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Total Synthesis of an Enantiomeric Pair of FR900482. 2.[1] Syntheses of the Aromatic and the Optically Active Aliphatic Segments

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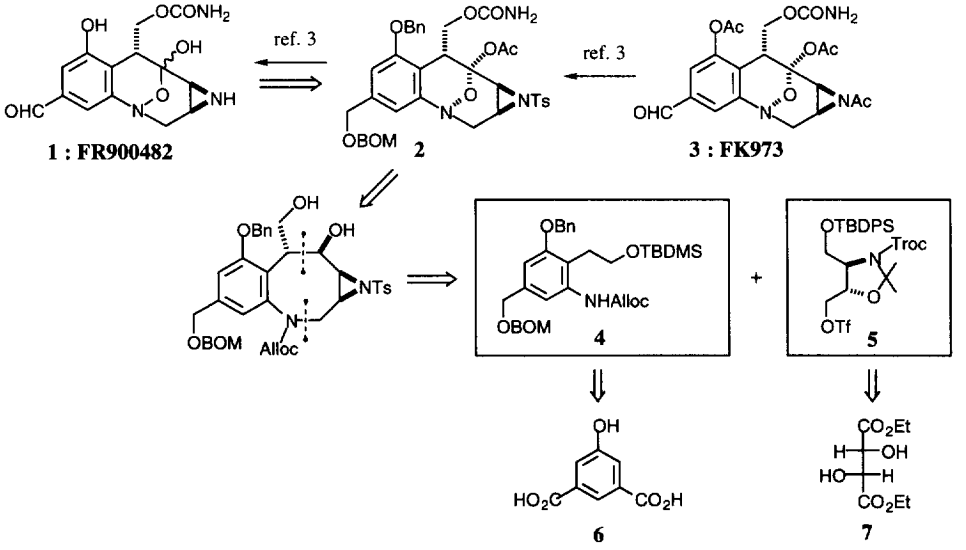
Abstract: *The synthesis of the aromatic segment **4** was achieved starting from commercially available 5-hydroxyisophthalic acid (**6**) by utilizing Claisen rearrangement of **9**, bromolactonization of **12**, and modified Curtius rearrangement of **16** as the key steps. Furthermore, the optically active aliphatic segments **5** and ent-**5** were synthesized in enantiomerically pure forms starting with natural (2R,3R)- and unnatural (2S,3S)-diethyl tartrate (**7** and ent-**7**), respectively: The synthetic scheme features epoxide formation of **26**, nucleophilic epoxide opening of **27** with an azide anion, reduction of the azide function in **33** to an amine, and formation of the N-protected 1,3-oxazolidine **35**.* © 1997 Elsevier Science Ltd.

(+)-FR900482 (**1**) isolated from the culture broth of *Streptomyces sandaensis* No.6897, displays prominent antitumor activity against various types of mammalian solid tumors.[2] As described in the preceding paper, we have succeeded in synthesizing the advanced key intermediate **2** starting with FK973 (**3**), the semisynthetic triacetyl derivative of **1**, and in developing an efficient synthetic pathway to **1** from **2** through which our total synthesis can proceed (**Scheme 1**).[3] Based on these preliminary studies, we next undertook the realization of the projected synthesis. In the second part of this series of papers, we present a full

Scheme 1. Synthetic Plan for FR900482 (**1**)



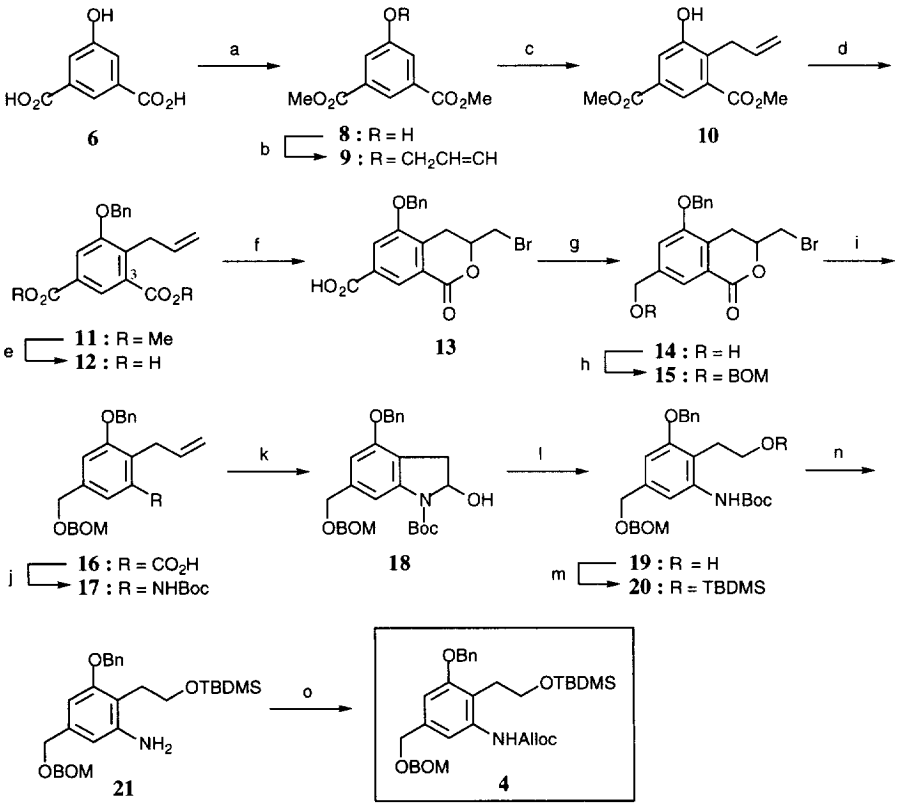
account of our efforts toward facile and efficient syntheses of the aromatic segment **4** and the optically active aliphatic segments **5**, *ent*-**5** starting with commercially available 5-hydroxyisophthalic acid (**6**) and both enatiomers of diethyl tartrate (**7** and *ent*-**7**), respectively.

Results and Discussion

1. Synthesis of the Aromatic Segment 4

At first, we pursued the synthesis of the aromatic segment **4** starting from 5-hydroxyisophthalic acid (**6**) as shown in **Scheme 2**. The synthesis involves the following three key steps: (i) Claisen rearrangement of the allyl ether **9** to install the requisite carbon chain into the aromatic ring (**9**→**10**); (ii) bromolactonization of **12** to protect the C-3 carboxyl groups (**12**→**13**); (iii) modified Curtius rearrangement of **16** to introduce an amino functionality (**16**→**17**).

Scheme 2. Synthesis of the Aromatic Segment **4**



a) $SOCl_2$, MeOH, reflux, 100% b) allylbromide, K_2CO_3, acetone, reflux, 98% c) *N,N*-diethylaniline, reflux, 88% d) BnBr, K_2CO_3, acetone, reflux, 99% e) 2M NaOH, THF, reflux, 95% f) Br_2, aq $NaHCO_3$, $CHCl_3$, 0°C, 72% g) $ClCO_2$-*i*-Pr, Et_3N, THF ; $NaBH_4$-H_2O, 95% h) BOMCl, *i*-Pr_2EtN, CH_2Cl_2, rt, 85% i) Zn, NH_4Cl, EtOH-H_2O, 93% j) DPPA, Et_3N, *t*-BuOH, rt→ reflux, 76% k) OsO_4, $NaIO_4$, dioxane-H_2O, rt, 73% l) $NaBH_4$, EtOH, rt, 100% m) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt, 97% n) TBDMSOTf, Py, CH_2Cl_2, rt ; TBAF, 92% o) AllocCl, aq $NaHCO_3$, CH_2Cl_2, rt, 98%

Thus, **6** was converted to the allyl ether **9** in 98% overall yield *via* the dimethyl ester **8** according to the reported methods[4-6] with several improvements of the reaction conditions. Claisen rearrangement of **9** was efficiently accomplished by refluxing in *N,N*-diethylaniline, affording the phenol **10** in 88% yield. Protection of the phenolic hydroxyl group in **10** followed by alkaline hydrolysis of the two methyl ester groups in the resulting benzyl ether **11**, led to the dicarboxylic acid **12** in 94% yield from **10**. In order to differentiate the two carboxyl groups in **12**, it was converted to the corresponding bromolactone **13** in 72% yield by reaction with bromine in the presence of aqueous hydrogen carbonate in chloroform. The remaining carboxyl group in **13** was then reduced *via* the mixed acid anhydride generated *in situ* by treatment with isopropyl chloroformate, giving rise to the benzyl alcohol **14** in 95% overall yield. Protection of the hydroxyl group in **14** as its benzyloxymethyl (BOM)[7] ether followed by reductive cleavage of the bromolactone moiety in the resulting BOM ether **15**, liberated the carboxylic acid **16** in 79% yield for the two steps.

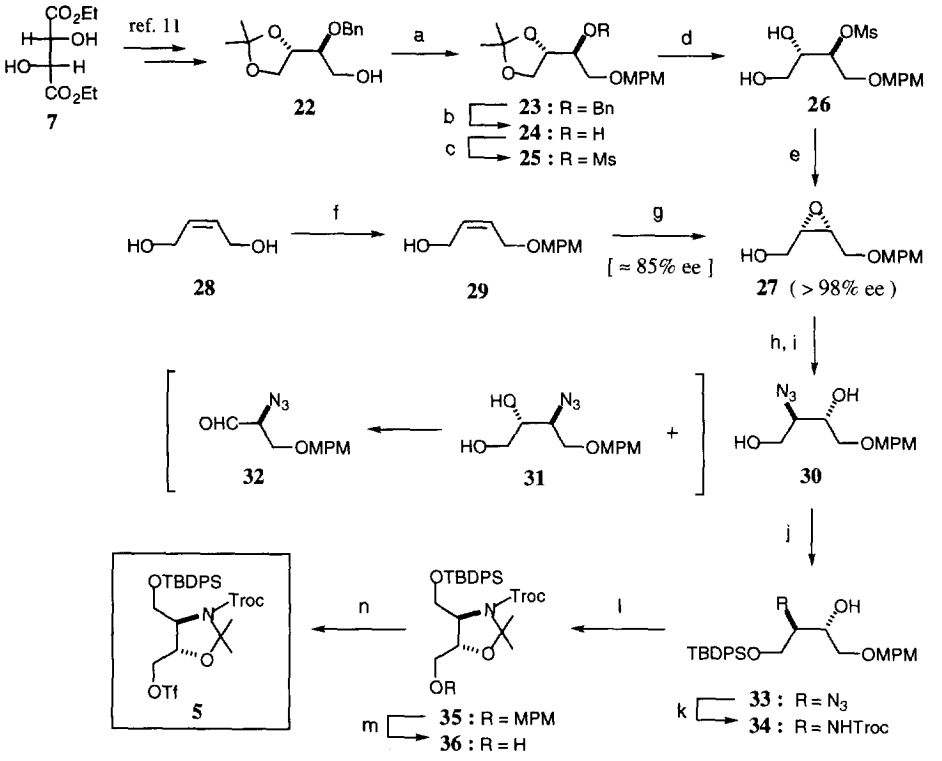
For converting the carboxyl group of **16** to an amino functionality, modified Curtius rearrangement was next attempted by employing the protocol reported by Shioiri *et al.*[8] Thus, **16** was treated with diphenylphosphoryl azide (DPPA) in the presence of triethylamine in refluxing *tert*-butyl alcohol, providing the *N-tert*-butoxycarbonyl (Boc) aniline **17** in 76% yield. Oxidative cleavage of the terminal olefin in **17** was carried out by employing the Lemieux-Johnson's procedure,[9] resulting in the formation of the cyclic hemiaminal **18** in 73% yield. Reduction of **18** with sodium borohydride followed by protection of the primary hydroxyl group in the resulting alcohol **19** furnished the *tert*-butyldimethylsilyl (TBDMS) ether **20** in 97% overall yield from **18**. Finally, exchange of the Boc protecting group in **20** with an allyloxycarbonyl (Alloc)[10] group gave the requisite aromatic segment **4** *via* the aniline **21** in 90% yield for the two steps.

2. Synthesis of the Optically Active Aliphatic Segment 5

Having completed the synthesis of the aromatic segment **4**, we next addressed ourselves to the elaboration of the optically active aliphatic segment **5** starting with natural (2*R*,3*R*)-diethyl tartrate (diethyl L-tartrate) (**7**) as shown in **Scheme 3**. The explored synthetic scheme features epoxide ring formation of **26**, nucleophilic epoxide ring opening of **27** with an azide anion, reduction of the azide group in **33** to an amino functionality, and formation of the *N*-protected 1,3-oxazolidine **35**.

The synthesis commenced with the known 2-*O*-benzyl-3,4-*O*-isopropylidene-L-threitol (**22**)[11] which was readily prepared from commercially available **7** *via* a three-step sequence involving acid-catalyzed benzylidene formation with benzaldehyde, reductive cleavage with a combination of lithium aluminium hydride and aluminium trichloride, and protection of the resulting vicinal diol with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid (TsOH). After protection of the primary hydroxyl group in **22** as its *p*-methoxyphenylmethyl (MPM) ether (97%), the benzyl (Bn) protecting group in the MPM ether **23** was then selectively removed by catalytic hydrogenolysis over Raney nickel,[12] affording the corresponding secondary alcohol **24** in 93% yield. Mesylation of the secondary hydroxyl group in **24** followed by acidic hydrolysis of the acetonide moiety in the resulting mesylate **25**, provided the vicinal diol **26** in 97% yield for the two steps. Epoxide ring formation of **26** was efficiently achieved by treatment with potassium carbonate in methanol, furnishing the epoxide **27** in 88% yield. The optical purity of **27** was estimated to be more than 98% ee by comparison of the 400MHz ^{1}H-NMR spectra of the corresponding (*S*)- and (*R*)-MTPA esters.[13] On the other hand, the optically active **27** could be produced more directly by employing the Sharpless asymmetric epoxidation[14] of the allyl alcohol **29**[15] prepared from commercially available *cis*-2-butene-1,4-diol (**28**). However, the optical purity

Scheme 3. Synthesis of the Optically Active Aliphatic Segment **5**



a) NaH, MPMCl, DMF, rt, 97% b) H_2, Raney Ni, EtOH, rt, 93% c) MsCl, Et_3N, CH_2Cl_2,0°C, 100% d) conc HCl, MeOH, rt, 97% e) K_2CO_3, MeOH, rt, 88% f) NaH, MPMCl, DMF, rt, 74% g) L-(+)-DET, Ti(O-*i*-Pr)$_4$, TBHP, CH_2Cl_2 -30°C, 59% h) NaN_3, NH_4Cl, EtOH, reflux, 92% i) $NaIO_4$, THF-H_2O, rt, 55% j) TBDPSCl, Et_3N, DMAP,CH_2Cl_2, rt, 91% k) PPh_3, THF-H_2O, rt ; TrocCl, aq $NaHCO_3$, rt, 98% l) TsOH, $Me_2C(OMe)_2$, acetone, rt, 97% m) DDQ, CH_2Cl_2-H_2O, rt, 98% n) Tf_2O, Et_3N, CH_2Cl_2, -78°C, 94%

of **27** prepared by the asymmetric epoxidation was found to be approximately 85% ee.[15] Furthermore, in a large scale experiment (>50 mmol), the enantiomeric excess of epoxidation product reduced to 75% ee, and moreover, a longer reaction time (>90 h) was required for completion of the reaction. Consequently, the sequence starting from **7** was selected to prepare a large quantity of **27** in an enantiomerically pure form.

To forward the synthetic scheme, nucleophilic epoxide ring opening in **27** with an azide anion[15,16] was next attempted. Thus, treatment of **27** with sodium azide in the presence of ammonium chloride in refluxing ethanol resulted in the formation of an inseparable mixture of regioisomers **30** and **31** in a ratio of *ca.* 3 : 2[17] in 92% combined yield. Upon exposure of this mixture to sodium periodate in THF-H2O, the desired azide alcohol **30** could be readily isolated in 55% yield from **27** by column chromatography on silica gel. Selective protection of the primary hydroxyl group in **30** provided the *tert*-butyldiphenysilyl (TBDPS) ether **33** in 91% yield. Reduction of the azide moiety in **33** with triphenylphosphine in THF-H2O at room temperature provided the corresponding amino alcohol, whose amino group was then selectively protected to form the *N*-2,2,2-trichloroethoxycarbonyl (Troc)[18] amine **34** in 98% overall yield. Further treatment of **34** with 2,2-dimethoxy-

propane in the presence of TsOH in acetone gave the *N*-protected 1,3-oxazolidine **35** in 97% yield. Finally, **35** was successfully converted to the requisite optically active aliphatic segment **5**[19] in 92% overall yield by deprotection[12] of the MPM group with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) followed by triflation[20] of the resulting alcohol **36**.

By employing unnatural (2*S*,3*S*)-diethyl tartrate (diethyl D-tartrate) (*ent*-**7**) instead of **7**, the enantiomeric aliphatic segment *ent*-**5** required for the total synthesis of unnatural (–)-FR900482 (*ent*-**1**) was prepared in a similar manner to that described above.

Conclusion

We have succeeded in developing a facile synthetic pathway to the aromatic segment **4** starting from commercially available 5-hydroxyisophthalic acid (**6**). Additionally, both enantiomers of the aliphatic segment **5** and *ent*-**5** were efficiently synthesized in enantiomerically pure forms by employing (2*R*,3*R*)- and (2*S*,3*S*)-diethyl tartrate (**7** and *ent*-**7**) as chiral starting materials. By utilizing **4**, **5**, and *ent*-**5** as the key segments, the total synthesis of both enantiomers of FR900482 (**1** and *ent*-**1**) was accomplished in a convergent manner. This is the subject of the following paper.[21]

Experimental

General. All melting points were determined with a Yamato MP-21 micro melting point apparatus and are uncorrected. Measurements of optical rotations were performed with a Horiba SEPA-200 automatic digital polarimeter. ^{1}H-NMR spectra were measured with a Bruker AC-200 (200 MHz) and a Brucker AM-400 (400 MHz) spectrometer. The chemical shifts were expressed in ppm using tetramethylsilane (δ=0) and/or residual solvents such as chloroform (δ=7.25) and benzene (δ=7.20) as internal standards. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-5300 spectrometer. Low resolution mass (MS) spectra were taken with a Hitachi RMU-6MG spectrometer, and high resolution mass (HRMS) spectra were obtained on a Hitachi M-80A spectrometer. Routine monitoring of reactions was carried out using Merck 60 F254 silica gel, glass-supported TLC plates. Flash column chromatography was performed with indicated solvents on Wakogel C-300. Solvents and commercial reagents were dried and purified before use. Tetrahydrofuran was distilled from sodium benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon.

Dimethyl 5-hydroxy-1,3-benzenedicarboxylate (8)

Thionyl chloride (80.2 ml, 1.1 mol) was added dropwise to a stirred solution of 5-hydroxyisophtalic acid (**6**) (100 g, 0.55 mol) in methanol (500 ml) at 0°C, and the mixture was heated at reflux for 1.5 h. After cooling, the mixture was concentrated *in vacuo* and then diluted with water (500 ml). The white precipitates were collected by filtration and dried *in vacuo* to give **8** (115 g, 100%) as a white solid. Recrystallization from ether-hexane afforded an analytical sample of **8** as colorless needles, mp 169-171°C [lit.,[4] mp 162-163°C, lit.,[5] mp 162-163.5°C, lit.,[6] mp 159-160°C]. IR (Nujol): 3380, 1725, 1705, 1600, 1460, 1430, 1265, 1250, 1010, 990 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.95 (6H, s, CO_2Me x 2), 6.00 (1H, br d, J=2.6 Hz, OH), 7.78 (2H, d, J=1.4 Hz, C4-H and C6-H), 8.25 (1H, t, J=1.4 Hz, C2-H). EIMS m/z: 210 (M^+), 179 [$(M-OMe)^+$], 151 [$(M-CO_2Me)^+$], 136 [$(M-CO_2Me-Me)^+$]. *Anal.* Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80%. Found: C, 57.10; H, 4.82%. These spectral data were identical with those reported.[4-6]

Dimethyl 5-allyloxy-1,3-benzenedicarboxylate (9)

Allyl bromide (68.0 ml, 0.79 mol) was added to a stirred solution of **8** (110 g, 0.52 mol) in dry acetone (560 ml) containing potassium carbonate (86.7 g, 0.63 mol) at room temperature, and the mixture was heated at reflux for 3 h. After cooling, the white precipitates were filtered off through a pad of celite. The filtrate was concentrated *in vacuo* to give a residue, which was diluted with ethyl acetate (2000 ml). The organic layer was washed with water and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a white solid, which was purified by recrystallization from methanol-water to give **9** (128 g, 98%) as a colorless needles, mp 71-72°C [lit.,[4] mp 71-72°C]. IR (CCl_4): 2970, 1730, 1600, 1435, 1340, 1315, 1240, 1120, 1105, 1045 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.94 (6H, s, CO_2Me x 2), 4.63 (2H, dt, J=6.7, 1.5 Hz, $OCH_2CH=CH_2$), 5.33 (1H, ddd, J=8.9, 3.1, 1.6 Hz, $OCH_2CH=CH_2$-*cis*), 5.44 (1H, ddd, J=15.7, 3.1, 1.6 Hz, $OCH_2CH=CH_2$-*trans*), 6.00-6.09 (1H, m, $OCH_2CH=CH_2$), 7.77 (2H, d, J=1.4 Hz, C4-H and C6-H), 8.28 (1H, t, J=1.3 Hz, C2-H). EIMS m/z: 250 (M^+), 235 [$(M-Me)^+$], 219 [$(M-OMe)^+$], 191 [$(M-CO_2Me)^+$]. *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64%. Found: C, 62.30; H, 5.62%. These spectral data were identical with those reported.[4]

Dimethyl 4-allyl-5-hydroxy-1,3-benzenedicarboxylate (10)

A solution of **9** (125 g, 0.50 mol) in *N,N*-diethylaniline (500 ml) was heated at reflux for 5 h. After cooling, the mixture was concentrated *in vacuo* to give a residue, which was diluted with ether (3000 ml). The organic layer was washed successively with 10% aqueous hydrochloric acid, water, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a white solid, which was purified by recrystallization from ether-hexane to afford **10** (110 g, 88%) as a colorless needles, mp 119-120°C. IR (Nujol): 3320, 1730, 1715, 1460, 1435, 1345, 1250, 1110, 865 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.82 (2H, br dt, J=8.0, 1.6 Hz, $CH_2CH=CH_2$), 3.91 (3H, s, CO_2Me), 3.93 (3H, s, CO_2Me), 5.00-5.16 (2H, m, $CH_2CH=CH_2$), 5.58 (1H, s, OH), 5.98-6.08 (1H, m, $CH_2CH=CH_2$), 7.67 (1H, d, J=1.7 Hz, C6-H), 8.10 (1H, d, J=1.7 Hz, C2-H). EIMS m/z: 250 (M^+), 235 [$(M-Me)^+$], 219 [$(M-OMe)^+$]. *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64%. Found: C, 62.28; H, 5.59%.

Dimethyl 4-allyl-5-benzyloxy-1,3-benzenedicarboxylate (11)

Benzyl bromide (47.6 ml, 0.40 mol) was added to a stirred solution of **10** (100 g, 0.40 mol) in dry acetone (380 ml) containing potassium carbonate (55.2 g, 0.40 mol) at room temperature, and the mixture was heated at reflux for 3 h. After cooling, the reaction mixture was diluted with ethyl acetate (2500 ml). The organic layer was washed successively with 3% aqueous hydrochloric acid, water, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 5:1) to give **11** (135 g, 99%) as a white solid. Recrystallization from hexane afforded an analytical sample of **11** as colorless needles, mp 96-97°C. IR (KBr): 3090, 3070, 3030, 3000, 2950, 2920, 2840, 1720, 1710, 1630, 1600, 1580, 1540, 1520, 1490, 1430, 1410, 1380, 1340, 1300, 1230, 1190, 1110, 1080, 1050, 1020, 1000, 920, 890, 880, 820, 790, 760, 720, 680, 640, 620 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.84 (2H, dt, J=6.2, 1.4 Hz, $CH_2CH=CH_2$), 3.91 (3H, s, CO_2Me), 3.93 (3H, s, CO_2Me), 4.98 (1H, dq, J=15.8, 1.7 Hz, $CH_2CH=CH_2$-*trans*), 4.99 (1H, dq, J=12.3, 1.7 Hz, $CH_2CH=CH_2$-*cis*), 5.16 (2H, s, OCH_2Ph), 5.93-6.03 (1H, m, $CH_2CH=CH_2$), 7.33-7.47 (5H, m, Bn), 7.74 (1H, d, J=1.6 Hz, C6-H), 8.12 (1H, d, J=1.6 Hz, C2-H). EIMS m/z: 340 (M^+), 309 [$(M-OMe)^+$], 249 [$(M-Bn)^+$]. *Anal.* Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92%. Found: C, 70.35; H, 5.89%.

4-Allyl-5-benzyloxy-1,3-benzenedicarboxylic acid (12)

A mixture of **11** (120 g, 0.35 mol) and 4 M sodium hydroxide (875 ml, 3.5 mol) in tetrahydrofuran (875 ml) was heated at reflux for 5 h. After cooling, the mixture was acidified to pH 3 with 37% aqueous hydrochloric acid and then concentrated *in vacuo*. The residue was extracted with ethyl acetate (3 x 800 ml), and the combined extracts were washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a white solid, which was purified by recrystallization from hexane-ethyl acetate to give **12** (105 g, 95%) as colorless prisms, mp 260-262°C. IR (KBr): 3070, 3000, 2970, 2860, 2630, 2540, 1680, 1630, 1600, 1570, 1490, 1470, 1450, 1430, 1330, 1300, 1260, 1230, 1170, 1115, 1080, 1040, 1020, 990, 940, 900, 830, 810, 780, 760, 740, 730, 680 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d6): δ 3.79 (2H, d, J=6.2 Hz, $CH_2CH=CH_2$), 4.91 (1H, dd, J=18.4, 1.9 Hz, $CH_2CH=CH_2$-*trans*), 4.94 (1H, dd, J=11.3, 1.9 Hz, $CH_2CH=CH_2$-*cis*), 5.23 (2H, s, OCH_2Ph), 5.86-5.96 (1H, m, $CH_2CH=CH_2$), 7.32-7.50 (5H, m, Bn), 7.71 (1H, d, J=1.5Hz, C6-H), 7.95 (1H, d, J=1.5Hz, C4-H), 13.20 (1H, br s, $W_{1/2}$=20 Hz, COOH). EIMS m/z: 312 (M^+), 221 [$(M-Bn)^+$]. *Anal.* Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16%. Found: C, 68.96; H, 5.05%.

5-Benzyloxy-3-bromomethyl-3,4-dihydro-1-oxo-1*H*-2-benzopyran-7-carboxylic acid (13)

Bromine (8.25 ml, 0.16 mol) was added dropwise to a stirred solution of **12** (50.0 g, 0.16 mol) in a mixture of 5% aqueous sodium hydrogen carbonate (800 ml) and chloroform (800 ml) at 0°C. After 5 min, the mixture was diluted with 10% aqueous sodium thiosulfate (30 ml) and then acidified to pH 3 with 37% aqueous hydrochloric acid. The resulting mixture was extracted with ether (3 x 2000 ml), and the combined extracts were washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a white solid, which was purified by column chromatography (chloroform-methanol, 10:1) to give **13** (45.1 g, 72%) as a white solid. Recrystallization from chloroform afforded an analytical sample of **13** as colorless prisms, mp 211-212°C. IR (KBr): 3050, 3020, 2950, 2910, 2860, 1720, 1685, 1605, 1580, 1490, 1450, 1430, 1380, 1355, 1340, 1300, 1260, 1220, 1200, 1155, 1105, 1055, 1030, 1010, 950, 930, 910, 880, 840, 755, 730, 690 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d6): δ 2.93 (1H, dd, J=17.3, 11.8 Hz, C4-*H*2), 3.31 (1H, dd, J=17.3, 3.4 Hz, C4-*H*2), 3.87 (1H, dd, J=11.2, 5.6 Hz, CH_2Br), 3.95 (1H, dd, J=11.2, 3.7 Hz, CH_2Br), 4.85-4.91 (1H, m, C3-H), 5.27 (1H, d, J=11.9 Hz, OCH_2Ph), 5.31 (1H, d, J=11.9 Hz, OCH_2Ph), 7.34-7.45 (5H, m, Bn), 7.83 (1H, d, J=1.4 Hz, C6-H), 8.10 (1H, d, J=1.4 Hz, C8-H), 13.36 (1H, br s, $W_{1/2}$=20 Hz, COOH). EIMS m/z: 392 [$(M+2)^+$, ^{81}Br], 390 (M^+, ^{79}Br). *Anal.* Calcd for $C_{18}H_{15}BrO_5$: C, 55.26; H, 3.86; Br, 20.43%. Found: C, 55.16; H, 3.80; Br, 20.37%.

5-Benzyloxy-3-bromomethyl-3,4-dihydro-7-hydroxymethyl-1*H*-2-benzopyran-1-one (14)

Isopropyl chloroformate (28.0 ml, 0.25 mol) was added dropwise to a stirred solution of **13** (88.5 g, 0.23 mol) in dry tetrahydrofuran (700 ml) containing triethylamine (40.9 ml, 0.29 mol) at 0°C under argon. After 20 min, a solution of sodium borohydride (25.8 g, 0.68 mol) in water (500 ml) was added dropwise, and the resulting mixture was further stirred for 40 min at 0°C. The reaction was quenched with saturated aqueous ammonium chloride (100 ml), and the mixture was diluted with ethyl acetate (2300 ml). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (chloroform-methanol, 20:1) to give **14** (81.1 g, 95%) as a white solid.

Recrystallization from chloroform afforded an analytical sample of **14** as colorless needles, mp 189-190°C. IR (KBr): 3510, 3450, 2940, 2890, 1715, 1620, 1590, 1500, 1440, 1390, 1365, 1320, 1280, 1260, 1220, 1210, 1185, 1135, 1060, 1040, 1010, 960, 880, 860, 780, 740, 700 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d6): δ 2.82 (1H, dd, J=16.9, 11.8Hz, C4-*H*2), 3.22 (1H, dd, J=16.9, 3.3 Hz, C4-*H*2), 3.85 (1H, dd, J=11.1, 5.6 Hz, C*H*2Br), 3.92 (1H, dd, J=11.1, 3.8 Hz, C*H*2Br), 4.53 (2H, d, J=5.8 Hz, C*H*2OH), 4.75-4.82 (1H, m, C3-H), 5.17 (1H, d, J=11.8 , OC*H*2Ph), 5.21 (1H, d, J=11.8 Hz, OC*H*2Ph), 5.37 (1H, t, J=5.8 Hz, OH), 7.34-7.54 (7H, m, aromatic protons). EIMS m/z: 378 [(M+2)$^+$, ^{81}Br], 376 (M$^+$, ^{79}Br). *Anal.* Calcd for C18H17BrO4: C, 57.31; H, 4.54; Br, 21.18%. Found: C, 57.49; H, 4.40; Br, 21.41%.

5-Benzyloxy-7-benzyloxymethoxymethyl-3-bromomethyl-3,4-dihydro-1*H*-2-benzopyran-1-one (15)

Benzyl chloromethyl ether (35.7 ml, 0.26 mol) was added to a stirred solution of **14** (48.3 g, 0.13 mol) in dry dichloromethane (500 ml) containing *N,N*-diisopropylethylamine (66.8 ml, 0.38 mol) at room temperature under argon. After 8 h, the mixture was diluted with ethyl acetate (2000 ml). The organic layer was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 5:1→3:1→1:1) to give **15** (54.1 g, 85%) as a white solid. Recrystallization from hexane afforded an analytical sample of **15** as colorless leaves, mp 75-76°C. IR (KBr): 3080, 3045, 2940, 2880, 2780, 1730, 1620, 1590, 1500, 1475, 1460, 1440, 1380, 1360, 1340, 1320, 1280, 1260, 1220, 1180, 1140, 1110, 1060, 1010, 980, 960, 910, 860, 850, 810, 780, 745, 700, 660, 610 cm^{-1}. ^{1}H-NMR (400 MHz, benzene-d6): δ 2.38 (1H, dd, J=16.9, 11.3 Hz, C4-*H*2), 2.80 (1H, dd, J=16.9, 3.5 Hz, C4-*H*2), 2.82 (1H, dd, J=10.8, 5.6, Hz, C*H*2Br), 2.86 (1H, dd, J=10.8, 5.1 Hz, C*H*2Br), 3.81-3.88 (1H, m, C3-H), 4.42 (2H, s, BOMOC*H*2), 4.50 (2H, s, PhC*H*2OCH2O), 4.55 (2H, s, PhCH2OC*H*2O), 4.64 (2H, s, OC*H*2Ph), 6.93 (1H, s, C6-H), 7.04-7.31 (10H, m, aromatic protons), 8.00 (1H, s, C8-H). CIMS (isobutane) m/z: 498 [(M+2)$^+$, ^{81}Br], 496 (M$^+$, ^{79}Br). *Anal.* Calcd for C26H25BrO5: C, 62.83; H, 5.07; Br, 16.07%. Found: C,62.82; H, 5.07; Br, 15.93%.

2-Allyl-3-benzyloxy-5-(benzyloxymethoxymethyl)benzoic acid (16)

Zinc powder (90.4 g, 1.4 mol) and ammonium chloride (37.0 g, 0.69 mol) were successively added to a stirred solution of **15** (68.8 g, 0.14 mol) in ethanol-water (19:1) (940 ml) at room temperature. The mixture was gradually warmed to 40°C and stirred at the same temperature for 1 h. After cooling, the mixture was filtrated, and the filtrate was concentrated *in vacuo* to give a residue, which was diluted with ethyl acetate (2000 ml). The organic layer was washed with 3% aqueous hydrochloric acid and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 3:1→1:1) to give **16** (53.8 g, 93%) as a white solid. Recrystallization from hexane-ethyl acetate afforded an analytical sample of **16** as colorless needles, mp 61-62.5°C. IR (KBr): 3080, 3050, 3030, 2950, 2900, 2640, 1700, 1640, 1620, 1580, 1500, 1480, 1460, 1420, 1380, 1345, 1300, 1220, 1170, 1150, 1130, 1050, 1000, 960, 920, 860, 790, 760, 700, 660, 610 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 3.88 (2H, d, J=6.2 Hz, C*H*2CH=CH2), 4.64 (4H, s, PhC*H*2OCH2OC*H*2), 4.85 (2H, s, PhCH2OC*H*2O), 4.96-5.02 (2H, m, CH2CH=C*H*2), 5.09 (2H, s, OC*H*2Ph), 5.97-6.07 (1H, m, CH2C*H*=CH2), 7.15 (1H, d, J=1.4 Hz, C4-H), 7.28-7.45 (10H, m, aromatic protons), 7.60 (1H, d, J=1.4 Hz, C6-H). CIMS (isobutane) m/z: 419 [(M+H)$^+$], 401 [(M+H-H2O)$^+$], 389, 371. *Anal.* Calcd for C26H26O5: C, 74.62; H, 6.26%. Found: C, 74.62; H, 6.25%.

2-Allyl-3-benzyloxy-5-benzyloxymethoxymethyl-*N*-(*tert*-butoxycarbonyl)aniline (17)

Diphenylphosphoryl azide (27.0 ml, 0.13 mol) was added to a stirred solution of **16** (52.4 g, 0.13 mol) in *tert*-butyl alcohol (620 ml) containing triethylamine (22.9 ml, 0.16 mol) and molecular sieves (4A, 100 g) at room temperature, and stirring was continued for 1.5 h. The mixture was heated at reflux for 5 h. After cooling, the mixture was filtrated, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (benzene) to give **17** (46.6 g, 76%) as a white solid. Recrystallization from ether-hexane afforded an analytical sample of **17** as colorless needles, mp 68-69 °C. IR (KBr): 3360, 3100, 3050, 3025, 2980, 2950, 2900, 1700, 1645, 1620, 1600, 1540, 1500, 1480, 1450, 1420, 1380, 1340, 1280, 1260, 1220, 1170, 1150, 1100, 1060, 1010, 990, 960, 930, 910, 880, 840, 780, 760, 740, 700, 660, 615 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.51 (9H, s, *tert*-Bu), 3.47 (2H, dt, J=5.8, 1.6 Hz, C*H*2CH=CH2), 4.62 (2H, s, BOMOC*H*2), 4.65 (2H, s, PhC*H*2OCH2O), 4.84 (2H, s, PhCH2OC*H*2O), 5.02 (1H, ddd, J=17.2, 3.4, 1.7 Hz, CH2CH=C*H*2-*cis*), 5.05 (2H, s, OC*H*2Ph), 5.08 (1H, ddd, J=10.1, 3.2, 1.6 Hz, CH2CH=C*H*2-*trans*), 5.86-5.96 (1H, m, CH2C*H*=CH2), 6.49 (1H, br s, W1/2=6.8 Hz, NH), 6.75 (1H, d, J=1.2 Hz, C4-H), 7.28-7.41 (10H, m, aromatic protons), 7.52 (1H, br s, W1/2=5.7Hz, C4-H). EIMS m/z: 489 (M$^+$), 415 [(M-*tert*-BuO+H)$^+$], 295 [(M-*tert*-BuO-CH2OBn)$^+$], 279, 253, 235, 204 [(M-*tert*-BuO-CH2OBn-Bn)$^+$]. *Anal.* Calcd for C30H35NO5: C, 73.59; H, 7.21; N, 2.86%. Found: C, 73.71; H, 7.30; N, 2.80%.

4-Benzyloxy-6-benzyloxymethoxymethyl-1-*tert*-butoxycarbonyl-2-hydroxyindoline (18)

Osmium tetroxide in water (1.0% solution, 26.9 ml, 1.1 mmol) and sodium periodate (56.7 g, 0.26 mol) were successively added to a stirred solution of **17** (51.8 g, 0.11 mmol) in 1,4-dioxane-water (4:3) (600 ml) at room temperature. After 13 h, the mixture was treated with 20% aqueous sodium thiosulfate (100 ml) and then diluted with ether (2000 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 5:1) to give **18** (38.0 g, 73%) as a colorless

caramel. IR (neat): 3480, 3100, 3080, 3050, 3025, 3000, 2950, 2900, 1700, 1610, 1505, 1450, 1380, 1320, 1260, 1180, 1140, 1100, 1050, 1000, 940, 880, 860, 840, 740, 700, 680, 660, 620, 550 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.59 (9H, s, *tert*-Bu), 2.98 (1H, d, J=17.4 Hz, C3-H), 3.27 (1H, dd, J=17.5, 7.7 Hz, C3-H), 4.00 (1H, br s, $W_{1/2}$=24 Hz, OH), 4.60 (2H, s, BOMOC*H*$_2$), 4.64 (2H, s, PhC*H*$_2$OCH$_2$O), 4.82 (2H, s, PhCH$_2$OC*H*$_2$O), 5.08 (2H, S, OC*H*$_2$Ph), 6.03 (1H, br s, $W_{1/2}$=48 Hz, C2-H), 6.63 (1H, br s, $W_{1/2}$=12 Hz, C5-H), 7.12-7.42 (11H, aromatic protons). EIMS m/z: 491 (M^+), 473 [$(M-H_2O)^+$], 435, 417 [(M-*tert*-BuO+H)$^+$], 373. HRMS calcd for $C_{29}H_{33}NO_6$ (M^+): 491.2309. Found: 491.2287.

3-Benzyloxy-5-benzyloxymethoxymethyl-2-(2-hydroxyethyl)-*N*-(*tert*-butoxycarbonyl)aniline (19)

Sodium borohydride (11.4 g, 0.30 mol) in ethanol (300 ml) was added dropwise to a stirred solution of **18** (36.9 g, 75 mmol) in ethanol (600 ml) at room temperature. After 40 min, the mixture was concentrated *in vacuo* to give a residue, which was diluted with ether (2000 ml). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 5:1→3:1) to give **19** (37.0 g, 100%) as a colorless caramel. IR (neat): 3450, 3340, 3100, 3080, 3050, 2990, 2950, 2900, 1730, 1710, 1620, 1595, 11545, 1500, 1460, 1445, 1375, 1330, 1275, 1255, 1170, 1120, 1055, 1030, 1010, 910, 890, 860, 840, 800, 740, 700, 640, 620 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.51 (9H, s, *tert*-Bu), 1.75 (1H, br s, $W_{1/2}$=12.3 Hz, OH), 2.95 (2H, t, J=5.5 Hz, C*H*$_2$CH$_2$OH), 3.88 (2H, br s, $W_{1/2}$=14.2 Hz, CH$_2$C*H*$_2$OH), 4.62 (2H, s, BOMOC*H*$_2$), 4.65 (2H, s, PhC*H*$_2$OCH$_2$O), 4.84 (2H, s, PhCH$_2$OC*H*$_2$O), 5.05 (2H, s, OC*H*$_2$Ph), 6.75 (1H, s, C4-H), 7.27-7.40 (10H, m, aromatic protons), 7.44 (1H, br s, $W_{1/2}$=5.5 Hz, C6-H), 7.61 (1H, br s, $W_{1/2}$=4.9 Hz, NH). EIMS m/z: 493 (M^+), 475 [$(M-H_2O)^+$], 460, 438, 420 [(M-*tert*-BuO)$^+$]. HRMS calcd for $C_{29}H_{35}NO_6$ (M^+): 493.2466. Found: 493.2465.

3-Benzyloxy-5-benzyloxymethoxymethyl-2-(2-*tert*-butyldimethylsiloxy)ethyl-*N*-(*tert*-butoxycarbonyl)aniline (20)

tert-Butyldimethylsilyl chloride (14.3 g, 95 mmol) was added in small portions to a stirred solution of **19** (36.1 g, 73 mmol) in dry dichloromethane (360 ml) containing triethylamine (15.3 ml, 0.11 mol) and a catalytic amount of 4-dimethylaminopyridine (893 mg, 7.3 mmol) at room temperature. After 2 h, the mixture was diluted with ether (2000 ml). The organic layer was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **20** (43.1 g, 97%) as a colorless caramel. IR (neat): 3360, 3100, 3075, 3050, 2960, 2945, 2900, 2870, 1735, 1620, 1595, 1535, 1505, 1460, 1450, 1395, 1385, 1330, 1260, 1210, 1170, 1090, 1055, 1035, 1010, 950, 920, 880, 840, 785, 740, 700, 670 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ -0.12 (6H, s, Si(Me)$_2$), 0.87 (9H, s, Si-*tert*-Bu), 1.52 (9H, s, Boc), 2.95 (2H, t, J=5.2 Hz, C*H*$_2$CH$_2$OTBDMS), 3.85 (2H, t, J=5.2 Hz, CH$_2$C*H*$_2$OTBDMS), 4.64 (2H, s, BOMOC*H*$_2$), 4.66 (2H, s, PhC*H*$_2$OCH$_2$O), 4.84 (2H, s, PhCH$_2$OC*H*$_2$O), 5.06 (2H, s, OC*H*$_2$Ph), 6.73 (1H, t, J=1.2 Hz, C4-H), 7.26-7.39 (10H, m, aromatic protons), 7.50 (1H, br s, $W_{1/2}$=6.0 Hz, C6-H), 8.1 (1H, br s, $W_{1/2}$=20 Hz, NH). CIMS (isobutane) m/z: 608 [$(M+H)^+$], 552 [(M+H-C_4H_8)$^+$], 534 [(M-*tert*-BuO)$^+$], 508 [(M+1-Boc+H)$^+$], 494 [(M+1-Boc-Me+2H)$^+$], 470, 414, 396, 338. HRMS calcd for $C_{35}H_{49}NO_6Si$ (M^+): 607.3331. Found: 607.3345.

3-Benzyloxy-5-benzyloxymethoxymethyl-2-(2-*tert*-butyldimethylsiloxy)ethylaniline (21)

tert-Butyldimethylsilyl trifluoromethanesulfonate (24.1 ml, 0.11 mol) was added dropwise to a stirred solution of **20** (42.6 g, 70 mmol) in dry dichloromethane (420 ml) containing pyridine (11.3 ml, 0.14 mol) at room temperature. After 4 h, tetrabutylammonium fluoride in tetrahydrofuran (1.0 M solution, 210 ml, 0.21 mol) was added slowly, and stirring was continued for 1 h at room temperature. The mixture was diluted with ether (2000 ml), and the organic layer was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 5:1) to give **21** (32.7 g, 92%) as a colorless caramel. IR (neat): 3460, 3380, 3250, 3100, 3080, 3050, 2970, 2945, 2900, 2870, 1630, 1590, 1505, 1460, 1445, 1385, 1370, 1350, 1260, 1220, 1175, 1140, 1090, 1060, 1010, 980, 910, 840, 820, 785, 745, 705, 670, 605 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ -0.36 (6H, s, Si(Me)$_2$), 0.86 (9H, s, Si-*tert*-Bu), 2.90 (2H, t, J=6.1 Hz, C*H*$_2$CH$_2$OTBDMS), 3.82 (2H, t, J=6.1 Hz, CH$_2$C*H*$_2$OTBDMS), 4.07 (2H, br s, $W_{1/2}$=25.2 Hz, NH$_2$), 4.55 (2H, s, BOMOC*H*$_2$), 4.66 (2H, s, PhC*H*$_2$OCH$_2$O), 4.83 (2H, s, PhCH$_2$OC*H*$_2$O), 5.03 (2H, S, OC*H*$_2$Ph), 6.36 (1H, d, J=1.2 Hz, C4-H or C6-H), 6.42 (1H, d, J=1.0 Hz, C4-H or C6-H), 7.29-7.43 (10H, m, aromatic protons). EIMS m/z: 507 (M^+), 450 [(M-*tert*-Bu)$^+$], 371 [(M-BnOCH$_2$O+H)$^+$], 312 [(M-BnOCH$_2$-Si(Me)$_2$+H)$^+$], 294, 222 [(M-BnOCH$_2$-Si(Me)$_2$-Bn+2H)$^+$], 192. HRMS calcd for $C_{30}H_{41}O_4NSi$ (M^+): 507.2806. Found: 507.2782.

3-Benzyloxy-5-benzyloxymethoxymethyl-2-(2-*tert*-butyldimethylsiloxy)ethyl-*N*-(allyloxycarbonyl) aniline (4)

Allyl chloroformate (19.7 ml, 0.19 mol) was added to a stirred mixture of **21** (31.4 g, 62 mmol) in dichloromethane (420 ml) and saturated aqueous sodium hydrogen carbonate (500 ml) at room temperature. After 13 h, the mixture was diluted with ether (2000 ml). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 5:1) to give **4** (35.9 g, 98%) as a colorless caramel. IR (neat): 2960,

2950, 2900, 2870, 1740, 1600, 1460, 1450, 1260, 1220, 1090, 1050, 840 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ -0.03 (6H, s, Si(Me)2), 0.85 (9H, s, Si-*tert*-Bu), 2.95 (2H, t, J=5.2 Hz, C*H*2CH2OTBDMS), 3.84 (2H, t, J=5.2 Hz, CH2C*H*2OTBDMS), 4.62 (2H, s, C*H*2OBOM), 4.63-4.67 (2H, m, C*H*2CH=CH2), 4.65 (2H, s, PhC*H*2OCH2O), 4.83 (2H, s, PhCH2OC*H*2O), 5.05 (2H, s, OC*H*2Ph), 5.24 (1H, dd, J=10.4, 1.3 Hz, CH2CH=C*H*2-*trans*), 5.36 (1H, ddd, J=17.2, 3.1, 1.5 Hz, CH2CH=C*H*2-*cis*), 5.91-6.20 (1H, m, CH2C*H*=CH2), 6.74 (1H, d, J=1.1 Hz, C4-H or C6-H), 7.26-7.44 (10H, m, aromatic proton), 7.47 (1H, br s, W1/2=16Hz, C4-H or C6-H), 8.41 (1H, br s, W1/2=20 Hz, NH). CIMS (isobutane) m/z: 592 [(M+H)$^+$], 576 [(M+H-Me)$^+$], 534 [(M-*tert*-Bu)$^+$], 504 [(M-2Me-*tert*-Bu)$^+$]. HRMS calcd for C30H36NO6Si [(M-*tert*-Bu)$^+$]: 534.2309. Found: 534.2307.

(2*S*,3*S*)-2-*O*-Benzyl-3,4-*O*-isopropylidenethreitol (22) and Its Enantiomer (*ent*-22)

a) Preparation of **22:** This compound was prepared from (2*R*,3*R*)-diethyl tartrate (diethyl L-tartrate) (**7**) according to the reported procedure.[11a] This material obtained as a colorless oil, showed [α]D^{20} -22.1° (c 1.21, $CHCl_3$) [lit.,[11a] [α]D^{22} -16.8° (c 1.31, $CHCl_3$), lit.,[12] [α]D -14.1° (c 0.6, $CHCl_3$)]. IR (neat): 3450, 2990, 2930, 2875, 1500, 1450, 1380, 1370, 1250, 1210, 1150, 1070, 850, 790, 740, 700, 600, 510 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, s, acetonide Me), 1.44 (3H, s, acetonide Me), 2.17 (1H, br t, J=5.7 Hz, OH), 3.56-3.63 (2H, m, C1-H2), 3.71-3.76 (1H, m, C2-H), 3.82 (1H, dd, J=8.4, 7.1 Hz, C4-*H*2), 4.02 (1H, dd, J=8.4, 6.6 Hz, C4-*H*2), 4.29-4.34 (1H, m, C3-H), 4.69 (1H, d, J=11.8 Hz, OC*H*2Ph), 4.77 (1H, d, J=11.8 Hz, OC*H*2Ph), 7.28-7.38 (5H, m, aromatic protons). CIMS (isobutane) m/z: 253 [(M+H)$^+$], 237 [(Me)$^+$]. HRMS calcd for C13H17O4 [(M-Me)$^+$]: 237.1127. Found: 237.1115. These IR and ^{1}H-NMR spectra were identical with those reported.[11a]

b) Preparation of *ent*-**22:** This compound was prepared from (2*S*,3*S*)-diethyl tartrate (diethyl D-tartrate) (*ent*-**7**) according to the reported procedure.[11a] This material showed [α]D^{20} +21.4° (c 1.04, $CHCl_3$) [lit.,[11a] [α]D +16.8° (c 1.30, $CHCl_3$)]. The ^{1}H-NMR spectrum of this sample was identical with that recorded for **22**.

(2*S*,3*S*)-2-*O*-Benzyl-3,4-*O*-isopropylidene-1-*O*-*p*-methoxybenzylthreitol (23) and Its Enantiomer (*ent*-23)

a) Preparation of **23:** Sodium hydride (60% dispersion in mineral oil, 13.3 g, 0.33 mol) in dry *N*,*N*-dimethylformamide (210 ml) was added dropwise to a stirred solution of **22** (70.0 g, 0.28 mol) in dry tetrahydrofuran (420 ml) containing *p*-methoxybenzyl chloride (40.3 ml, 0.28 mol) at 0°C, and stirring was continued for 1.5 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride (25 ml), and the mixture was diluted with ethyl acetate (2000 ml). The organic layer was washed with water and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 3:1→2:1) to give **23** (100 g, 97%) as a colorless oil. [α]D^{20} -3.9° (c 1.50, $CHCl_3$). IR (neat): 2990, 2940, 2900, 2870, 1610, 1580, 1515, 1460, 1380, 1370, 1300, 1250, 1210, 1170, 1160, 1090, 1040, 850, 820, 740, 700, 510 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.36 (3H, s, acetonide Me), 1.40 (3H, s, acetonide Me), 3.55-3.57 (2H, m, C1-H2), 3.58-3.63 (1H, m, C2-H), 3.74 (1H, dd, J=8.3, 7.4 Hz, C4-*H*2), 3.81 (3H, s, OMe), 3.96 (1H, dd, J=8.4, 6.5 Hz, C4-*H*2), 4.26 (1H, m, C3-H), 4.42 (1H, d, J=11.6 Hz, OC*H*2PhOMe), 4.44 (1H, d, J=11.6 Hz, OC*H*2PhOMe), 4.72 (1H, d, J=12.1 Hz, OC*H*2Ph), 4.77 (1H, d, J=12.1 Hz, OC*H*2Ph), 6.87 (2H, d, J=8.7 Hz, MeOPh-*H*2), 7.23 (2H, J=6.6 Hz, MeOPh-*H*2), 7.28-7.38 (5H, m, Bn). CIMS (isobutane) m/z: 371 [(M-1)$^+$], 357 [(M-Me)$^+$], 314 [(M-C3H6O)$^+$], 296, 281 [(M-Bn)$^+$], 265 [(M-OBn)$^+$], 251 [(M-CH2PhOMe)$^+$], 237, 223, 211, 206, 195, 175, 163, 149, 137, 121, 91, 56, 40, 27, 15. HRMS calcd for C19H22O4 [(M-C3H6O)$^+$]: 314.1518. Found: 314.1493.

b) Preparation of *ent*-**23:** The same treatments of *ent*-**22** (80.0 g, 0.32 mol) as described for the preparation of **23** from **22** gave *ent*-**23** (112 g, 95%) as a colorless oil. [α]D^{20} +4.0° (c 1.51, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **23**.

(2*S*,3*S*)-3,4-*O*-Isopropylidene-1-*O*-*p*-methoxybenzylthreitol (24) and Its Enantiomer (*ent*-24)

a) Preparation of **24:** A mixture of **23** (100 g, 0.27 mol) and Raney® nickel (20 g) in ethanol (1000 ml) was stirred for 1 h at room temperature under hydrogen atmosphere (1 atm). The catalyst was filtered off under argon, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (hexane-ethyl acetate, 3:1→1:1) to give **24** (70.5 g, 93%) as a colorless oil. [α]D^{20} +5.7° (c 1.30, $CHCl_3$). IR (neat): 3500, 2980, 2940, 2900, 1740, 1610, 1580, 1510, 1480, 1370, 1300, 1250, 1210, 1170, 1160, 1060, 1040, 960, 910, 850, 760, 710, 640, 580, 520 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.36 (3H, s, acetonide Me), 1.43 (3H, s, acetonide Me), 2.44 (1H, d, J=5.2 Hz, OH), 3.45-3.52 (2H, m, C1-H2), 3.75 (1H, quint, J=5.5 Hz, C2-H), 3.79-3.83 (1H, m, C4-*H*2), 3.81 (3H, s, OMe), 4.00 (1H, dd, J=8.3, 6.6 Hz, C4-*H*2), 4.14-4.18 (1H, m, C3-H), 4.48 (2H, s, OC*H*2PhOMe), 6. 88 (2H, d, J=8.7 Hz, MeOPh-*H*2), 7.25 (2H, d, J=8.7 Hz, MeOPh-*H*2). EIMS m/z: 282 (M$^+$), 267 [(M-Me)$^+$], 224 [(M-C3H6O)$^+$], 206, 193, 162, 137, 121, 101, 78, 59, 43. HRMS calcd for C15H22O5 (M$^+$): 282.1467. Found: 282.1445.

b) Preparation of *ent*-**24:** Treatments of *ent*-**23** (110.0 g, 0.30 mol) in the same manner as described for the preparation of **24** from **23** afforded *ent*-**24** (79.6 g, 95%) as a colorless oil. [α]D^{20} -6.5° (c 1.49, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **24**.

(2*S*,3*S*)-3,4-*O*-Isopropylidene-2-*O*-methanesulfonyl-1-*O*-*p*-methoxybenzylthreitol (25) and Its Enantiomer (*ent*-25)

a) Preparation of **25:** Methanesulfonyl chloride (20.2 ml, 0.26 mol) was added dropwise to a stirred solution of **24** (60.0 g, 0.21 mol) in dry dichloromethane (600 ml) containing triethylamine (38.5 ml, 0.28 mol) at 0°C under argon. After 30 min, the reaction was quenched with saturated aqueous sodium hydrogen carbonate (30 ml), and the mixture was diluted with ethyl acetate (2000 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 3:1→1:1) to give **25** (77.0 g, 100%) as a colorless oil. $[\alpha]_D^{20}$ -7.7° (c 1.43, $CHCl_3$). IR (neat): 2990, 2940, 2900, 2870, 2840, 1610, 1580, 1510, 1460, 1410, 1360, 1300, 1250, 1220, 1170, 1100, 1060, 1040, 960, 920, 850, 820, 760 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.35 (3H, s, acetonide Me), 1.42 (3H, s, acetonide Me), 3.08 (3H, s, SO_2Me), 3.65-3.73 (2H, m, C1-H2), 3.81 (3H, s, OMe), 3.87, (1H, dd, J=8.9, 6.5 Hz, C4-*H*2), 4.05 (1H, dd, J=8.9, 6.6 Hz, C4-*H*2), 4.27-4.32 (1H, m, C3-H), 4.46 (1H, d, J=11.4 Hz, OC*H*2PhOMe), 4.51 (1H, d, J=11.4 Hz, OC*H*2PhOMe), 4.72-4.76 (1H, m, C2-H), 6.88 (2H, d, J=8.7 Hz, MeOPh-*H*2), 7.23 (2H, d, J=8.7 Hz, MeOPh-*H*2). EIMS m/z: 360 (M^+), 345 [(M-Me)$^+$], 302 [(M-C_3H_6O)$^+$], 271, 207, 189, 175, 162, 150, 135, 121, 101, 43. HRMS calcd for $C_{16}H_{24}O_7S$ (M^+): 360.1243. Found: 360.1215.

b) Preparation of *ent*-**25:** Similar treatments of *ent*-**24** (79.0 g, 0.28 mol) to those described for the preparation of **25** from **24** gave *ent*-**25** (98.8 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ +7.3° (c 1.65, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **25**.

(2*S*,3*S*)-3-*O*-Methanesulfonyl-4-*O*-*p*-methoxybenzylthreitol (26) and Its Enantiomer (*ent*-26)

a) Preparation of **26:** Thirty seven percent aqueous hydrochloric acid (50.0 ml, 0.51 mol) was added dropwise to a stirred solution of **25** (70.0 g, 0.19 mol) in methanol (700 ml) at 0°C, and stirring was continued for 30 min at room temperature. The mixture was nuetralized with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate (3 x 1400 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:2→ethyl acetate) to give **26** (60.3 g, 97%) as a colorless oil. $[\alpha]_D^{20}$ +1.0° (c 1.25, $CHCl_3$). IR (neat): 3400, 3020, 2940, 2900, 2870, 2840, 1730, 1610, 1580, 1510, 1460, 1440, 1420, 1340, 1300, 1250, 1170, 1110, 1030, 970, 920, 820, 760, 660, 640, 530 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.43 (1H, br t, J=5.7 Hz, C4-OH), 2.72 (1H, br d, J=6.2 Hz, C3-OH), 3.07 (3H, s, SO_2Me), 3.68-3.72 (2H, m, C1-H2), 3.75 (1H, dd, J=11.1, 3.5 Hz, C4-*H*2), 3.80-3.85 (1H, m, C4-*H*2), 3.81 (3H, s, OMe), 3.86-3.91 (1H, m, C3-H), 4.48 (1H, d, J=11.3 Hz, OC*H*2PhOMe), 4.53 (1H, d, J=11.4 Hz, OC*H*2PhOMe), 4.85-4.89 (1H, m, C2-H), 6.89 (2H, d, J=8.7 Hz, MeOPh-*H*2), 7.24 (2H, d, J=8.7 Hz, MeOPh-*H*2). EIMS m/z: 320 (M^+), 228, 197, 137, 121, 79. HRMS calcd for $C_{13}H_{20}O_7S$ (M^+): 320.0930. Found: 320.0937.

b) Preparation of *ent*-**26:** Treatments of *ent*-**25** (98.3 g, 0.27 mol) in a similar manner to those described for the preparation of **26** from **25** gave *ent*-**26** (84.8 g, 97%) as a colorless oil. $[\alpha]_D^{20}$ -0.3° (c 1.20, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **26**.

***cis*-4-*p*-Methoxybenzyloxy-2-butene-1-ol (29)**

cis-1,4-Butenediol (**28**) (1.75 ml, 18 mmol) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 630 mg, 16 mmol) in dry *N*,*N*-dimethylformamide (15 ml) at 0°C. After 15 min, *p*-methoxybenzyl chloride (2.12 ml, 16 mmol) was added, and stirring was continued for 3 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride (2 ml), and the mixture was diluted with ethyl acetate (40 ml). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:1→1:2) to give **29** (2.79 g, 74%) as a colorless oil. IR (neat): 3350, 2950, 2880, 1620, 1520, 1250, 1040, 980, 910, 830, 760, 670, 640, 530 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.80 (3H, s, OMe), 4.00-4.20 (4H, m, C1-H2 and C4-H2), 4.46 (2H, s, OC*H*2PhOMe), 5.60-6.00 (2H, m, C2-H and C3-H), 6.85 (2H, d, J=8.2 Hz, MeOPh-*H*2), 7.25 (2H, d, J=8.5 Hz, MeOPh-*H*2). EIMS m/z: 208 (M^+), 137, 121. HRMS calcd for $C_{12}H_{16}O_3$ (M^+): 208.1099. Found: 208.1091. These IR and ^{1}H-NMR spectra were identical with those reported.[15]

(2*S*,3*R*)-4-*p*-methoxybenzyloxy-2,3-epoxy-1-butanol (27) and Its Enantiomer (*ent*-27)

a) Preparation of **27** from **26** : Potassium carbonate (77.6 g, 0.56 mol) was added in small portions to a stirred solution of **26** (60.0 g, 0.19 mol) in methanol (600 ml) at room temperature. After 30 min, the mixture was neutralized with 3% aqueous hydrochloric acid and diluted with ethyl acetate (1800 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:1→1:2) to give **27** (37.0 g, 88%) as a white solid. Recrystallization from isopropyl ether afforded an analytical sample of **27** as colorless needles, mp 36-37°C and $[\alpha]_D^{20}$ -27.4° (c 0.78, $CHCl_3$). IR (KBr): 3440, 3000, 2925, 2850, 1610, 1510, 1460, 1420, 1380, 1300, 1250, 1170, 1100, 1030, 920, 880, 750, 580, 520 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.15 (1H, br s, $W_{1/2}$=40 Hz, OH), 3.20-3.24 (1H, m, C2-H or C3-H), 3.26-3.29 (1H, m, C2-H or C3-H), 3.61 (1H, dd, J=11.1, 5.1 Hz, C4-*H*2), 3.68-3.78 (2H, m, C1-H2), 3.70 (1H, dd, J=11.1, 6.0 Hz, C4-*H*2), 3.81 (3H, s, OMe), 4.46 (1H, d, J=11.4

Hz, OC*H*2PhOMe), 4.55 (1H, d, J=11.4 Hz, OC*H*2PhOMe), 6.89 (2H, d, J=8.7 Hz, MeOPh-*H*2), 7.26 (2H, d, J=8.8 Hz, MeOPh-*H*2). EIMS m/z: 224 (M^+), 137, 121 [$(MPM)^+$], 77, 43. HRMS calcd for $C_{12}H_{16}O_4$ (M^+): 224.1048. Found: 224.1050. These IR and ^{1}H-NMR spectra were identical with those reported.[15] In order to comfirm the optical integrity of **27** prepared from **26**, **27** was derived to the corresponding (*S*)- and (*R*)-MTPA esters as described in sections c) and d). Comparison of their 400MHz ^{1}H-NMR spectra obviously disclosed that the optical purity of **27** was more than 98% ee.

b) Preparation of *ent*-**27** from *ent*-**26:** The same treatments of *ent*-**26** (84.2 g, 0.26 mol) as described for the preparation of **27** from **26** gave *ent*-**27** (50.0 g, 85%) as colorless needles, mp 36-37°C and $[\alpha]_D^{20}$ +27.1° (c 0.84, $CHCl_3$). The IR, ^{1}H-NMR, mass spectra of this sample were identical with those recorded for **27**.

c) Preparation of (*S*)-MTPA Ester of **27**: (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*R*)-MTPACl] (0.12 ml, 0.62 mmol) was added to a stirred solution of **27** (107 mg, 0.48 mmol) in pyridine (1.2 ml) at room temperature. After 30 min, the mixture was diluted with ethyl acetate (30 ml). The organic layer was washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 3:1) to give (*S*)-MTPA ester of **27** (205 mg, 98%) as a colorless oil. $[\alpha]_D^{20}$ -57.0° (c 1.37, $CHCl_3$). IR (neat): 3060, 3000, 2925, 2910, 2850, 1750, 1610, 1580, 1510, 1360, 1250, 1170, 1120, 1100, 1080, 1030, 1000, 940, 840, 820, 760, 720, 700, 640, 580, 510 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.77-2.80 (1H, m, C2-H), 2.83-2.86 (1H, m, C3-H), 3.22 (1H, dd, J=11.3, 5.5 Hz, C4-*H*2), 3.25 (1H, dd, J=11.3, 4.6 Hz, C4-*H*2), 3.29 (3H, s, PhO*Me*), 3.39 (3H, s, MTPA-O*Me*), 3.94 (1H, dd, J=12.1, 7.1 Hz, C1-*H*2), 4.13-4.17 (1H, m, C1-*H*2), 4.16-4.19 (1H, m, OC*H*2PhOMe), 4.23 (1H, d, J=11.6 Hz, OC*H*2PhOMe), 6.78 (2H, d, J=8.7 Hz, MeOPh-*H*2), 7.00-7.14 (5H, m, Ph), 7.68 (2H, d, J=8.7 Hz, MeOPh-*H*2). EIMS m/z: 440 (M^+). HRMS calcd for $C_{22}H_{23}F_3O_6$ (M^+): 440.1447. Found: 440.1440.

d) Preparation of (*R*)-MTPA Ester of **27**: **27** (64.3 mg, 0.29 mmol) was acylated with (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride [(*S*)-MTPACl] in the same manner as described for the preparation of of (*S*)-MTPA ester of **27** to give (*R*)-MTPA ester of **27** (122 mg, 97%) as a colorless oil. $[\alpha]_D^{20}$ +25.2° (c 1.08, $CHCl_3$). IR (neat): 3060, 3000, 2950, 2910, 2850, 1750, 1610, 1580, 1510, 1450, 1380, 1360, 1250, 1170, 1120, 1100, 1080, 1030, 1000, 940, 840, 820, 760, 760, 720, 640, 580, 510 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.71-2.75 (1H, m, C2-H), 2.82-2.85 (1H, m, C3-H), 3.22 (1H, dd, J=11.3, 5.7 Hz, C4-*H*2), 3.25-3.29 (1H, m, C4-*H*2), 3.40 (3H, s, PhO*Me*), 3.40 (3H, s, MTPA-O*Me*), 4.01 (1H, dd, J=12.2, 3.8 Hz, C1-*H*2), 4.12 (1H, dd, J=12.2, 7.4 Hz, C1-*H*2), 4.17 (1H, d, J=11.6 Hz, OC*H*2PhOMe), 4.25 (1H, d, J=11.6 Hz, OC*H*2PhOMe), 6.79 (2H, d, J=8.7 Hz, MeOPh-*H*2), 7.00-7.10 (5H, m, Ph), 7.68 (2H, d, J=7.8 Hz, MeOPh-*H*2). EIMS m/z: 440 (M^+). HRMS calcd for $C_{22}H_{23}F_3O_6$ (M^+): 440.1447. Found: 440.1446.

e) Preparation of **27** from **29:** (2*S*,3*S*)-diethyl tartrate (0.855 ml, 5.0 mmol) and titanium(IV) isopropoxide (1.10 ml, 4.0 mmol) were successively added to a stirred solution of *tert*-butyl hydroperoxide (3.0M solution in isooctane, 4.00 ml, 12 mmol) in dry dichloromethane (15 ml) containing molecular sieves 4A (2.50 g) at -10°C. A solution of **29** (2.11 g, 10 mmol) in dry dichloromethane (5 ml) was added slowly to the above mixture at -20°C, and stirring was continued for 70 h at the same temperature. Saturated aqueous (2*S*,3*S*)-tartaric acid (3 ml) and celite (4.0 g) were successively added, and the resulting mixture was filtrated. The filtrate was treated with 10% aqueous sodium hydroxide (5 ml) for 1 h at room temperature, and then extracted with dichloromethane (3 x 100 ml). The combined extracts were washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:1) to give **27** (1.68 g, 74%) as a colorless caramel, $[\alpha]_D^{20}$ -22.1° (c 1.21, $CHCl_3$). The IR, ^{1}H-NMR and mass spectra of this sample were identical with those recorded in a). Enantiomeric excess of the asymmetric epoxidation product **27** was determined to be 85% ee by comparision of the 400MHz ^{1}H-NMR spectra of the corresponding (*S*)- and (*R*)-MTPA esters which were prepared in a similar manner to that described in c) and d).

(2*R*,3*S*)-2-Azido-4-*p*-methoxybenzyloxy-1,3-butanediol (30) and Its Enantiomer (*ent*-30)

a) Preparation of **30:** Ammonium chloride (27.6 g, 0.52 mol) and sodium azide (33.6 g, 0.52 mol) were successively added to a stirred solution of **27** (52.6 g, 0.23 mol) in ethanol (350 ml) at room temperature, and the mixture was heated at reflux for 17 h. After cooling, the mixture was diluted with ethyl acetate (2000 ml) and then filtrated. The filtrate was concentrated *in vacuo* to give a crude mixture of **30** and **31** (57.7 g, 92%) as a colorless oil. The ratio of **30** to **31** was determined to be *ca.* 3:2 by the 400MHz ^{1}H-NMR analysis of the unpurified reaction product.

Sodium periodate (46.2 g, 0.22 mol) was added in amall portions to a stirred solution of a mixture of **30** and **31** (57.7 g, 0.22 mol) in tetrahydrofuran-water (1:1) (400 ml) at room temperature. After 20 min, the mixture was diluted with ethyl acetate (1600 ml) and brine (300 ml). The organic layer was washed with 20% aqueous sodium thiosulfate, saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1→1:1→1:2) to give **30** (more polar, 31.7 g, 55%) and (*S*)-2-azido-3-(*p*-methoxybenzyl-oxy)propanal (**32**) (less polar, 11.2 g, 37%).

30: colorless oil. $[\alpha]_D^{20}$ -31.6° (c 1.16, $CHCl_3$). IR (neat): 3400, 2930, 2860, 2100, 1610, 1510, 1460, 1250, 1080, 1030, 820 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.53 (1H, t, J=5.4 Hz, C1-OH), 2.74 (1H, d, J=5.2 Hz, C2-OH), 3.50-3.64 (1H, m, C2-H), 3.52 (1H, dd, J=9.6, 5.3 Hz, C4-*H*2), 3.56 (1H, dd, J=9.6, 6.0 Hz, C4-*H*2), 3.80 (3H, s, OMe), 3.75-3.91 (2H, m, C1-H2), 3.90-3.99 (1H, m, C3-H), 4.50 (2H, s, OC*H*2PhOMe), 6.89 (2H, dt, J=8.3, 2.4 Hz, MeOPh-*H*2), 7.25 (2H, dt, J=8.3, 2.8 Hz, MeOPh-

*H*2). CIMS (isobutane) m/z: 240 [(M+H-N2)$^+$], 238 [(M-N2H)$^+$], 208 [(M-N2-CH2OH)$^+$], 137 [(MPMO)$^+$], 121 [(MPM)$^+$]. SIMS (3-NBA+NaCl): 290 [(M+Na)$^+$]. HRMS calcd for C12H16NO4 [(M-N2H)$^+$]: 238.1078. Found: 238.1090. Calcd for C11H14NO3 [(M-N2-CH2OH)$^+$]: 208.0972. Found: 208.0956.

32: colorless oil. IR (neat): 3400, 2930, 2850, 2120, 1730, 1610, 1510, 1250, 1100, 1030, 820 cm^{-1}. ^{1}H-NMR (200 MHz, CDCl3): δ 3.81 (3H, s, OMe), 3.86 (2H, d, J=6.0 Hz,, C3-H2), 4.00 (1H, t, J=4.0 Hz, C2-H), 4.50 (2H, s, OC*H*2PhOMe), 6.90 (2H, d, J=8.1 Hz, MeOPh-*H*2), 7.25 (2H, d, J=8.1 Hz, MeOPh-*H*2), 9.63 (1H, s, CHO).

b) Preparation of *ent*-**30:** Treatments of *ent*-**27** (48.5 g, 0.22 mol) in the same manner as described for the preparation of **30** from **27** gave *ent*-**30** (30.6 g, 53%) and *ent*-**32** (10.1 g, 36%). *ent*-**30:** colorless oil. [α]D^{20} +31.2° (c 1.13, CHCl3). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **30**. *ent*-**32:** colorless oil. The ^{1}H-NMR spectrum of this sample was identical with that recorded for **32**.

(1*S*,2*R*)-2-Azido-3-*tert*-butyldiphenylsiloxy-1-*p*-methoxybenzyloxymethylpropanol (33) and Its Enantiomer (*ent*-33)

a) Preparation of **33:** *tert*-Butyldiphenylsilyl chloride (33.5 ml, 0.13 mol) was added to a stirred solution of **30** (31.3 g, 0.12 mol) in dry dichloromethane (300 ml) containing triethylamine (17.9 ml, 0.13 mol) and a catalytic amount of 4-dimethylaminopyridine (572 mg, 4.7 mmol) at room temperature. After 17 h, the mixture was diluted with ether (1500 ml). The organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1→4:1) to give **33** (53.9 g, 91%) as a colorless oil. [α]D^{20} -20.9° (c 1.00, CHCl3). IR (neat): 3450, 2930, 2850, 2100, 1610, 1510, 1250, 1110, 1030, 820, 700, 500 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.07 (9H, s, *tert*-Bu), 2.41 (1H, d, J=5.2 Hz, OH), 3.47 (1H, dd, J=9.6, 6.2 Hz, C4-*H*2), 3.48 (1H, dd, J=9.6, 5.3 Hz, C4-*H*2), 3.57 (1H, dt, J=8.6, 4.6 Hz, C2-H), 3.80 (3H, s, OMe), 3.80-3.93 (3H, m, C3-H and C1-H2), 4.44 (2H, s, OC*H*2PhOMe), 6.86 (2H, dt, J=8.7, 2.4 Hz, MeOPh-*H*2), 7.21 (2H, dt, J=8.7, 2.4 Hz, MeOPh-*H*2), 7.36-7.47 (6H, m, aromatic protons), 7.62-7.70 (4H, m, aromatic protons). CIMS (isobutane) m/z: 478 [(M+H-N2)$^+$], 448 [(M-*tert*-Bu)$^+$], 420 [(M-*tert*-Bu-N2)$^+$], 299 [(M-*tert*-Bu-N2-MPM)$^+$], 137 [(MPMO)$^+$], 121 [(MPM)$^+$]. SIMS (3-NBA+NaCl): 528 [(M+Na)$^+$]. HRMS calcd for C24H26N3O4Si [(M-*tert*-Bu)$^+$]: 448.1484. Found: 448.1714.

b) Preparation of *ent*-**33:** Similar treatments of *ent*-**30** (30.2 g, 0.11 mol) to those described for the preparation of **33** from **30** gave *ent*-**33** (53.1 g, 93%) as a colorless oil. [α]D^{20} +20.5° (c 1.05, CHCl3). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **33**.

(1*S*,2*R*)-3-*tert*-Butyldiphenylsiloxy-2-(2,2,2-trichloroethoxycarbonyl)amino-1-*p*-methoxybenzyloxymethylpropanol (34) and Its Enantiomer (*ent*-34)

a) Preparation of **34:** Triphenylphosphine (32.9 g, 0.13 mol) was added to a stirred solution of **33** (52.8 g, 0.10 mol) in tetrahydrofuran-water (1:1) (600 ml) at room temperature. After 17 h, sodium hydrogen carbonate (43.9 g, 0.52 mol) and 2,2,2-trichloroethyl chloroformate (17.3 ml, 0.13 mol) were successively added, and stirring was continued for 30 min at room temperature. The reaction mixture was diluted with ether (2000 ml). The organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 5:1→3:1) to give **34** (67.1 g, 98%) as a colorless oil. [α]D^{20} -12.7° (c 1.02, CHCl3). IR (neat): 3430, 3070, 2940, 2930, 2850, 1740, 1610, 1510, 1250, 1110, 820, 700 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.07 (9H, s, *tert*-Bu), 2.85 (1H, d, J=2.6 Hz, OH), 3.45 (1H, dd, J=9.5, 7.0 Hz, C1-*H*2), 3.49 (1H, dd, J=9.5, 5.0 Hz, C1-*H*2), 3.80 (3H, s, OMe), 3.77 (1H, dd, J=9.9, 4.7 Hz, C4-*H*2), 3.81 (1H, dd, J=9.9, 5.4 Hz, C4-*H*2), 3.80-3.91 (1H, m, C2-H or C3-H), 4.17-4.26 (1H, m, C2-H or C3-H), 4.47 (2H, s, OC*H*2PhOMe), 4.66 (1H, d, J=12.0 Hz, OC*H*2CCl3), 4.71 (1H, d, J=12.0 Hz, OC*H*2CCl3), 5.46 (1H, d, J=8.8 Hz, NH), 6.87 (2H, dt, J=8.7, 2.5 Hz, MeOPh-*H*2), 7.23 (2H, dt, J=8.7, 2.5 Hz, MeOPh-*H*2), 7.35-7.47 (6H, m, aromatic protons), 7.61-7.68 (4H, m, aromatic protons). CIMS (isobutane) m/z: 602 [(M-*tert*-Bu)$^+$, ^{37}Cl x 3], 600 [(M-*tert*-Bu)$^+$, ^{37}Cl x 2, ^{35}Cl x 1], 598 [(M-*tert*-Bu)$^+$, ^{37}Cl x 1, ^{35}Cl x 2], 596 [(M-*tert*-Bu)$^+$, ^{35}Cl x 3]. HRMS calcd for C27H29Cl3NO6Si [(M-*tert*-Bu)$^+$, ^{37}Cl x 3]: 602.0740. Found: 602.0765, [(M-*tert*-Bu)$^+$, ^{37}Cl x 2, ^{35}Cl x 1]: 600.0769. Found: 600.0774, [(M-*tert*-Bu)$^+$, ^{37}Cl x 1, ^{35}Cl x 2]: 598.0798. Found: 598.0762, [(M-*tert*-Bu)$^+$, ^{35}Cl x 3]: 596.0827. Found: 596.0806.

b) Preparation of *ent*-**34:** Treatments of *ent*-**33** (52.5 g, 0.10 mol) in a similar manner to that described for the preparation of **34** from **33** gave *ent*-**34** (66.1 g, 97%) as a colorless oil. [α]D^{20} +12.0° (c 1.17, CHCl3). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **34**.

(4*R*,5*S*)-4-*tert*-Butyldiphenylsiloxymethyl-2,2-dimethyl-5-*p*-methoxybenzyloxymethyl-3-(2,2,2-trichloroethoxycarbonyl)oxazolidine (35) and Its Enantiomer (*ent*-35)

a) Preparation of **35:** 2,2-Dimethoxypropane (122 ml, 1.0 mol) and *p*-toluenesulfonic acid (572 mg, 3.0 mmol) were successively added to a stirred solution of **34** (65.7 g, 0.10 mol) in acetone (300 ml) at room temperature. After 21 h, the mixture was neutralized with saturated aqueous sodium hydrogen carbonate and then diluted with ether (2000 ml). The organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 5:1→3:1) to give **35** (67.6 g, 97%) as a colorless oil. [α]D^{20} -17.8° (c 0.98, CHCl3). IR

(neat): 3060, 2930, 2850, 1720, 1610, 1510, 1090, 1040, 820, 700, 500 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.03 (9H, s, *tert*-Bu), 1.50-1.73 (6H, m, acetonide Me x 2), 3.52-4.10 (5H, m, C1-H2, C4-H2 and C2-H or C3-H), 3.79 (3H, s, OMe), 4.46-4.80 (5H, m, OCH_2CCl_3, OCH_2PhOMe and C2-H or C3-H), 6.85 (2H, d, J=8.4 Hz, MeOPh-*H2*), 7.20-7.29 (2H, m, MeOPh-*H2*), 7.32-7.46 (6H, m, aromatic protons), 7.62 (4H, d, J=6.1 Hz, aromatic protons). CIMS (isobutane) m/z: 642 [(M-*tert*-Bu)$^+$, ^{37}Cl x 3], 640 [(M-*tert*-Bu)$^+$, ^{37}Cl x 2, ^{35}Cl x 1], 638 [(M-*tert*-Bu)$^+$, ^{37}Cl x 1, ^{35}Cl x 2], 636 [(M-*tert*-Bu)$^+$, ^{35}Cl x 3]. HRMS calcd for $C_{30}H_{33}NO_6Cl_3Si$ [(M-*tert*-Bu)$^+$, ^{37}Cl x 2, ^{35}Cl x 1]: 640.1081. Found: 640.1060, [(M-*tert*-Bu)$^+$, ^{37}Cl x 1, ^{35}Cl x 2]: 638.1110. Found: 638.1102, [(M-*tert*-Bu)$^+$, ^{35}Cl x 3]: 636.1140. Found: 636.1137.

b) Preparation of *ent*-**35:** The same treatments of *ent*-**34** (65.3 g, 0.10 mol) as described for the preparation of **35** from **34** gave *ent*-**35** (63.7 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ +17.7° (c 1.07, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **35**.

(4*R*,5*S*)-4-*tert*-Butyldiphenylsiloxymethyl-2,2-dimethyl-5-hydroxymethyl-3-(2,2,2-trichloroethoxycarbonyl)oxazolidine (36) and Its Enantiomer (*ent*-36)

a) Preparation of **36:** 2,3-Dichloro-5,6-dicyanobenzoquinone (26.6 g, 0.12 mol) was added to a stirred solution of **35** (62.5 g, 90 mmol) in dichloromethane (450 ml) containing water (24 ml) at room temperature. After 1.5 h, the mixture was diluted with ether (2000 ml) and saturated aqueous sodium hydrogen carbonate (300 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1→4:1) to give **36** (50.8 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ -18.7° (c 0.99, $CHCl_3$). IR (neat): 2930, 2850, 1720, 1510, 1410, 1250, 1110, 820, 700, 500 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.06 (9H, s, *tert*-Bu), 1.49-1.77 (6H, m, acetonide Me x2), 1.86-1.96 (1H, m, OH), 3.59-4.12 (5H, m, C1-H2, C4-H2 and C2-H or C3-H), 4.34-4.83 (3H, m, OCH_2CCl_3 and C2-H or C3-H), 7.33-7.50 (6H, m, aromatic protons), 7.62 (4H, d, J=6.5 Hz, aromatic protons). CIMS (isobutane) m/z: 574 [(M+H)$^+$, ^{35}Cl x 3], 558 [(M-Me)$^+$, ^{35}Cl x 3], 522 [(M-*tert*-Bu)$^+$, ^{37}Cl x 3], 520 [(M-*tert*-Bu)$^+$, ^{37}Cl x 2, ^{35}Cl x 1], 518 [(M-*tert*-Bu)$^+$, ^{37}Cl x 1, ^{35}Cl x 2], 516 [(M-*tert*-Bu)$^+$, ^{35}Cl x 3]. HRMS calcd for $C_{25}H_{31}Cl_3NO_5Si$ [(M-Me)$^+$, ^{37}Cl x 1, ^{35}Cl x 2]: 560.1005. Found: 560.1021, [(M-Me)$^+$, ^{35}Cl x 3]: 558.1035. Found: 558.1051.

b) Preparation of *ent*-**36:** Treatments of *ent*-**35** (52.1 g, 75 mmol) in the same manner for the preparation of **36** from **35** gave *ent*-**36** (40.5 g, 94%) as a colorless oil. $[\alpha]_D^{20}$ +18.5° (c 0.67, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **36**.

(4*R*,5*S*)-[4-*tert*-Butyldiphenylsiloxymethyl-2,2-dimethyl-3-(2,2,2-trichloroethoxycarbonyl)oxazolidin-5-yl]methyltrifluoromethanesulfonate (5) and Its Enantiomer (*ent*-5)

a) Preparation of **5:** Trifluoromethanesulfonic anhydride (7.62 ml, 45 mmol) was added dropwise to a stirred solution of **36** (20.0 g, 35 mmol) in dry dichloromethane (300 ml) containing triethylamine (14.5 ml, 0.10 mol) at -78°C under argon. After 20 min, the reaction was quenched with saturated aqueous sodium hydrogen carbonate (20 ml), and the mixture was extracted with ether (2 x 1000 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **5** (23.2 g, 94%) as a colorless oil. IR (neat): 2950, 2930, 2850, 1720, 1470, 1410, 1340, 1240, 1210, 1140, 1100, 1060, 950, 820, 700, 610, 500 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.07 (9H, s, *tert*-Bu), 1.45-1.80 (6H, m, acetonide Me x 2), 3.53-4.82 (3H, m, C4-H2 and C2-H or C3-H), 4.40-4.82 (5H, m, C1-H2, OCH_2CCl_3 and C2-H or C3-H), 7.28-7.53 (6H, m, aromatic protons), 7.55-7.70 (4H, m, aromatic protons). Due to the presence of rotamers in the 2,2,2-trichloroethyl carbamate group, extensive line broadening and, in some instance, doubling of signals were observed for this ^{1}H-NMR spectrum. This triflate **5** was immediately used for the next coupling reaction[21] due to its instability.

b) Preparation of *ent*-**5:** Similar treatments of *ent*-**36** (14.7 g, 26 mmol) to those described for the preparation of **5** from **36** gave *ent*-**5** (16.4 g, 91%) as a colorless oil. The ^{1}H-NMR spectrum of this sample was identical with that recorded for **5**.

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19. After purification by column chromatography on silica gel, the aliphatic segment **5** was immediately used for the next coupling reaction[21] with the aromatic segment **4** due to its instability.
20. When the corresponding mesylate and iodide were used as substrates for the subsequent coupling reaction with the aromatic segment **4**,[21] none of the desired product was obtained and the unreacted starting material was always recovered. To our delight, the triflate **5** was found to serve as an excellent electophile for the objective coupling reaction.[21] For recent examples for the usefulness of some trifrate derivatives as good electrophiles, see, a) Fairbanks, A. J., Fleet, G. W. J., *Tetrahedron*, **1995**, *51*, 3881-3894. b) Takao, K., Ochiai, H., Yoshida, K., Hasizuka, T., Koshimura, H., Tadano, K., Ogawa, S., *J. Org. Chem.*, **1995**, *60*, 8179-8193.
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