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A Short and Efficient Synthesis of Phytosphingosines Using Asymmetric Dihydroxylation

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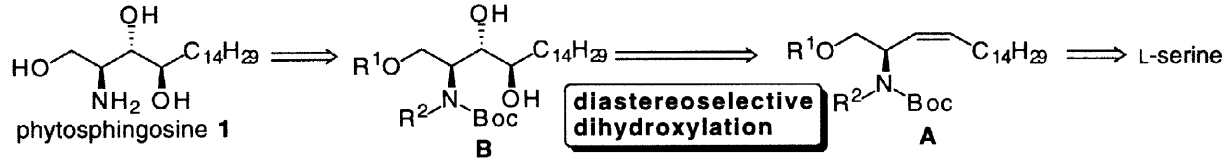
Abstract: A short synthesis of the phytosphingosine derivatives and their stereoisomers by using asymmetric dihydroxylation of the optically active olefins derived from L-serine is described.

Sphingophospholipids as well as glycerophospholipids are the main constituents of cell membrane.[1] Recently it has been revealed that the metabolites of sphingophospholipids play an important role in the signal transduction and that they are related to cell proliferation, differentiation and apoptosis. For example, sphingosine functions as a protein kinase C inhibitor,[2] and ceramide and sphingosine-1-phosphate work as second messengers in the signal transduction.[3] It is also reported that phytosphingosine **1** exsists abundantly in kidney,[4a] liver[4b] and intestine[4c] of human being. Because of interest in its biological activities, many synthetic methods of **1** have been reported so far,[5] but many of them took a large number of steps and were not satisfactory in view of the stereoselective synthesis of its isomers. In the course of our search for biologically active sphingolipids, we needed to establish a new synthetic method not only for **1** but also for its stereoisomers. In this report, we wish to describe a concise synthetic method for the phytosphingosine derivatives including their stereoisomers using diastereoselective dihydroxylation as a key step.

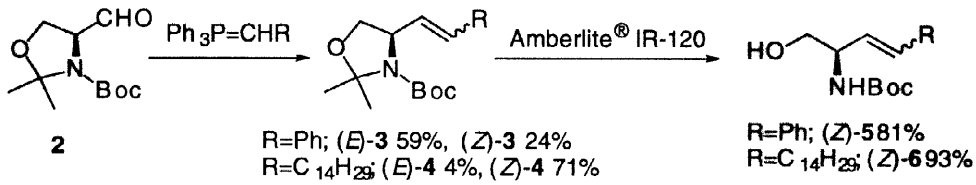
Our synthetic plan is shown in Scheme 1. The diastereoselective dihydroxylation of the optically active olefin **A**, which is readily accessible from L-serine, would afford the protected phytosphingosine derivative **B** in a stereoselective fashion. According to this procedure, all the four stereoisomers at C3 and C4 would be selectively obtained by the proper choice of the olefin geometry and the π-face selectivity. In order to ascertain the viability of this method, and furthermore to broaden it to the synthesis of the phytosphingosine analogs which have an aryl group instead of a long alkyl group, we first studied the dihydroxylation of the benzylidene derivatives.



Scheme 1

PII: S0040-4020(98)00615-2

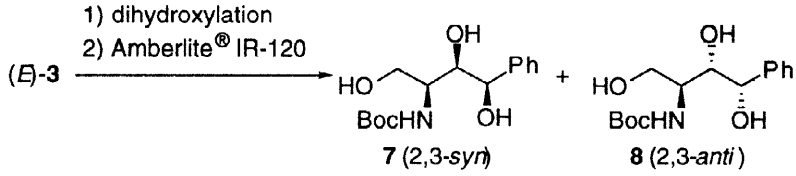
Olefines **3**,**4**,**5** and **6**, the substrates for dihydroxylation, were obtained in optically pure forms[6] in good yields via Wittig olefination of **2** which was easily obtained according to the literature (Scheme 2).[7]



Scheme 2

We hoped that the stereogenic center at C2 of the substrates could affect the diastereoselectivity, and so attempted dihydroxylation of (*E*)-**3** under the substrate-stereocontrolled conditions first. Dihydroxylation of (*E*)-**3** with 1mol% OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) followed by hydrolysis gave **7** (2,3-*syn*) and **8** (2,3-*anti*) in a good combined yield, but the diastereoselectivity was a disappointing one (run 1, Table 1). Next we tried an asymmetric dihydroxylation method using AD-mix-α.[8] Under these conditions, **8** was obtained with high 2,3-*anti* selectivity (run 2). On the contrary, high 2,3-*syn* selectivity was achieved by using AD-mix-β (run 3).[8] These results indicated that the chiral center at C2 position of (*E*)-**3** had little effect on the diastereoselectivity in the dihydroxylation.

Table 1. Dihydroxylation of (*E*)-3



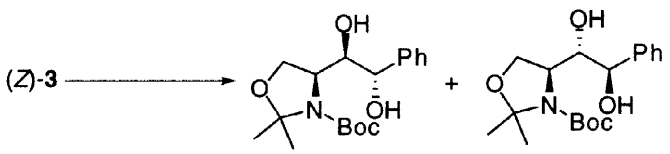
run	conditions of dihydroxylation	yield (%)[a]	**7** : **8**[b]
1	OsO_4(1mol%), NMO[c]	71	45 : 55
2	AD-mix-α[d] (0.2mol%)	70	1 : 99
3	AD-mix-β[d] (0.2mol%)	60	99 : 1

a) isolated yield *b*) based on isolated ratio *c*) *N*-methylmorpholine *N*-oxide
d) AD-mix-α : $K_2OsO_2(OH)_4$, (DHQ)$_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3
AD-mix-β : $K_2OsO_2(OH)_4$, (DHQD)$_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3

Next we examined dihydroxylation of (*Z*)-**3** (Table 2). Both the yield and the diastereoselectivity, however, were not satisfied in any case using either OsO_4 /NMO or AD-mix reagents.[9] The reluctance of (*Z*)-**3** to the oxidation using AD-mix reagents might be owing to the steric congestion around the double bond brought by both the isopropylidene and the Boc groups. Therefore, (*Z*)-**5**, in which the isopropylidene group was removed, was subjected to dihydroxylation, together with the expectation that the free hydroxyl and the NHBoc groups might affect the diastereoselectivity (Table 3). As we anticipated, dihydroxylation of (*Z*)-**5** with OsO_4 and NMO proceeded smoothly to give **11** and **12** in high yield (run 1). Interestingly, 2,3-*syn* selectivity was

observed at the same time. It is worth discussing this result in contrast with the Kishi's rule. [10] Kishi reported that in the allyl alcohols the reagent approached C-C π face from the opposite direction of the allylic OH group in the conformation which might be favored on the basis of $A^{(1,3)}$-strain. In (*Z*)-**5**, in which the allylic NHBoc group instead of the allylic OH group was present, the reagent preferentially came from the same side of the allylic NHBoc group. We speculate that this *syn* selectivity might be attributed to the directing effect of the NHBoc group.[11] In search of the better conditions, we found that by using AD-mix reagents satisfactory diastereoselectivities were realized (run 2, 3).[12] Thus, it was established that all the four diastereomers at C3, C4 positions of the *N*-Boc phytosphingosine derivative could be synthesized in good yields and high selectivities by the appropriate combination of the substrate and AD-mix reagents.

Table 2. Dihydroxylation of (*Z*)-3

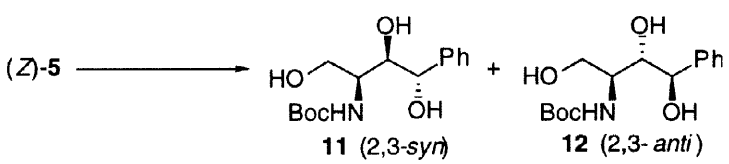


9 (2,3-*syn*) **10** (2,3-*anti*)

run	conditions	yield (%)[a]	**9** : **10** [b]
1	OsO_4 (1mol%), NMO	54	52 : 48
2	AD-mix-α (0.2mol%)	13	85 : 15
3	AD-mix-β (0.2mol%)	4	50 : 50

a) isolated yield *b*) based on isolated ratio

Table 3. Dihydroxylation of (*Z*)-5



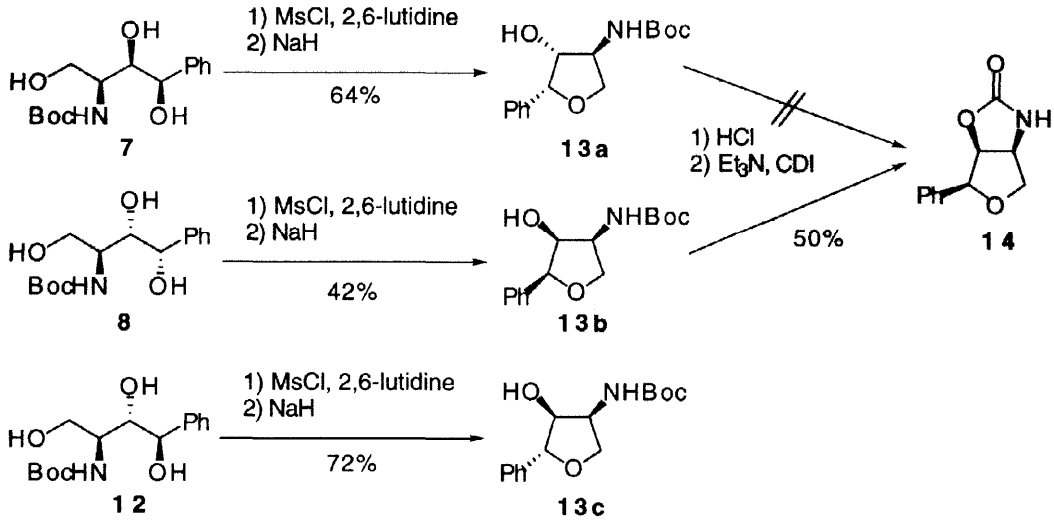
11 (2,3-*syn*) **12** (2,3-*anti*)

run	conditions	yield (%)[a]	**11**: **12**[b]
1	OsO_4 (1mol%), NMO	92	71 : 29
2	AD-mix-α (0.2mol%)	55	86 : 14
3	AD-mix-β (0.2mol%)	55	16 : 84

a) isolated yield *b*) based on isolated ratio

The configurations at C3 and C4 of the four isomers **7**,**8**,**11** and **12** were determined as follows (Scheme 3). The isomers **7**,**8** and **12** were converted to the corresponding tetrahydrofurans **13a-c**. The compound **13b** derived from **8** was subjected to the reaction with *N*,*N*'-carbonyldiimidazole (CDI) to give the oxazolidinone **14**, while the compound **13a** derived from **7** was refused to cyclize. So it was concluded that **7**

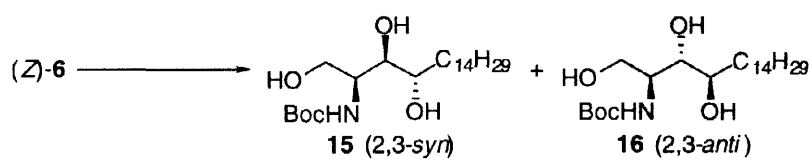
had the configuration of 2,3-*syn* and **8** had that of 2,3-*anti*. On the other hand, the stereochemistry of **13c** derived from **12** was determined by X-ray crystallographic analysis to be the configuration of (2*R*,3*S*,4*S*).[13] Accordingly, **11** and **12** were deduced to have the configuration of 2,3-*syn* and that of 2,3-*anti*, respectively.



Scheme 3

With the stereoselective method established, we next tried to synthesize phytosphingosine and its diastereomer at C3 and C4 positions (Table 4). (*Z*)-**4** was hydrolyzed into (*Z*)-**6** and the dihydroxylation of the latter with AD-mix-α proceeded with good 2,3-*syn* selectivity to give **15** in high yield (run 2). On the other hand, the reaction using AD-mix-β led in good yield and selectivity to **16** of which configuration is the same as that of the natural phytosphingosine **1** (run 3). In the case of using AD-mix reagents having bulky ligands, higher yield of the dihydroxylation of (*Z*)-**6** than that of (*Z*)-**5** was attained, and this might be attributed to the difference of the bulkiness between of alkyl group and Ph group.

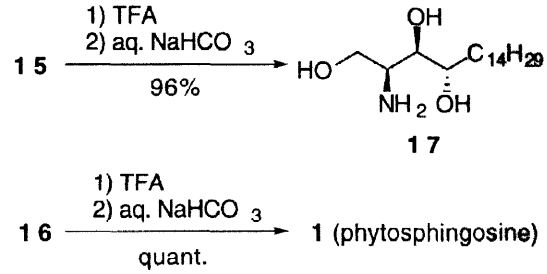
Table 4. Dihydroxylation of (*Z*)-6



run	conditions	yield (%)[a]	15: 16[b]
1	OsO_4(1mol%), NMO	84	71: 29
2	AD-mix-α (0.2mol%)	86	83: 17
3	AD-mix-β (0.2mol%)	89	17: 83

a) isolated yield *b*) based on isolated ratio

Finally, the removal of the Boc group with TFA, followed by neutralization, transformed **16** and **15** into phytosphingosine **1** and its diastereomer **17** (Scheme 4).[14]



Scheme 4

In summary, we have established the stereoselective synthetic method for the phytosphingosines utilizing the dihydroxylation reaction. This procedure is simple, and furthermore convenient because the stereoisomers of phytosphingosine and its derivatives could be stereoselectively obtainable starting from easily available L-serine.

Acknowledgement: We are thankful to Dr. T. Da-te and co-workers in our company for the X-ray crystallographic analysis.

Experimental

Melting points were measured using a Yamato melting apparatus and uncorrected. Optical rotations were measured on a Perkin-Elmer 243 automatic polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz) spectrometer and JEOL GSX-400 (400 MHz) with TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer 1640 spectrophotometer. MS spectra were obtained on a Hitachi M-2000A double-focusing mass spectrometer. High-resolution MS (HRMS) spectrum was obtained on a JOEL JMS-HX100 mass spectorometer. Elemental analyses were measured on Perkin-Elmer 2400 microanalyzer. Column chromatography was performed on silica gel (Kieselgel 60, 70-230 mesh, E. Merck).

Preparation of olefins 3.[6b]

To a suspension of benzyltriphenylphosphonium bromide (28.4 g, 65.4 mmol; prepared from triphenylphosphine and benzyl bromide) in THF (1 l) was added dropwise KHMDS solution (108 ml, 59.2 mmol 0.5 M in toluene) below -70°C under nitrogen atmosphere. The solution was stirred for 0.5h below -70°C and then stirred for 1h at 0°C. And then, the solution was cooled below -70°C again, and aldehyde **2**[6a] (10.0 g, 43.4 mmol) in THF (100 ml) was added dropwise at the same temperature, and the mixture was stirred for 4h at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted with AcOEt. The organic extract was washed with brine and dried over $MgSO_4$. After evaporation of the solvent under the reduced pressure the white solid (triphenylphosphine oxide) was removed by filtration and washed with Et_2O. The filtrate was concentrated and the residue was purified by column chromatography (hexane : AcOEt = 50 : 1) to give (*E*)-**3** (7.73 g, 59% yield) and (*Z*)-**3** (3.13 g, 24% yield) as colorless crystals, which were recrystallized from hexane.

(2*R*,1'*E*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-(2'-phenylethenyl)oxazolidine ((*E*)-3): mp 81°C; $[\alpha]^{27}_{D}$ -88.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.44 (s, 9H), 1.55 (s, 3H), 1.66 (s, 3H), 3.83 (dd, *J* = 2.3, 8.8 Hz, 1H), 4.11 (dd, *J* = 6.0, 8.8 Hz, 1H), 4.44 (m, 1H), 6.15 (dd, *J* = 8.0, 15.6 Hz, 1H), 6.50 (d, *J* = 14.6Hz, 1H), 7.23-7.41 (m, 5H); IR (KBr) 2981, 2925, 2874, 2855, 1697 cm^{-1}; MS (SIMS) *m/z* 304 (M^++1); Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 70.99; H, 7.95; N, 4.43.

(2*R*,1'*Z*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-(2'-phenylethenyl)oxazolidine ((*Z*)-3): mp 72°C; $[\alpha]^{27}_{D}$ +68.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.29 (s, 9H), 1.52 (s, 3H), 1.64 (s, 3H), 3.84 (m, 1H), 4.16 (m, 1H), 4.86 (br, 1H), 5.71 (t, *J* = 10.0 Hz, 1H), 6.52 (d, *J* = 11.0 Hz, 1H), 7.1-7.5 (m, 5H); IR (KBr) 3440, 3020, 2986, 2970, 2930, 2855, 1691 cm^{-1}; MS (SIMS) *m/z* 304 (M^++1); Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.12; H, 8.18; N, 4.41.

Preparation of olefins 4.[6b]

To a suspension of pentadecanephosphonium bromide (12.0 g, 21.6 mmol; prepared from triphenylphosphine and 1-bromopentadecane) in THF (220 ml) was added dropwise *n*-butyllithium (12.3 ml, 19.7 mmol, 1.6 M in hexane) below -70°C under nitrogen atmosphere. The solution was allowed to warm to 0°C and stirred for 0.5h. And then, the solution was cooled below -70°C again, and aldehyde **2**[6a] (3.0 g, 13.1 mmol) in THF (13 ml) was added dropwise at the same temperature. The mixture was stirred for 2h at rt. The

reaction mixture was quenched with saturated aqueous NH_4Cl (1 l) and extracted with AcOEt. The organic extract was washed with brine and dried over $MgSO_4$. After evaporation of the solvent under the reduced pressure, the white solid (triphenylphosphine oxide) was removed by filtration and washed with Et_2O. The filtrate was concentrated and the residue was purified by column chromatography (hexane : AcOEt = 100 : 1) to give (*Z*)-**4** (3.95 g, 71% yield) and (*E*)-**4** (208 mg, 3.8% yield) as colorless syrups.

(2*R*,1'*Z*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-(1'-hexadecenyl)oxazolidine ((*Z*)-4): $[\alpha]^{26}_D$ +53.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, *J* = 6.2 Hz, 3H), 1.2-1.6 (m, 39H), 2.09 (m, 2H) 3.64 (dd, *J* = 3.3, 8.6 Hz, 1H), 4.05 (dd, *J* = 6.3, 8.6 Hz, 1H), 4.62 (br, 1H), 5.37(d, *J* =10.9 Hz, 1H), 5.49 (d, *J* = 10.9 Hz, 1H); IR (film) 2926, 2825, 1702 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{26}H_{49}NO_3$ 424.3791, found 424.3778.

(2*R*,1'*E*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-(1'-hexadecenyl)oxazolidine ((*E*)-4): ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, *J* = 6.4 Hz, 3H), 1.2-1.4 (m, 39H), 2.02 (q, *J* = 6.6 Hz, 2H), 3.71 (dd, *J* = 2.1, 8.7 Hz, 1H), 4.05 (dd, *J* = 6.1, 8.7 Hz, 1H), 4.24 (br, 1H), 5.35-5.70 (m, 2H); IR (film) 2970, 2925, 2835, 1702 cm^{-1}; MS (SIMS) *m/z* 424 (M^++1).

(2*R*, 3*Z*)-2-[(*tert*-Butoxycarbonyl)amino]-4-phenyl-3-butenol ((*Z*)-5).

To a solution of the olefin (*Z*)-**3** in MeOH/H_2O (9 : 1, 20 ml) was added Amberlite® IR-120 resin (6.0 g) at rt. The mixture was stirred at rt for 15h and the resin was filtrered, washed with MeOH. After the filtrate was evaporated under the reduced pressure, the residue was purified by column chromatography (hexane : AcOEt = 2 : 1) to give unreacted (*Z*)-**3** (165 mg, 17% recovery) and (*Z*)-**5** (585 mg, 67% yield, 81% based on the comsumed (*Z*)-**3**), which was recrystallized from hexane: mp 91°C; $[\alpha]^{23}_D$ +106 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.43 (s, 9H), 3.66-3.73 (m, 2H), 4.75 (m, 2H), 5.56 (dd, *J* = 9.1, 11.7 Hz, 1H), 6.62 (d, *J* = 11.7 Hz, 1H), 7.23-7.40 (m, 5H); IR (KBr) 3388, 2978, 1698, 1519 cm^{-1}; MS (SIMS) *m/z* 264 (M^++1); Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.30; H, 7.91; N, 5.14.

(2*R*, 3*Z*)-2-[(*tert*-Butoxycarbonyl)amino]-3-hexadecenol ((*Z*)-6).

This reaction was carried out according to the procedure for (*Z*)-**5** except using CH_3CN/H_2O (50 : 1) as solvent. From (*Z*)-**4** (3.10 g, 7.32 mmol) was obtained (*Z*)-**6** (2.61 mg, 93% yield) as a colorless crystal, which was recrystallized from hexane: mp 56°C; $[\alpha]^{27}_D$ +21.4 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, *J* = 6.2 Hz, 3H), 1.1-1.4 (m, 24H), 1.45 (s, 9H), 1.8-2.3 (m, 3H), 3.5-3.6 (m, 2H), 4.49 (br, 1H), 5.25 (dd, *J* = 8.9, 10.7 Hz, 1H), 5.60 (dt, *J* = 7.3, 10.7 Hz, 1H); IR (KBr) 3367, 2923, 2851, 1684, 1520 cm^{-1}; MS (SIMS) *m/z* 384 (M^++1); Anal. Calcd for $C_{23}H_{45}NO_3$: C, 72.01; H, 11.82; N, 3.65. Found: C, 71.73; H, 11.52; N, 3.81.

Dihydroxylation of olefins (*E*)-3, (*Z*)-3, (*Z*)-5 and (*Z*)-6

a) Using OsO_4 and *N*-methylmorpholine *N*-oxide (NMO).

To a solution of OsO_4 (0.5% *t*-BuOH solution, 336 mg, 6.6×10^{-3} mmol) and NMO (156 mg, 1.32

mmol) in acetone/H_2O (8 : 1, 6.6 ml) was added (*E*)-**3** (200 mg, 0.66 mmol) at 0°C under nitrogen atmosphere. The mixture was stirred at rt for 18h, quenched with Na_2SO_3 (950 mg, 7.54 mmol) and extracted with AcOEt. The organic extract was washed with brine and dried over $MgSO_4$. After evaporation of the solvent under the reduced pressure, the residue was purified by column chromatography (hexane : AcOEt = 4 : 1) to give diastereomeric mixture of the corresponding diols as a colorless syrup. To the solution of the diols in MeOH/H_2O (9 : 1, 3 ml) was added Amberlite® IR-120 resin (600 mg) at rt. The mixture was stirred at rt for 7h and the resin was filtered, washed with MeOH and THF. After the filtrate was evaporated under the reduced pressure, the residue was purified by column chromatography (hexane : AcOEt = 3 : 2) to give **7** (2,3-*syn* form, 62 mg, 32% yield) and **8** (2,3-*anti* form, 76 mg, 39%yield) as colorless crystals. (*Z*)-**3**, (*Z*)-**5** and (*Z*)-**6** were also dihydoxylated in a similar way.

b) Using AD-mix-α or β.

To a solution of AD-mix-α (4.62 g, 6.6×10^{-3} mmol) and $CH_3SO_2NH_2$ (314 mg, 3.30 mmol) in *t*-BuOH/H_2O (1 : 1, 33 ml) was added (*E*)-**3** (1.00 g, 3.30 mmol) at 0°C under nitrogen atmosphere. The mixture was stirred at rt for 24h, quenched with Na_2SO_3 (4.95 g) and extracted with AcOEt. The organic extract was washed with 1N KOH, H_2O, brine and dried over $MgSO_4$. After evaporation of the solvent under the reduced pressure, the diols were treated with Amberlite® IR-120 resin and purified as above to give **7** (2,3-*syn* form, 8.5 mg, 0.9% yield) and **8** (2,3-*anti* form, 681 mg, 69%yield) as colorless crystals. (*Z*)-**3**, (*Z*)-**5** and (*Z*)-**6** were also dihydoxylated in a similar way.

(2*S*,3*R*,4*R*)-2-[(*tert*-Butoxycarbonyl)amino]-4-phenyl-1,3,4-butanetriol (7): recrystallized from isopropyl ether; mp 75°C; $[\alpha]^{27}_D$ +5.94 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.47 (s, 9H), 2.56 (t, *J* = 5.7 Hz, 1H), 2.97 (br, 1H), 3.44 (br, 1H), 3.58-3.70 (m, 3H), 3.92 (dt, *J* = 7.5, 2.1 Hz, 1H), 4.67 (dd, *J* = 3.0, 7.5 Hz, 1H), 5.33 (d, *J* = 7.5 Hz, 1H), 7.36 (m, 5H); IR (KBr) 3420, 3313, 2975, 1671, 1531 cm^{-1}; MS (SIMS) *m/z* 298 (M^++1); Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.16; H, 8.03; N, 4.33.

(2*S*,3*S*,4*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-phenyl-1,3,4-butanetriol (8): recrystallized from AcOEt; mp 187°C; $[\alpha]^{27}_D$ +17.0 (*c* 0.10, MeOH); ^1H NMR (d_6-DMSO, 200 MHz) δ 1.39 (s, 9H), 3.52 (m, 4H), 4.48 (t, *J* = 7.2 Hz, 1H), 4.64 (d, *J* = 3.2 Hz, 1H), 5.07 (d, *J* = 5.3 Hz, 1H), 6.53 (d, *J* = 7.0 Hz, 1H), 7.19-7.37 (m, 5H); IR (KBr) 3400, 3298, 2995, 2936, 1675, 1532 cm^{-1}; MS (SIMS) *m/z* 298 (M^++1); Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.58; H, 7.74; N, 4.59.

(4*S*, 1'*R*, 2'*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-(1', 2'-dihydroxy-2'-phenylethyl)-2,2-dimethyloxazolidine (9): recrystallized from isopropyl ether; mp 129°C; $[\alpha]^{26}_D$ -35.1 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.52 (s, 12H), 1.63 (s, 3H), 3.01 (br, 1H), 3.72-3.80 (m, 2H), 3.93-4.00 (m, 1H), 4.37 (br, 1H), 4.62 (br, 1H), 7.28-7.43 (m, 5H); IR (KBr) 3554, 3288, 2978, 1702 cm^{-1}; MS (SIMS) *m/z* 338 (M^++1); Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 63.81; H, 7.98; N, 4.07.

(4*S*, 1'*S*, 2'*R*)-2-[(*tert*-Butoxycarbonyl)amino]-4-(1', 2'-dihydroxy-2'-phenylethyl)-2,2-

dimethyloxazolidine (10): recrystallized from isopropyl ether; mp 147°C; $[\alpha]^{26}_{D}$ -45.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.46 (s, 15H), 2.97 (br, 1H), 3.75-4.30 (m, 5H), 4.74 (t, *J* = 5.7 Hz, 1H), 7.31-7.44 (m, 5H); IR (KBr) 3444, 3370, 2975, 2940, 2380, 1677 cm^{-1}; MS (SIMS) *m/z* 338 (M^++1); Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.03; H, 8.05; N, 4.07.

(2*S*,3*R*,4*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-phenyl-1,3,4-butanetriol (11): recrystallized from isopropyl ether; mp 91°C; $[\alpha]^{24}_{D}$ -42.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.49 (s, 9H), 1.81 (br, 1H), 2.79 (d, *J* = 6.6 Hz, 1H), 3.75-3.99 (m, 3H), 4.14 (br, 1H), 4.34 (dd, *J* = 4.0, 8.9 Hz, 1H), 4.73 (d, *J* = 4.0 Hz, 1H), 5.51 (d, *J* = 8.8 Hz, 1H), 7.29-7.44 (m, 5H); IR (KBr) 3402, 3025, 2982, 2920, 1697, 1686 cm^{-1}; MS (SIMS) *m/z* 298 (M^++1); Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.57; H, 7.64; N, 4.66.

(2*S*,3*S*,4*R*)-2-[(*tert*-Butoxycarbonyl)amino]-4-phenyl-1,3,4-butanetriol (12): recrystallized from isopropyl ether; mp 97°C; $[\alpha]^{24}_{D}$ -29.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 9H), 3.20 (d, *J* = 4.9 Hz, 1H), 3.43 (br, 1H), 3.51 (br, 1H), 3.70-4.05 (m, 3H), 4.73 (d, *J* = 5.1 Hz, 1H), 5.36 (d, *J* = 7.7 Hz, 1H), 7.29-7.42 (m, 5H); IR (KBr) 3285, 3075, 2978, 2940, 2898, 1672 cm^{-1}; MS (SIMS) *m/z* 298 (M^++1); Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.46; H, 7.80; N, 4.71.

(2*S*,3*R*,4*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1,3,4-octadecanetriol (15): recrystallized from hexane; mp 83°C; $[\alpha]^{26}_{D}$ -28.1 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.25 (br, 24H), 1.45 (s, 9H), 1.56 (m, 1H), 1.71 (m, 1H), 3.33 (m, 1H), 3.48 (d, *J* = 4.4 Hz, 1H), 3.60 (dd, *J* = 5.0, 7.7 Hz, 1H), 3.69 (br, 1H), 3.76 (m, 1H), 3.85 (m, 1H), 3.94 (m, 1H), 4.27 (d, *J* = 3.7 Hz, 1H), 5.45 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 14.1, 22.7, 25.8, 28.3, 29.4, 29.7, 31.9, 32.8, 51.0, 64.5, 71.1, 76.2, 80.4, 157.6; IR (KBr) 3396, 2920, 2840, 1671, 1527, 1470, 1393, 1369, 1300, 1250, 1173, 1090, 1072, 1040 1017, 988, 721 cm^{-1}; MS (SIMS) *m/z* 418 (M^++1); Anal. Calcd for $C_{23}H_{47}NO_5$: C, 66.15; H,11.34; N, 3.35. Found: C, 65.90; H, 11.04; N, 3.52.

(2*S*,3*S*,4*R*)-2-[(*tert*-Butoxycarbonyl)amino]-1,3,4-octadecanetriol (16): recrystallized from hexane; mp 87°C; $[\alpha]^{26}_{D}$ +7.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.25 (br, 24H), 1.44 (s, 9H), 1.49 (m, 1H), 1.66 (m, 1H), 3.64-3.73 (m, 4H), 3.84-3.87 (m, 3H), 4.13 (br, 1H), 5.53 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 14.1, 22.7, 26.0, 28.4, 29.4, 29.6, 29.7, 30.2, 31.8, 31.9, 32.9, 52.8, 61.8, 73.0, 75.9, 80.1, 156.4; IR (KBr) 3323, 2922, 2840, 1672, 1548, 1470, 1458, 1394, 1364, 1305, 1257, 1175, 1109, 1061, 1045, 1030, 929, 872, 852, 786, 721, 659, 470 cm^{-1}; MS (SIMS) *m/z* 418 (M^++1); Anal. Calcd for $C_{23}H_{47}NO_5$: C, 66.15; H,11.34; N, 3.35. Found: C, 66.07; H, 11.04; N, 3.53.

(2*S*, 3*R*, 4*S*)-2-amino-1,3,4-octadecanetriol (17).

Triol **15** (418 mg, 1.0 mmol) in TFA/ H_2O (20 : 1, 4 ml) was stirred at rt for 15 min. The solution was diluted with CH_2Cl_2 (10 ml), then neutralized with saturated aqueous $NaHCO_3$. The white solid was filtered, washed with H_2O to give **17** (304 mg, 96% yield) as a colorless crystal, which was recrystallized from CH_3CN: mp 86°C [lit.[5h] mp 75°C]; $[\alpha]^{26}_{D}$ -3.7 (*c* 1.0, pyridine) [lit.[5h] $[\alpha]^{20}_{D}$ -12.3 (*c* 0.6, pyri-dine)][14]; ^1H

NMR (d_6-DMSO, 400 MHz) δ 0.86 (t, J = 6.6 Hz, 3H), 1.24 (br, 24H), 1.44 (m, 1H), 1.54 (m, 1H), 2.92 (m, 1H), 3.14 (d, J = 7.2 Hz, 1H), 3.25 (dd, J = 7.6, 10.0 Hz, 1H), 3.36 (dd, J = 6.2, 9.8 Hz, 2H); ^{13}C NMR (d_6-DMSO, 400 MHz) δ 13.9, 22.1, 25.4, 28.7, 29.1, 29.3, 29.4, 31.3, 33.9, 52.8, 64.0, 71.6, 72.3; IR (KBr) 3350, 2918, 2840, 1607, 1596, 1470, 1123, 1069, 1049, 1029, 1017, 983, 970, 940, 929, 909, 850, 720, 643 cm^{-1}; MS (SIMS) *m/z* 318 (M^++1); Anal. Calcd for $C_{18}H_{39}NO_3$: C, 68.09; H, 12.38; N, 4.41. Found: C, 67.95; H, 11.99; N, 4.23.

(2*S*, 3*S*, 4*R*)-2-amino-1,3,4-octadecanetriol (phytosphingosine (1)).

This reaction was carried out according to the procedure for **15**. From **16** (1.30 g, 3.11 mmol) was ob-tained **1** (997 mg, quant.) as a colorless crystal, which was recrystallized from CH_3CN: mp 103°C [lit.[5h] mp 103°C]; $[\alpha]^{26}_D$+9.5 (*c* 1.0, pyridine) [lit.[5h] $[\alpha]^{20}_D$ +7.9 (*c* 1.0, pyridine)]; ^{1}H NMR (d_6-DMSO, 400 MHz) δ 0.86 (t, J = 6.6 Hz, 3H), 1.24 (br, 24H), 1.43 (m, 1H), 1.59 (m, 1H), 2.67 (m, 1H), 3.04 (dd, J = 7.2, 7.6 Hz 1H), 3.33-3.38 (m, 2H), 3.51 (dd, J = 3.6, 10.0 Hz, 1H); ^{13}C NMR (d_6-DMSO, 400 MHz) δ 13.9, 22.1, 25.0, 28.7, 29.1, 29.3, 29.5, 31.3, 33.4, 56.1, 63.3, 73.4, 73.9; IR (KBr) 3350, 2920, 2852, 1605, 1515, 1468, 1380, 1350, 1330, 1285, 1270, 1150, 1140, 1037, 980, 963, 948, 928, 860, 721 cm^{-1}; MS (SIMS) *m/z* 318 (M^++1); Anal. Calcd for $C_{18}H_{39}NO_3$: C, 68.09; H,12.38; N, 4.41. Found: C, 67.62; H, 12.11; N, 4.27.

Formation of the tetrahydrofuran derivatives 13a-c.

To a solution of **7** (430 mg, 1.45 mmol) in 2,6-lutidine was added methanesulfonyl chloride (261 μl, 4.05 mmol) at 0°C. The mixture was stirred at rt for 8h, then quenched with 10% aqueous HCl, extracted with AcOEt, washed with H_2O, brine and dried over $MgSO_4$. After evaporation of the solvent under the reduced pressure, the residue was purified by column chromatography (hexane : AcOEt = 1 : 1) to give the mesylate (464 mg, 1.24 mmol) as a white solid. To a solution of this mesylate in CH_2Cl_2 was added NaH (62.5% in oil, 143 mg, 3.72 mmol) at 0°C. The solution was stirred at rt for 1h, then quenched with saturated aqueous NH_4Cl. After evaporation of the solvent under the reduced pressure, the residue was purified by column chromatography (hexane : AcOEt = 4 : 1) to give tetrahydrofuran **13a** (273 mg, 70% yield) as a colorless crystal, which was recrystallized from isopropyl ether. **13b** and **13c** were obtained in the same pro-cedure.

(2*R*,3*R*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-3-hydroxy-2-phenyltetrahydrofuran (13a): mp 110°C; $[\alpha]^{24}_D$ -36.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.48 (s, 9H), 1.69 (br, 1H), 3.76 (dd, J = 2.7, 9.4 Hz, 1H), 4.05-4.35 (br, 2H), 4.81 (br, 1H), 5.08 (d, J = 3.6 Hz, 1H), 7.30-7.43 (m, 5H); IR (KBr) 3388, 2982, 2950, 2900, 1685, 1507 cm^{-1}; MS (SIMS) *m/z* 280 (M^++1); Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.15; H, 7.49; N, 4.97.

(2*S*,3*S*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-3-hydroxy-2-phenyltetrahydrofuran (13b): mp 129°C; $[\alpha]^{24}_D$ +30.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.37 (d, J = 2.7 Hz, 1H), 1.46 (s, 9H), 3.82 (t, J = 8.6 Hz, 1H), 4.22 (m, 1H), 4.29 (t, J = 8.1 Hz, 1H), 4.55 (m, 1H), 5.05 (d, J = 2.9 Hz, 1H), 5.20 (m, 1H), 7.32-7.45 (m, 5H); IR (KBr) 3349, 2970, 2948, 2898, 1685, 1535 cm^{-1}; MS (SIMS) *m/z* 280 (M^++1); Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.55; H, 7.57; N, 4.95.

(2*R*,3*S*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-3-hydroxy-2-phenyltetrahydrofuran (13c): mp 112°C; $[\alpha]^{25}_{D}$ +27.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 9H), 2.61 (d, *J* = 4.2 Hz, 1H), 3.75 (dd, *J* = 6.8, 8.6 Hz, 1H), 4.15 (q, *J* = 4.5 Hz, 1H), 4.23 (q, *J* = 6.7 Hz, 1H), 4.39 (dd, *J* = 6.8, 8.6 Hz, 1H), 4.79 (d, *J* = 4.2 Hz, 1H), 5.11 (d, *J* = 6.6 Hz, 1H), 7.30-7.36 (m, 5H); IR (KBr) 3430, 3420, 3355, 2980 2970, 2930, 2875, 1697, 1675, 1533 cm^{-1}; MS (SIMS) *m/z* 280 (M^++1); Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.45; H, 7.54; N, 4.97.

(1*S*,5*S*,8*S*)-4-aza-2,7-dioxa-3-oxo-8-phenylbicyclo[3.3.0]octane (14).

A solution of **13b** (300mg, 1.07 mmol) in 4N HCl-dioxane (3 ml) was stirred at rt for 13h. After evaporation of the solvent under the reduced pressure, the precipitated HCl salt of the corresponding amine was collected by filtration. To a suspension of this salt in CH_2Cl_2 was added Et_3N (0.37 ml, 2.68 mmol) and *N*,*N*'-carbonyldiimidazole (435 mg, 2.68 mmol) at 0°C. The solution was stirred at rt for 6h. The reaction mixture was diluted with AcOEt, washed with 10% aqueous citric acid and dried over $MgSO_4$. After evaporation of the solvent under the reduced pressure, the residue was purified by column chromatography (hexane : AcOEt = 1 : 2 → $CHCl_3$: MeOH = 19 : 1) to give **14** (109 mg, 50%) as a colorless crystal, which was re-crystallized from hexane-AcOEt: mp 224°C; $[\alpha]^{25}_{D}$ +200 (*c* 0.11, MeOH); ^{1}H NMR (d_6-DMSO, 200 MHz) δ 3.65 (dd, *J* = 4.1, 10.0 Hz, 1H), 3.92 (d, *J* = 10.0 Hz, 1H), 4.43 (dd, *J* = 4.3, 7.4 Hz, 1H), 4.69 (d, *J* = 3.8 Hz, 1H), 5.18 (dd, *J* = 3.9, 7.4 Hz, 1H), 7.31-7.35 (m, 5H), 7.90 (s, 1H); IR (KBr) 3275, 1741, 1715 cm^{-1}; MS (SIMS) *m/z* 206 (M^++1); Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.33; H, 5.63; N, 6.79.

Preparation of MTPA amides (*E*)-18a-b, (*Z*)-18a-b and(*Z*)-19a-b.

(*E*)-3 (200 mg, 0.659 mmmol) was treated with 4 N HCl-dioxane solution. After deprotection, the mixture was neutralized with saturated aqueous $NaHCO_3$ and extraced with $CHCl_3$. The extract was washed with brine and dried over $MgSO_4$ and evaporated to give amino alcohol as a coloress solid (105 mg, 97%). To a mixture of the amino alcohol (10 mg, 0.0613 mmol) and Et_3N (10.2 μl, 0.0735 mmol) in CH_2Cl_2 (0.2 ml) was added (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (11.4 μl, 0.0623 mmol). The reaction mixture was stirred for 12 h and directly subjected to the purification by preparative TLC (hexane:AcOEt=2:1) to give (*E*)-**18a** (17.4 mg, 74%, 99% de determined by ^{1}H NMR). (*Z*)-**18a** and (*Z*)-**19a** were also obtained in the same procedure. Using (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, (*E*)-**18b**, (*Z*)-**18b** and(*Z*)-**19b** were also obtained in the same procedure and determined to be 99% de by ^{1}H NMR.

(2*S*)-2-Methoxy-2-phenyl-3,3,3-trifluoro-*N*-[(2'*R*,3'*E*)-1'-hydroxy-4'-phenylbut-3'-en-2'-yl]-propanamide (*E*)-18a: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.11 (br, 1H), 3.41 (s, 3H), 3.73-3.82 (m, 2H), 4.77 (m, 1H), 6.18 (dd, *J* = 6.1, 16.1 Hz, 1H), 6.63 (d, *J* = 16.1 Hz, 1H), 7.23-7.45 (m, 10H), 7.56-7.58 (m, 2H); IR (film) 3460, 3408, 1677 cm^{-1}; MS (SIMS) *m/z* 380 (M^++1).

(2*R*)-2-Methoxy-2-phenyl-3,3,3-trifluoro-*N*-[(2'*R*,3'*E*)-1'-hydroxy-4'-phenylbut-3'-en-2'-yl]-propanamide (*E*)-18b: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05 (br, 1H), 3.49 (s, 3H), 3.77-3.85 (m, 2H), 4.75-4.80 (m, 1H), 6.15 (dd, *J* = 6.1, 15.9 Hz, 1H), 6.44 (d, *J* = 15.9 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.22-7.32 (m, 5H), 7.35-7.43 (m, 3H), 7.55-7.57 (m, 2H); IR (film) 3410, 3052, 3023, 2980, 2951, 2875,

2848, 1684 cm^{-1}; MS (SIMS) *m/z* 380 (M^++1).

(2*S*)-2-Methoxy-2-phenyl-3,3,3-trifluoro-*N*-[(2'*R*, 3'*Z*)-1'-hydroxy-4'-phenylbut-3'-en-2'-yl]-propanamide (*Z*)-18a: ^1H NMR ($CDCl_3$, 400 MHz) δ 2.35 (br, 1H), 3.34 (s, 3H), 3.67-3.75 (m, 2H), 5.00-5.07 (m, 1H), 5.64 (dd, *J* = 9.6, 11.8 Hz, 1H), 6.68 (d, *J* = 11.7 Hz, 1H), 7.11 (d, *J* = 6.6 Hz, 1H), 7.24-7.38 (m, 5H), 7.39-7.43 (m, 3H), 7.53-7.55 (m, 2H); IR (film) 3415, 3050, 3005, 2951, 2870, 2830, 1683 cm^{-1}; MS (SIMS) *m/z* 380 (M^++1).

(2*R*)-2-Methoxy-2-phenyl-3,3,3-trifluoro-*N*-[(2'*R*, 3'*Z*)-1'-hydroxy-4'-phenylbut-3'-en-2'-yl]-propanamide (*Z*)-18b: ^1H NMR ($CDCl_3$, 400 MHz) δ 2.38 (br, 1H), 3.39 (s, 3H), 3.70-3.79 (m, 2H), 5.00-5.06 (m, 1H), 5.64 (dd, *J* = 9.5, 11.7 Hz, 1H), 6.66 (d, *J* = 11.7 Hz, 1H), 7.09 (d, *J* = 6.6 Hz, 1H), 7.23-7.37 (m, 5H), 7.38-7.41 (m, 3H), 7.48-7.50 (m, 2H); IR (film) 3415, 3050, 3010, 2951, 2870, 2830, 1684 cm^{-1}; MS (SIMS) *m/z* 380 (M^++1).

(2*S*)-2-Methoxy-2-phenyl-3,3,3-trifluoro-*N*-[(2'*R*, 3'*Z*)-1'-hydroxyoctadec-3'-en-2'-yl]propanamide (*Z*)-19a: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.26-1.37 (m, 24H), 2.12-2.17 (m, 3H), 3.38 (s, 3H), 3.65-3.71 (m, 2H), 4.81-4.88 (m, 1H), 5.32-5.37 (m, 1H), 5.64-5.70 (dd, *J* = 7.3, 10.7 Hz 1H), 6.94 (d, *J* = 6.8 Hz, 1H), 7.39-7.43 (m, 3H), 7.54-7.56 (m, 2H); IR (film) 3416, 2926, 2835, 1684 cm^{-1}; MS (SIMS) *m/z* 500 (M^++1).

(2*R*)-2-Methoxy-2-phenyl-3,3,3-trifluoro-*N*-[(2'*R*, 3'*Z*)-1'-hydroxyoctadec-3'-en-2'-yl]propanamide (*Z*)-19b: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.28-1.30 (m, 24H), 2.09 (q, *J* = 7.1 Hz, 2H), 2.18 (br, 1H), 3.43 (s, 3H), 3.68-3.71 (m, 2H), 4.80-4.86 (m, 1H), 5.31-5.36 (m, 1H), 5.62-5.66 (m, 1H), 6.93 (d, *J* = 6.8 Hz, 1H), 7.38-7.41 (m, 3H), 7.50-7.51 (m, 2H); IR (film) 3416, 2925, 2835, 1681 cm^{-1}; MS (SIMS) *m/z* 500 (M^++1).

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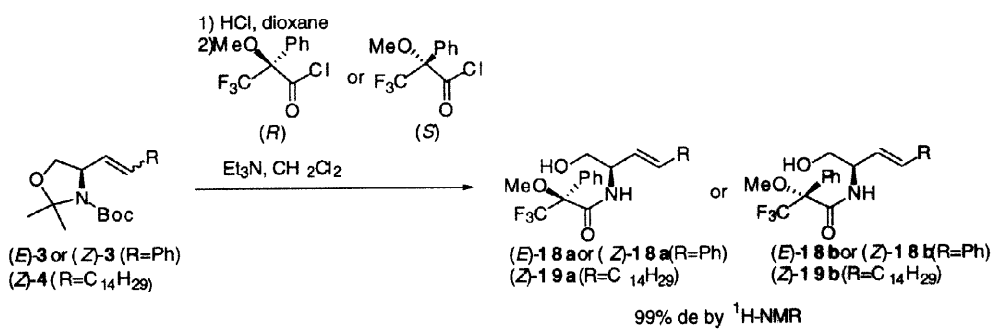
6. To ascertain the enantiomeric purities of the olefines **3**, **4**, they were converted to the Mosher's amides **18**, **19**with (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The diastereomeric excesses of **18** and **19** were determined to be 99% by ^{1}H NMR. The ^{1}H NMR data are shown in experimental section.



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8. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
9. The dihydroxylation using the bulky DHQ or DHQD ligated osmium reagent was very sluggish. Most of (Z)-**3** was almost recovered along with a small amount of phenyl ketone compounds, which would be oxydized products of diols **9** and **10**.
10. a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947.
11. a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. In this review, they referred that the diastereofacial selectivity in the dihydroxylation of 1-substituted 2-cyclohexenes was dramatically influenced by the allylic substituents. They explained that this phenomenon would be attributed to the hydrogen bonding interaction between OsO_4 and the allylic substituent, in which the acidity of the latter was a crucial factor. Accordingly, the acidic NH proton of the allylic NHBoc group of (Z)-**5** and (Z)-**6** might affect the selectivity so as to make *syn* attack of the reagent prefered. b) Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761.
12. In general, it is known to be difficult to achieve stereoselective dihydroxylation of (Z)-olefins using AD-mix reagents. The high selectivities attained here might be explained by the effect of hydrogen bonding between homoallyl alcohol moiety of the deprotected (Z)-olefins and oxo group on osmium as suggested by Sharpless: see, VanNieuwenhze, M. S.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 843.
13. The X-ray crystallographic data of the compound **13c** have been deposited to Cambridge Crystallographic Data Center.
14. Only one report[5h] of the optical rotation of the compound **17** has ever been made, but the reason for the large difference between the value of the optical rotation obtained by us and the reference's one is not clear.