m, 2H), 2.70 (br s, 1H), 2.80~2.95 (m, 1H), 3.78 (s, 3H), 4.19 (dd, *J*= 7.0, 4.0 Hz, 1H), 4.72 (m, 1H), 5.00 (m, 1H); ^{13}Cnmr ($CDCl_3$), δ 24.6, 29.8, 34.5, 46.9, 52.1, 72.1, 107.3, 151.4, 174.8; ms (EI), *m/z* 170 (M^+, 1), 152 (12), 111 (11), 90 (16), 81(100), 67(11).

The *threo/erythro* ratio of **13** was determined by ^{1}Hnmr analysis. A diastereomeric mixture of (±)-**13** was prepared as follows. To a solution of LDA, prepared from *n*-BuLi (1.4 *M* in hexane, 28.5ml, 39.9 mmol) and diisopropylamine (5.06 ml, 38.6mmol) in THF (23 ml), was added dropwise **11** (1.77 g, 11.4 mmol) in THF (9ml) at -78 °C. The resulting mixture was stirred for 15 h at -78 °C, quenched by water, and the resulting solution was washed with ether. After acidification to pH 1 with 6*N* hydrochloric acid, the aqueous layer was saturated with NaCl and extracted three times with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was treated with a solution of CH_2N_2 in ether to afford the crude product. Purification of the crude product by silica gel chromatography (hexane:ethyl acetate=10:1) gave (±)-**13** as a diastereomeric mixture (1.05 g, 54% yield, *threo* : *erythro*=65:35). Data for the *threo* isomer are described above. Data for the *erythro* isomer: ^{1}HNmr ($CDCl_3$), δ 1.45~2.00 (m, 4H), 2.25~2.40 (m, 2H), 2.80~2.95 (m, 1H), 3.78 (s, 3H), 4.45 (dd, *J*= 5.0, 3.3 Hz, 1H), 4,93 (m, 1H), 5.07 (m, 1H); ^{13}Cnmr ($CDCl_3$), δ 24.5, 29.7, 33.9, 46.8, 52.3, 71.9, 106.0, 152.4, 175.0.

After its conversion to the (*R*)-MTPA ester, the %ee was calculated by integrations of the two peaks (C<u>H</u>-OMTPA). ^{1}HNmr ($CDCl_3$), δ 5.13 (d, *J*=5.2 Hz, 1H) for (2*R*, 1*R*')-isomer; δ 5.18 (d, *J*=5.2 Hz, 1H) for (2*S*, 1*S*')-isomer.

Determination of the Absolute Configuration of 13.

Data for (*R*)-MTPA ester: ^{1}HNmr ($CDCl_3$), δ 1.20~1.90 (m, 4H), 2.18 (m, 2H), 3.00 (m, 1H), 3.67 (s, 3H), 3.78 (s, 3H), 4.63 (m, 1H), 4.88 (m, 1H), 5.13 (d, *J*=5.2 Hz, 1H), 7.40 (m, 3H), 7.63 (m, 2H) ; Data for (*S*)-MTPA ester: ^{1}HNmr ($CDCl_3$), δ 1.21~1.98 (m, 4H), 2.29 (m, 2H), 3.06 (m, 1H), 3.50 (s, 3H), 3.76 (s, 3H), 4.82 (m, 1H), 4.99 (m, 1H), 5.18 (d, *J*=5.2 Hz, 1H), 7.40 (m, 3H), 7.63 (m, 2H). The absolute configuration at the hydroxy center was determined to be *R* by the modified Mosher method.

(2*R*, 1'*R*)-Methyl 2-methoxy-2-(2'-methylidene-1'-cyclopentyl)acetate (14).

To a solution of **13** (0.6g, 3.5 mmol) in ether (40 ml) was added CH_3I (4.4 ml, 71.0 mmol) and Ag_2O (16 g, 71.0 mmol). The resulting mixture was stirred for 40 h at room temperature, filtered, and concentrated under reduced pressure to afford **14** (0.66 g, quant.). ^{1}HNmr ($CDCl_3$), δ 1.45~1.95 (m, 4H), 2.25~2.40

(m, 2H), 2.78~2.90 (m, 1H), 3.40 (s, 3H), 3.73 (d, *J*= 6.3 Hz, 1H), 3.77 (s, 3H), 4.94 (m, 1H), 4.99 (m, 1H) .

(2*R*, 1'*R*)-2-Methoxy-2-(2'-methylidene-1'-cyclopentyl)ethanol (15).

To a suspension of $LiAlH_4$ (0.3 g, 7.9 mmol) in ether (5 ml) was added dropwise **14** (0.66 g, 3.6 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C and then $Na_2SO_4 \cdot 10H_2O$ was added. After stirring for 1 h at room temperature, the resulting mixture was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure to afford the crude alcohol (**15**) (0.57 g, quant.). ^{1}HNmr ($CDCl_3$), δ 1.37~1.95 (m, 4H), 2.32 (m, 3H), 2.74~2.86 (m, 1H), 3.30~3.80 (m, 3H), 3.44 (s, 3H), 4.94 (s, 1H), 4.97 (s, 1H).

(2*R*, 1'*R*)-2-Methoxy-2-(2'-methylidene-1'-cyclopentyl)acetaldehyde (16).

To a solution of $(COCl)_2$ (0.45 ml, 5.5 mmol) in CH_2Cl_2 (5 ml) was added DMSO (0.78 ml, 10.93 mmol) at -78 °C. The resulting mixture was stirred for 1 h at that temperature and then a solution of **15** (0.569 g, 3.6 mmol) in CH_2Cl_2 (5 ml) was added dropwise. After stirring for 30 min at that temperature, $(i\text{-}C_3H_7)_2NC_2H_5$ (3.9 ml, 22.6 mmol) was added, the resulting mixture was allowed to warm to room temperature over 2 h and quenched by addition of 1*N* HCl. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product (**16**) (0.35 g, 62% yield). ^{1}HNmr ($CDCl_3$), δ 1.10~1.95 (m, 4H), 2.20~2.40 (m, 2H), 2.75~2.94 (m, 1H), 3.44 (s, 3H), 3.63 (dd, *J*= 6.3, 2.2 Hz, 1H), 4.99 (m, 1H), 5.02 (m, 1H), 9.67 (d, *J*= 2.2 Hz, 1H).

(2*R*, 1'*R*)-1,1-Dibromo-3-methoxy-3-(2'-methylidene-1'-cyclopentyl)propene (17).

To a solution of CBr_4 (0.995 g, 0.3 mmol) in CH_2Cl_2 (6 ml) was added PPh_3 (0.787 g, 0.3 mmol) at 0 °C. The resulting mixture was stirred for 0.5 h at that temperature and then Zn powder (0.196 g, 0.3 mmol) was added. After stirring for 15 h at room temperature, a solution of **16** (0.046 g, 0.3 mmol) in CH_2Cl_2 (6 ml) was added. The resulting mixture was stirred for 2 h at room temperature and then poured into a mixture of pH 7 buffer and ether. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product. Purification of the crude product by silica gel chromatography (hexane:ethyl acetate=10:1) gave **17** (0.049 g, 53% yield). ^{1}HNmr ($CDCl_3$), δ 1.10~1.90 (m, 4H), 2.15~2.32 (m, 2H), 2.60 (m, 1H), 3.25 (s, 3H), 3.83 (dd, *J*= 9.0, 7.2 Hz, 1H), 4.90 (m, 1H), 5.00 (m, 1H), 6.28 (d, *J*= 9.0 Hz, 1H).

(2*R*, 1'*R*)-3-Methoxy-3-(2'-methylidene-1'-cyclopentyl)-1-trimethylsilylpropyne (18).

To a solution of **17** (0.049 g, 0.17 mmol) in THF (2 ml) was added dropwise *n*-BuLi (1.34*N* in hexane, 0.24 ml, 0.34 mmol) at -78 °C. The resulting mixture was stirred for 1 h at that temperature and for 1 h at room temperature and then TMSCl (0.65 ml, 5.1 mmol) was added at 0 °C. After stirring for 1 h at 0 °C, the resulting mixture was poured into a mixture of pH 7 buffer and ether. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were dried over $MgSO_4$, filtered,

and concentrated under reduced pressure to afford the crude product. Purification of the crude product by silica gel chromatography (hexane : ethyl acetate=15 : 1) gave **18** (0.024 g, 51% yield). Ir (neat), 2172, 1657, 1104 cm^{-1}; ^{1}Hnmr ($CDCl_3$), δ 0.16 (s, 9H), 1.45~1.95 (m, 4H), 2.25~2.35 (m, 2H), 2.63~2.73 (m, 1H), 3.42 (s, 3H), 3.99 (d, *J*= 5.8 Hz, 1H), 4.96~5.07 (m, 2H); ^{13}Cnmr ($CDCl_3$), δ 0.9, 24.7, 28.9, 34.2, 47.4, 56.6, 75.4, 90.7, 104.3, 107.0, 152.0; ms (EI), *m/z* 222 (M^+, 2), 207 (12), 141 (100), 113 (42), 73(17).

Product (**18**) was distingished by ^{1}Hnmr from the *erythro*-rich authentic sample previously reported,[20] threreby confirming the *threo* stereochemistry. Data for *erythro*-**18:** ^{1}HNmr ($CDCl_3$), δ 0.17 (s, 9H), 1.45~1.95 (m, 4H), 2.25~2.35 (m, 2H), 2.63~2.73 (m, 1H), 3.39 (s, 3H), 3.90 (d, *J*= 6.0 Hz, 1H), 4.96~5.07 (m, 2H); ^{13}Cnmr ($CDCl_3$), δ -0.3, 24.3, 28.7, 34.2, 48.1, 56.6, 74.2, 90.7, 104.3, 107.1, 152.0.

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