Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3251–3262

TETRAHEDRON: *ASYMMETRY*

An efficient synthesis of enantiomerically pure 2-[(2*R*)-arylmorpholin-2-yl]ethanols, key intermediates of tachykinin receptor antagonist

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Received 17 July 1998; accepted 10 August 1998

Abstract

We report herein an efficient and practical synthetic method for the preparation of enantiomerically pure 2-[(2*R*)-arylmorpholin-2-yl]ethanols **1a–d**, key intermediates of tachykinin receptor antagonist. Sharpless catalytic asymmetric dihydroxylation of **4a–d** was employed to introduce the required absolute stereochemistry, and cyclization of **7a–d** was accomplished by the Mitsunobu reaction.

1. Introduction

The tachykinins, a family of neuropeptides comprising substance P (SP), neurokinin A (NKA) and neurokinin B (NKB), are involved in a variety of biological actions such as pain transmission, vasodilation, smooth muscle contraction, and neurogenic inflammation. Airway inflammation and bronchoconstriction in asthma and chronic airway-obstructive disease continue to be the major foci of clinical interest in tachykinin research. Based on the different orders of potency of natural tachykinins, three distinct receptor types have been identified, i.e. NK_1 (SP-preferring), NK_2 (NKA-preferring), and NK_3 (NKB-preferring).[1] Among several classes of recently reported tachykinin receptor antagonists, there is speculation that a combined $NK_1/NK_2/NK_3$ receptor antagonist might be an effective drug in asthma and chronic airway obstruction. In the course of our study to find a combined antagonist, we recently reported morpholine analogues which had balanced binding affinities to both NK_1 and NK_2 receptors.[2] Independently, Sanofi's group discovered SR-144190, an NK_2 receptor-selective antagonist which also possesses the morpholine moiety.[3] Preliminary studies indicated that the stereochemistry of the 2-substituents of the morpholine ring has great impact on the binding activity to tachykinin receptor, and the (*R*)-configuration has been shown to be an essential requirement for more potent binding affinities. For

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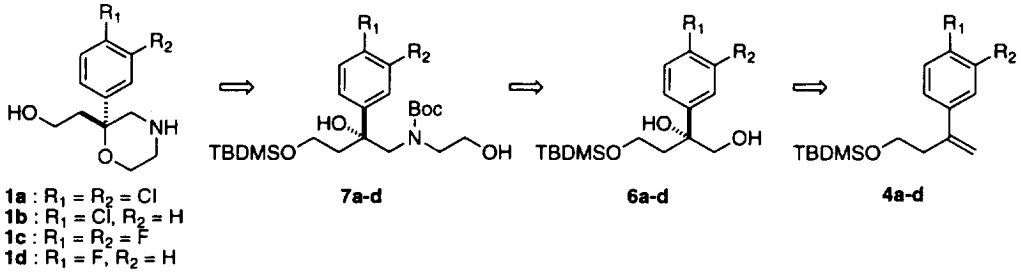
0957-4166/98/$ - see front matter
PII: S0957-4166(98)00336-X

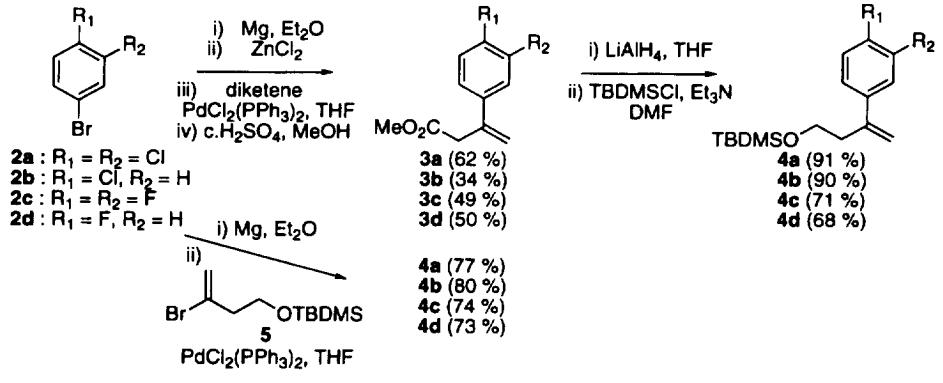
the synthesis of these enantiomerically pure morpholine analogues, 2-[(2*R*)-arylmorpholin-2-yl]ethanols **1a–d** are recognized as key intermediates. In various phases of a program we have been conducting to develop a novel tachykinin receptor antagonist, we have relied on the use of large amounts of enantiomerically pure **1a–d**. We report herein an efficient and practical method for the preparation of homochiral **1a–d**. The key features of our approach are the Sharpless asymmetric dihydroxylation (AD) of 3-aryl-3-buten-1-ol *tert*-butyldimethylsilyl (TBDMS) ethers **4a–d**, and the Mitsunobu reaction for dehydration of **7a–d** (Scheme 1).



Scheme 1.

2. Results and discussion

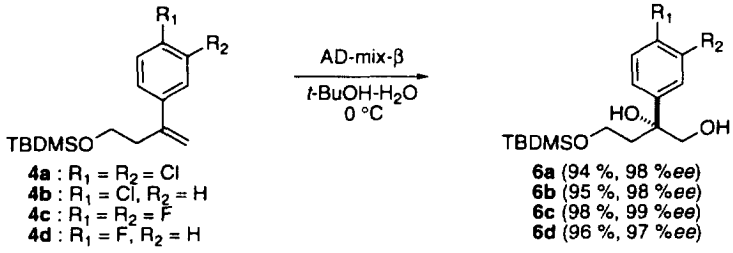
At first, we explored two complementary approaches to the conversion of bromobenzenes **2a–d** to olefins **4a–d**. Methyl 3-aryl-3-butenoates **3a–d** were prepared from corresponding bromobenzenes **2a–d** and diketene by the palladium-catalyzed Grignard coupling reaction, followed by esterification in the presence of conc. H_2SO_4 in MeOH in moderate yield.[4] Compounds **4a–d** were cleanly provided by reduction of esters **3a–d** with $LiAlH_4$ followed by protection of primary alcohol with *tert*-butyldimethylsilyl chloride and triethylamine in DMF. Compounds **4a–d** were also obtained directly by the palladium-catalyzed cross-coupling reaction of arylmagnesium bromide with vinylbromide **5**[5] in good conversion yield (Scheme 2).



Scheme 2.

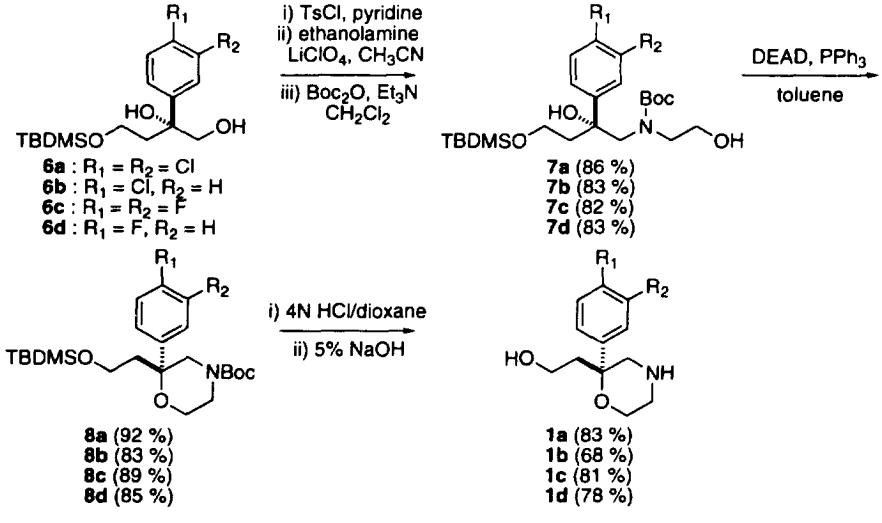
For the preparation of homochiral (*R*)-diols **6a–d**, we examined Sharpless AD to olefins **4a–d**. Among the various chiral ligands for Sharpless AD, Sharpless data suggested that the phthalazine ligand (PHAL) is recommended for the 1,1-disubstituted olefins.[6] In fact, in our initial survey of the available ligands, $(DHQD)_2PHAL$[7] (98% *ee* for **6a**) performed better than the $(DHQD)_2PYR$[8] (66% *ee* for **6a**). These oxidations were carried out by treating the olefins **4a–d** with AD-mix-β® [$K_2OsO_2(OH)_4$ (0.004 mol%),

$(DHQD)_2PHAL$ (0.01 mol%), $K_3Fe(CN)_6$ (3 equiv.), and K_2CO_3 (3 equiv.)] in *t*-BuOH–H_2O at 0°C for 6–8 h. The results of the oxidations are summarized in Scheme 3. The homochiral (*R*)-diols **6a–d** were obtained as colorless oils in quantitative yield (**6a**: $[\alpha]_D^{25}$ +11.4 (*c* 1.0; MeOH); **6b**: $[\alpha]_D^{25}$ +15.6 (*c* 1.1; MeOH); **6c**: $[\alpha]_D^{25}$ +14.1 (*c* 1.5; MeOH); **6d**: $[\alpha]_D^{25}$ +14.0 (*c* 1.2; MeOH)).



Scheme 3.

The *ee*-values of diols **6a–d** could be determined by chiral HPLC analysis [**6a**: column, Chiralcel OF (4.6φ×250 mm); eluent, 99:1 *n*-hexane:2-propanol mixture; flow rate, 1.0 ml/min; $t_R(R)$=15.6 min, $t_R(S)$=18.0 min. **6b**: column, Chiralcel OD (4.6φ×250 mm); eluent, 95:5 *n*-hexane:2-propanol mixture; flow rate, 0.5 ml/min; $t_R(R)$=24.2 min, $t_R(S)$=21.9 min. **6c**: column, Chiralcel OF (4.6φ×250 mm); eluent, 95:5 *n*-hexane:2-propanol mixture; flow rate, 1.0 ml/min; $t_R(R)$=13.6 min, $t_R(S)$=16.3 min. **6d**: column, Chiralcel OD (4.6φ×250 mm); eluent, 95:5 *n*-hexane:2-propanol mixture; flow rate, 0.5 ml/min; $t_R(R)$=22.2 min, $t_R(S)$=19.2 min]. After selective formation of the primary tosylate, substitution with ethanolamine was performed in the presence of $LiClO_4$ in acetonitrile at 100°C,[9] and the protection of the resulting secondary amine with Boc_2O and triethylamine cleanly provided **7a–d** in good yield. In the continued construction of the morpholine ring, mild conditions were required to retain the stereochemistry of the chiral center. Although the initial efforts at dehydration with **7a–d** were problematic, the Mitsunobu reaction proved successful.[10] Treatment of **7a–d** with diethyl azodicarboxylate (DEAD) and triphenylphosphine in toluene at rt cleanly provided homochiral morpholine derivatives **8a–d** in good yield without undesired stereomutation. The desired enantiomerically pure 2-[(2*R*)-arylmorpholin-2-yl]ethanols **1a–d** were obtained by deprotection of Boc and the TBDMS group via treatment of 4N HCl/dioxane at 60°C followed by base treatment (Scheme 4).



Scheme 4.

The *ee*-values of **1a–d** could be directly determined by chiral HPLC analysis [column, Chiralpak AD (4.6ϕ×250 mm); eluent, 85:15 *n*-hexane:2-propanol mixture; flow rate, 1.0 ml/min; $t_R(R)$=12.5 min (**1a**), 9.8 min (**1b**), 12.6 min (**1c**), 15.0 min (**1d**); $t_R(S)$=19.8 min (**1a**), 11.6 min (**1b**), 18.5 min (**1c**), 18.7 min (**1d**)]. Recrystallization from a mixture of *n*-hexane and ethyl acetate yielded **1a–d** of >99.9% *ee* in the form of white crystals in 80–90% recovery [**1a**: mp 90–91°C, $[\alpha]_D^{25}$ +19.2 (*c* 1.0; MeOH); **1b**: mp 170–171°C, $[\alpha]_D^{25}$ +28.0 (*c* 1.0; MeOH); **1c**: mp 133–134°C, $[\alpha]_D^{25}$ +22.6 (*c* 1.0; MeOH); **1d**: mp 139–140°C, $[\alpha]_D^{25}$ +33.6 (*c* 1.0; MeOH)].

The stereochemistry of **1a** was confirmed by X-ray analysis of α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) amide of **1a**. A single-crystal X-ray structure determination of the (*R*)-MTPA amide of **1a** unambiguously established the relative configuration, and hence, the absolute stereochemistry of **1a** is *R*, as shown in Fig. 1.[11]

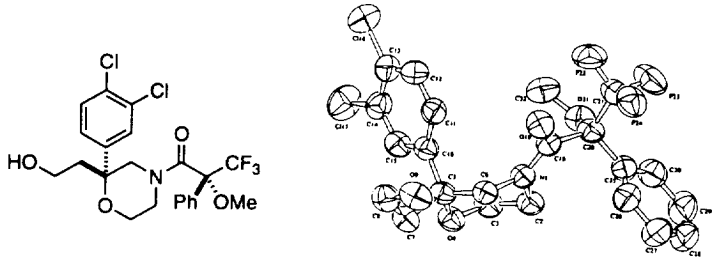


Fig. 1. X-Ray ORTEP of (*R*)-MTPA amide of (*R*)-**1a**

This synthesis also led, of course, to the synthesis of 2-[(2*S*)-arylmorpholin-2-yl]ethanols with the opposite configuration by using $(DHQ)_2PHAL$ instead of $(DHQD)_2PHAL$ as the chiral ligand for the Sharpless ADs of **4a–d**.

In conclusion, we have thus synthesized excellent yields of **1a–d**, key intermediates of tachykinin receptor antagonist with high enantiomeric purity, through the use of Sharpless AD and the Mitsunobu reaction as the key steps. Further work in this area is now in progress.

3. Experimental

3.1. General

All melting points were measured on a Yanaco MP-500D micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO P-1030 digital polarimeter. The IR spectra were measured on a JASCO FT/IR 8300 or JASCO FT/IR 8900 spectrophotometer as KBr plates or as $CHCl_3$ solution, and peaks are reported in cm^{-1}. ^1H NMR spectra were recorded on a JEOL JNM-GSX 400 spectrometer in $CDCl_3$. ^1H NMR chemical shifts are reported in ppm downfield of internal tetramethylsilane. Mass spectra were recorded using a JEOL JMS-BU 20 or JMS-700 spectrometer. Thin layer chromatography (TLC) was used routinely to monitor the progress and purity of compounds and was performed on Merck Kieselgel 60 F_{254} plates. For flash column chromatography, silica gel (Kieselgel 60, 230–400 mesh) was employed.

3.2. Methyl 3-(3,4-dichlorophenyl)-3-butenoate ***3a***

11.3 g (0.47 mol) of magnesium flakes were added to 300 ml of diethyl ether, followed by a small amount of iodine. The mixture was then allowed to stand for 1 h, after which a solution of 1-bromo-3,4-

dichlorobenzene **2a** (102.9 g, 0.46 mol) in diethyl ether (150 ml) was slowly added dropwise. A further 150 ml of diethyl ether was added, and then anhydrous $ZnCl_2$ (60.3 g, 0.44 mol) was slowly added and the mixture was stirred for 1 h. Dichlorobis(triphenylphosphine)palladium(II) (3.10 g, 4.42 mmol) was then added, and a solution of diketene (34.2 ml, 0.43 mol) in diethyl ether (600 ml) was added dropwise. The reaction mixture was stirred at rt for 30 min, after which the mixture was poured into ice-cold 1N aqueous HCl (1000 ml) and extracted with diethyl ether. The combined organic layer was extracted with aqueous 1N NaOH solution. The combined aqueous layer was acidified with conc. HCl, whilst ice-cooling, and extracted with diethyl ether, and then the combined organic layer was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the residue was dissolved in MeOH (350 ml). Conc. H_2SO_4 (10 ml) was added, and the solution was heated under reflux for 30 min. The reaction mixture was cooled and neutralized with a saturated aqueous solution of $NaHCO_3$. MeOH was then removed *in vacuo*, and the residue was extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$, and then the solvent was removed *in vacuo*. The residue was distilled under reduced pressure to obtain **3a** (69.1 g, 62% yield) as a pale yellow oil, bp 144–146°C (5 mmHg). IR ($CHCl_3$): 1737, 1631, 1552, 1475, 1438, 1171 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (1H, d, *J*=2.2 Hz), 7.40 (1H, d, *J*=8.2 Hz), 7.25 (1H, dd, *J*=8.2, 2.2 Hz), 5.55 (1H, s), 5.30 (1H, s), 3.67 (3H, s), 3.49 (2H, s); MS (EI) *m/z*: 244 (M^+).

3.3. *Methyl 3-(4-chlorophenyl)-3-butenoate* ***3b***

According to a similar procedure for the preparation of **3a**, **3b** (18.7 g) was prepared in 34% yield from **2b** (50.0 g, 0.26 mol). The final purification by distillation under reduced pressure gave a colorless oil, bp 120–123°C (4 mmHg). IR ($CHCl_3$): 1736, 1494, 1437, 1340, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (2H, d, *J*=8.7 Hz), 7.30 (2H, d, *J*=8.7 Hz), 5.53 (1H, s), 5.25 (1H, s), 3.66 (3H, s), 3.50 (2H, s); MS (EI) *m/z*: 210 (M^+).

3.4. *Methyl 3-(3,4-difluorophenyl)-3-butenoate* ***3c***

According to a similar procedure for the preparation of **3a**, **3c** (15.9 g) was prepared in 49% yield from **2c** (29.6 g, 0.15 mol). The final purification by distillation under reduced pressure gave a colorless oil, bp 94–96°C (4 mmHg). IR ($CHCl_3$): 1737, 1602, 1519, 1437, 1272, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.08–7.10 (2H, m), 7.12–7.15 (1H, m), 5.51 (1H, s), 5.27 (1H, s), 3.67 (3H, s), 3.49 (2H, s); MS (EI) *m/z*: 212 (M^+).

3.5. *Methyl 3-(4-fluorophenyl)-3-butenoate* ***3d***

According to a similar procedure for the preparation of **3a**, **3d** (27.7 g) was prepared in 50% yield from **2d** (50.0 g, 0.29 mol). The final purification by distillation under reduced pressure gave a colorless oil, bp 100–102°C (5 mmHg). IR ($CHCl_3$): 1736, 1604, 1512, 1437, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (2H, d, *J*=8.7 Hz), 7.39 (2H, d, *J*=8.7 Hz), 5.49 (1H, s), 5.22 (1H, s), 3.66 (3H, s), 3.51 (2H, s); MS (EI) *m/z*: 194 (M^+).

3.6. *3-(3,4-Dichlorophenyl)-3-butenol* tert-*butyldimethylsilyl ether* ***4a***

$LiAlH_4$ (7.50 g, 0.20 mol) was suspended in 350 ml of anhydrous THF, and a solution of methyl 3-(3,4-dichlorophenyl)-3-butenoate **3a** (48.2 g, 0.20 mol) in anhydrous THF (350 ml) was slowly added dropwise under a nitrogen atmosphere at 0°C over a period of 15 min. The reaction mixture was stirred

at the same temperature for 30 min, after which 350 ml of H_2O and 350 ml of 10% aqueous solution of NaOH were slowly added. The mixture was then stirred at rt for 1 h. It was then filtered through Celite and the filtrate was extracted with AcOEt. The combined organic extracts were then dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the residue was dried under reduced pressure. The residue was then dissolved in anhydrous DMF (150 ml), and then triethylamine (32.9 ml, 0.24 mol), 4-dimethylaminopyridine (4.80 g, 0.04 mol) and *tert*-butyldimethylsilyl chloride (35.6 g, 0.24 mol) were added, in that order, whilst ice-cooling. The mixture was then stirred, whilst ice-cooling, for 2 h. At the end of this time, AcOEt (500 ml) was added to the reaction mixture, and the mixture was washed, in turn, with ice-cooled 10% aqueous HCl and brine. It was then dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by silica gel flash column chromatography, using a gradient elution method, with mixtures of *n*-hexane and AcOEt ranging from 50:1 to 20:1 by volume as the eluent, to obtain **4a** (59.3 g, 91%) as a colorless oil. IR ($CHCl_3$): 2956, 2930, 2858, 1472, 1257, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (1H, d, *J*=2.1 Hz), 7.38 (1H, d, *J*=8.1 Hz), 7.24 (1H, dd, *J*=8.1, 2.1 Hz), 5.35 (1H, s), 5.16 (1H, s), 3.70 (2H, t, *J*=6.9 Hz), 2.67 (2H, t, *J*=6.9 Hz), 0.89 (9H, s), 0.00 (6H, s).

3.7. 3-(4-Chlorophenyl)-3-butenol tert-*butyldimethylsilyl ether* ***4b***

According to a similar procedure for the preparation of **4a**, **4b** (23.6 g) was prepared in 90% yield from **3b** (18.6 g, 88.3 mmol) as a colorless oil. IR ($CHCl_3$): 2957, 2931, 2859, 1493, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (2H, d, *J*=8.6 Hz), 7.28 (2H, d, *J*=8.6 Hz), 5.32 (1H, s), 5.11 (1H, s), 3.69 (2H, t, *J*=7.4 Hz), 2.70 (2H, t, *J*=7.4 Hz), 0.89 (9H, s), 0.00 (6H, s).

3.8. 3-(3,4-Difluorophenyl)-3-butenol tert-*butyldimethylsilyl ether* ***4c***

According to a similar procedure for the preparation of **4a**, **4c** (15.0 g) was prepared in 71% yield from **3c** (15.0 g, 70.7 mmol) as a colorless oil. IR ($CHCl_3$): 2956, 2930, 2858, 1600, 1516, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.05–7.29 (3H, m), 5.30 (1H, s), 5.13 (1H, s), 3.70 (2H, t, *J*=6.6 Hz), 2.67 (2H, t, *J*=6.6 Hz), 0.87 (9H, s), 0.00 (6H, s).

3.9. 3-(4-Fluorophenyl)-3-butenol tert-*butyldimethylsilyl ether* ***4d***

According to a similar procedure for the preparation of **4a**, **4d** (27.2 g) was prepared in 68% yield from **3d** (27.6 g, 0.14 mol) as a colorless oil. IR ($CHCl_3$): 2957, 2931, 2859, 1509, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (1H, d, *J*=8.7 Hz), 7.35 (1H, d, *J*=8.7 Hz), 6.99 (1H, d, *J*=8.7 Hz), 6.97 (1H, d, *J*=8.7 Hz), 5.26 (1H, s), 5.06 (1H, s), 3.68 (2H, t, *J*=7.3 Hz), 2.69 (2H, t, *J*=7.3 Hz), 0.85 (9H, s), −0.02 (6H, s).

3.10. 3-(3,4-Dichlorophenyl)-3-butenol tert-*butyldimethylsilyl ether* ***4a***

Magnesium flakes (6.50 g, 0.27 mol) were added to 100 ml of diethyl ether, and a small amount of iodine was added to the mixture. Diethyl ether solution (150 ml) containing 1-bromo-3,4-dichlorobenzene **2a** (55.2 g, 0.24 mol) was then added dropwise over a period of 30 min, and the mixture was stirred for 15 min at room temperature under a nitrogen atmosphere to give a Grignard reagent. A THF solution (250 ml) containing 3-bromo-3-butenol *tert*-butyldimethylsilyl ether **5**[5] (20.3 g, 81.4 mmol) and dichlorobis(triphenylphosphine)palladium(II) (1.70 g, 2.42 mmol) was added to the mixture, and the

reaction mixture was stirred for 3 h at rt under a nitrogen atmosphere. At the end of this time, the reaction mixture was poured into an aqueous solution of NH_4Cl and extracted with AcOEt. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by silica gel flash column chromatography, using *n*-hexane as the eluent, to give **4a** (20.7 g, 77% yield). The physicochemical properties of this compound were the same as those of the product produced as described in Section 3.6.

3.11. 3-(4-Chlorophenyl)-3-butenol tert-*butyldimethylsilyl ether* ***4b***

According to a similar procedure for the preparation of **4a**, **4b** (2.18 g) was prepared in 80% yield from **2b** (5.00 g, 26.1 mmol) and **5** (2.30 g, 9.23 mmol). The physicochemical properties of this compound were the same as those of the product produced as described in Section 3.7.

3.12. 3-(3,4-Difluorophenyl)-3-butenol tert-*butyldimethylsilyl ether* ***4c***

According to a similar procedure for the preparation of **4a**, **4c** (0.41 g) was prepared in 74% yield from **2c** (1.00 g, 5.18 mmol) and **5** (0.46 g, 1.85 mmol). The physicochemical properties of this compound were the same as those of the product produced as described in Section 3.8.

3.13. 3-(4-Fluorophenyl)-3-butenol tert-*butyldimethylsilyl ether* ***4d***

According to a similar procedure for the preparation of **4a**, **4d** (8.30 g) was prepared in 73% yield from **2d** (20.0 g, 0.11 mol) and **5** (10.2 g, 0.41 mol). The physicochemical properties of this compound were the same as those of the product produced as described in Section 3.9.

*3.14. 4-*tert-*Butyldimethylsilyloxy-(2R)-(3,4-dichlorophenyl)butane-1,2-diol* ***6a***

AD-mix-β (80.0 g) was dissolved in 300 ml of *t*-butanol and 300 ml of water, and 3-(3,4-dichlorophenyl)-3-butenol *tert*-butyldimethylsilyl ether **4a** (19.1 g, 57.6 mmol) was added, whilst cooling, at 0°C. The mixture was then stirred at 0°C for 8 h. At the end of this time, 90.0 g of sodium sulfite was added, and the mixture was stirred at rt for 1 h. It was then extracted with AcOEt, and the combined organic extracts were dried over anhydrous $MgSO_4$. The solvent was then removed *in vacuo*, and the residue was purified by silica gel flash column chromatography, using a gradient elution method, with mixtures of *n*-hexane and AcOEt ranging from 5:1 to 1:1 by volume as the eluent to obtain **6a** (19.8 g, 94% yield) as a colorless oil of optical purity 98% *ee*. The *ee*-value of **6a** was determined by chiral HPLC analysis [column, Chiralcel OF (4.6ϕ×250 mm); eluent, 99:1 *n*-hexane:2-propanol mixture; flow rate, 1.0 ml/min; $t_R(R)$=15.6 min, $t_R(S)$=18.0 min]. $[\alpha]_D^{25}$ +11.4 (*c* 1.0; MeOH); IR ($CHCl_3$): 3421, 2957, 2932, 1471, 1390, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (1H, d, *J*=2.1 Hz), 7.43 (1H, d, *J*=8.1 Hz), 7.24 (1H, dd, *J*=8.1, 2.1 Hz), 5.00 (1H, s), 3.80 (1H, ddd, *J*=10.4, 3.8, 3.8), 3.5–3.7 (3H, m), 2.51 (1H, dd, *J*=8.0, 5.2 Hz), 2.37 (1H, ddd, *J*=15.0, 11.1, 4.0 Hz), 1.86 (1H, ddd, *J*=15.0, 2.9, 2.9 Hz), 0.89 (9H, s), 0.04 (3H, s), −0.01 (3H, s); MS (FAB) *m/z*: 365 $(M+H)^+$.

*3.15. 4-*tert-*Butyldimethylsilyloxy-(2R)-(4-chlorophenyl)butane-1,2-diol* ***6b***

According to a similar procedure for the preparation of **6a**, **6b** (24.8 g) was prepared in 95% yield from **4b** (23.5 g, 79.1 mmol) as a colorless oil of optical purity 98% *ee*. The *ee*-value of **6b** was

determined by chiral HPLC analysis [column, Chiralcel OD (4.6ϕ×250 mm); eluent, 95:5 *n*-hexane:2-propanol mixture; flow rate, 0.5 ml/min; $t_R(R)$=24.2 min, $t_R(S)$=21.9 min]. $[\alpha]_D^{25}$ +15.6 (*c* 1.1; MeOH); IR ($CHCl_3$): 3430, 2957, 2932, 1491, 1391, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (2H, d, *J*=8.7 Hz), 7.31 (2H, d, *J*=8.7 Hz), 4.90 (1H, s), 3.76 (1H, ddd, *J*=10.4, 4.0, 3.9 Hz), 3.5–3.7 (3H, m), 2.48 (1H, dd, *J*=8.4, 5.2 Hz), 2.36 (1H, ddd, *J*=14.9, 11.3, 4.0 Hz), 1.86 (1H, ddd, *J*=14.9, 2.9, 2.9 Hz), 0.86 (9H, s), 0.00 (3H, s), −0.05 (3H, s); MS (FAB) *m/z*: 331 $(M+H)^+$.

*3.16. 4-*tert*-Butyldimethylsilyloxy-(2R)-(3,4-difluorophenyl)butane-1,2-diol* **6c**

According to a similar procedure for the preparation of **6a**, **6c** (16.3 g) was prepared in 98% yield from **4c** (15.0 g, 50.3 mmol) as a colorless oil of optical purity 99% *ee*. The *ee*-value of **6c** was determined by chiral HPLC analysis [column, Chiralcel OF (4.6ϕ×250 mm); eluent, 95:5 *n*-hexane:2-propanol mixture; flow rate, 1.0 ml/min; $t_R(R)$=13.6 min, $t_R(S)$=16.3 min]. $[\alpha]_D^{25}$ +14.1 (*c* 1.5; MeOH); IR ($CHCl_3$): 3423, 2957, 2932, 1609, 1515, 1290 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.05–7.35 (3H, m), 4.98 (1H, s), 3.80 (1H, ddd, *J*=10.4, 4.0, 4.0 Hz), 3.5–3.7 (3H, m), 2.54 (1H, dd, *J*=8.2, 5.2 Hz), 2.37 (1H, ddd, *J*=14.9, 11.0, 4.0 Hz), 1.86 (1H, ddd, *J*=14.9, 2.9, 2.9 Hz), 0.89 (9H, s), 0.04 (3H, s), −0.02 (3H, s); MS (FAB) *m/z*: 333 $(M+H)^+$.

*3.17. 4-*tert*-Butyldimethylsilyloxy-(2R)-(4-fluorophenyl)butane-1,2-diol* **6d**

According to a similar procedure for the preparation of **6a**, **6d** (3.44 g) was prepared in 96% yield from **4d** (3.20 g, 11.4 mmol) as a colorless oil of optical purity 97% *ee*. The *ee*-value of **6d** was determined by chiral HPLC analysis [column, Chiralcel OD (4.6ϕ×250 mm); eluent, 95:5 *n*-hexane:2-propanol mixture; flow rate, 0.5 ml/min; $t_R(R)$=22.2 min, $t_R(S)$=19.2 min]. $[\alpha]_D^{25}$ +14.0 (*c* 1.2; MeOH); IR ($CHCl_3$): 3433, 2957, 2932, 1605, 1509, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (1H, d, *J*=8.7 Hz), 7.39 (1H, d, *J*=8.7 Hz), 7.05 (1H, d, *J*=8.7 Hz), 7.03 (1H, d, *J*=8.7 Hz), 4.91 (1H, s), 3.78 (1H, ddd, *J*=10.3, 3.8, 3.7 Hz), 3.5–3.7 (3H, m), 2.53 (1H, dd, *J*=8.0, 5.1 Hz), 2.39 (1H, ddd, *J*=14.7, 11.0, 4.1 Hz), 1.89 (1H, ddd, *J*=14.7, 2.8, 2.8 Hz), 0.88 (9H, s), 0.02 (3H, s), −0.04 (3H, s); MS (FAB) *m/z*: 315 $(M+H)^+$.

*3.18. 4-*tert*-Butyldimethylsilyloxy-(2R)-(3,4-dichlorophenyl)-1-[N-(*tert*-butoxycarbonyl)-*N*-(2-hydroxyethyl)amino]-2-butanol* **7a**

4-*tert*-Butyldimethylsilyloxy-(2*R*)-(3,4-dichlorophenyl)butane-1,2-diol **6a** (39.9 g, 0.11 mol) was dissolved in pyridine (80 ml), and *p*-toluenesulfonyl chloride (31.3 g, 0.16 mol) was added to the resulting solution. The mixture was then stirred overnight at rt under a nitrogen atmosphere. At the end of this time, the reaction mixture was diluted with water and extracted with AcOEt. The organic extract was washed with water and brine, after which it was dried over anhydrous $MgSO_4$. The solvent was then removed *in vacuo*. The residue was dissolved in acetonitrile, and lithium perchlorate (35.0 g, 0.33 mol) and 2-aminoethanol (33.4 g, 0.55 mol) were added to the resulting solution. The mixture was then heated at 100°C for 16 h. At the end of this time, the reaction mixture was cooled to rt, diluted with AcOEt, and washed with brine. The organic layer was then separated and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the residue was dissolved in CH_2Cl_2 (700 ml). Triethylamine (22.8 ml, 0.16 mol) and 26.3 g (0.12 mol) of di-*t*-butyl dicarbonate were added to the resulting solution, and the mixture was stirred at rt for 12 h. The reaction mixture was then poured into water and extracted with CH_2Cl_2. The organic extract was washed with brine and then dried over anhydrous $MgSO_4$. The solvent was

then removed *in vacuo*, and the residue was purified by silica gel flash column chromatography, using a gradient elution method, with mixtures of *n*-hexane and AcOEt ranging from 4:1 to 7:3 by volume as the eluent, to give **7a** (47.8 g, 86% yield) as a colorless oil. $[\alpha]_D^{25}$ +3.9 (*c* 0.7; MeOH); IR ($CHCl_3$): 3420, 2957, 2933, 1687, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.15–7.65 (3H, m), 5.19 and 5.46 (total 1H, each broad s), 2.9–4.0 (9H, m), 1.9–2.3 (2H, m), 1.42 (9H, s), 0.83 (9H, s), −0.04 (3H, s), −0.11 (3H, s); MS (FAB) *m/z*: 508 $(M+H)^+$.

*3.19. 4-*tert*-Butyldimethylsilyloxy-(2R)-(4-chlorophenyl)-1-[N-(*tert*-butoxycarbonyl)-N-(2-hydroxyethyl)amino]-2-butanol* ***7b***

According to a similar procedure for the preparation of **7a**, **7b** (12.0 g) was prepared in 83% yield from **6b** (10.0 g, 30.2 mmol) as a colorless oil. $[\alpha]_D^{25}$ +5.7 (*c* 1.1; MeOH); IR ($CHCl_3$): 3421, 2956, 2932, 1685, 1463, 1411, 1367, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.2–7.5 (4H, m), 5.13 and 5.41 (total 1H, each broad s), 3.1–4.0 (9H, m), 1.9–2.3 (2H, m), 1.44 (9H, s), 0.84 (9H, s), −0.03 (3H, s), −0.11 (3H, s); MS (FAB) *m/z*: 474 $(M+H)^+$.

*3.20. 4-*tert*-Butyldimethylsilyloxy-(2R)-(3,4-difluorophenyl)-1-[N-(*tert*-butoxycarbonyl)-N-(2-hydroxyethyl)amino]-2-butanol* ***7c***

According to a similar procedure for the preparation of **7a**, **7c** (19.2 g) was prepared in 82% yield from **6c** (16.1 g, 48.4 mmol) as a colorless oil. $[\alpha]_D^{25}$ +2.4 (*c* 0.3; MeOH); IR ($CHCl_3$): 3423, 2957, 2933, 1686, 1514, 1369, 1282 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.15–7.50 (3H, m), 5.27 and 5.54 (total 1H, each broad s), 3.1–4.0 (9H, m), 2.0–2.4 (2H, m), 1.53 (9H, s), 0.94 (9H, s), 0.09 (3H, s), 0.07 (3H, s); MS (FAB) *m/z*: 476 $(M+H)^+$.

*3.21. 4-*tert*-Butyldimethylsilyloxy-(2R)-(4-fluorophenyl)-1-[N-(*tert*-butoxycarbonyl)-N-(2-hydroxyethyl)amino]-2-butanol* ***7d***

According to a similar procedure for the preparation of **7a**, **7d** (4.12 g) was prepared in 83% yield from **6d** (3.43 g, 10.9 mmol) as a colorless oil. $[\alpha]_D^{25}$ +2.0 (*c* 0.5; MeOH); IR ($CHCl_3$): 3425, 2957, 2933, 1684, 1509, 1369, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.3–7.5 (2H, m), 7.0–7.1 (2H, m), 5.13 and 5.40 (total 1H, each broad s), 3.1–4.0 (9H, m), 2.0–2.4 (2H, m), 1.45 (9H, s), 0.84 (9H, s), −0.03 (3H, s), −0.11 (3H, s); MS (FAB) *m/z*: 458 $(M+H)^+$.

*3.22. 2-[4-*tert*-Butoxycarbonyl-(2R)-(3,4-dichlorophenyl)morpholin-2-yl]ethanol* tert*-butyldimethylsilyl ether* ***8a***

4-*tert*-Butyldimethylsilyloxy-(2*R*)-(3,4-dichlorophenyl)-1-[*N*-(*tert*-butoxycarbonyl)-*N*-(2-hydroxyethyl)amino]-2-butanol **7a** (43.5 g, 85.5 mmol) and triphenylphosphine (26.9 g, 0.10 mol) were dissolved in toluene (450 ml). Toluene solution (44.7 g of 40% w/v) containing 0.10 mol of diethyl azodicarboxylate was added dropwise to the resulting solution at rt under a nitrogen atmosphere, and the mixture was stirred overnight. At the end of this time, the solvent was then removed *in vacuo*, and the residue was purified by silica gel flash column chromatography, using a gradient elution method, with mixtures of *n*-hexane and AcOEt ranging from 20:1 to 10:1 by volume as the eluent, to give **8a** (38.6 g, 92% yield) as a colorless oil. $[\alpha]_D^{25}$ +32.7 (*c* 0.6; MeOH); IR ($CHCl_3$): 2957, 2931, 1687, 1473, 1462, 1428 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (1H, broad s), 7.43 (1H, d, *J*=8.8 Hz), 7.28 (1H, dd,

J=8.8, 2.2 Hz), 3.00–4.55 (8H, m), 1.80–2.10 (2H, m), 1.43 and 1.52 (total 9H, each broad s), 0.85 (9H, s), −0.01 (6H, s); MS (FAB) *m/z*: 490 $(M+H)^+$.

*3.23. 2-[4-*tert*-Butoxycarbonyl-(2R)-(4-chlorophenyl)morpholin-2-yl]ethanol* tert-*butyldimethylsilyl ether* ***8b***

According to a similar procedure for the preparation of **8a**, **8b** (9.49 g) was prepared in 83% yield from **7b** (11.9 g, 25.0 mmol) as a colorless oil. $[\alpha]_D^{25}$ +40.0 (*c* 1.2; MeOH); IR ($CHCl_3$): 2956, 2930, 1686, 1428, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (2H, d, J=8.7 Hz), 7.32 (2H, d, J=8.7 Hz), 3.0–4.5 (8H, m), 1.8–2.1 (2H, m), 1.43 and 1.49 (total 9H, each broad s), 0.85 (9H, s), −0.03 (6H, s); MS (FAB) *m/z*: 456 $(M+H)^+$.

*3.24. 2-[4-*tert*-Butoxycarbonyl-(2R)-(3,4-difluorophenyl)morpholin-2-yl]ethanol* tert-*butyldimethylsilyl ether* ***8c***

According to a similar procedure for the preparation of **8a**, **8c** (16.2 g) was prepared in 89% yield from **7c** (19.0 g, 39.9 mmol) as a colorless oil. $[\alpha]_D^{25}$ +33.6 (*c* 0.2; MeOH); IR ($CHCl_3$): 2958, 2931, 1687, 1519, 1428, 1276 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.1–7.4 (3H, m), 3.0–4.5 (8H, m), 1.8–2.1 (2H, m), 1.51 (9H, broad s), 0.87 (9H, s), 0.02 (6H, s); MS (FAB) *m/z*: 458 $(M+H)^+$.

*3.25. 2-[4-*tert*-Butoxycarbonyl-(2R)-(4-fluorophenyl)morpholin-2-yl]ethanol* tert-*butyldimethylsilyl ether* ***8d***

According to a similar procedure for the preparation of **8a**, **8d** (3.38 g) was prepared in 85% yield from **7d** (4.12 g, 9.00 mmol) as a colorless oil. $[\alpha]_D^{25}$ +37.4 (*c* 0.6; MeOH); IR ($CHCl_3$): 2956, 2930, 1699, 1511, 1426, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (1H, d, J=8.7 Hz), 7.40 (1H, d, J=8.7 Hz), 7.04 (1H, d, J=8.7 Hz), 7.02 (1H, d, J=8.7 Hz), 3.0–4.5 (8H, m), 1.9–2.1 (2H, m), 1.43 and 1.50 (total 9H, each broad s), 0.85 (9H, s), −0.03 (6H, s); MS (FAB) *m/z*: 440 $(M+H)^+$.

3.26. 2-[(2R)-(3,4-Dichlorophenyl)morpholin-2-yl]ethanol ***1a***

2-[4-*tert*-Butoxycarbonyl-(2*R*)-(3,4-dichlorophenyl)morpholin-2-yl]ethanol *tert*-butyldimethylsilyl ether **8a** (38.6 g, 78.7 mmol) was dissolved in 500 ml of a 4N solution of hydrogen chloride in dioxane, and the mixture was stirred at 60°C for 3 h. At the end of this time, the solvent was removed *in vacuo*, a 1N aqueous HCl solution (500 ml) was added to the resulting residue, and the mixture was washed with diethyl ether. The aqueous layer was adjusted to pH 14 by the addition of 2N aqueous NaOH solution, and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was recrystallized from AcOEt (175 ml) and *n*-hexane (210 ml), to obtain **1a** (18.0 g, 83% yield) as white crystals of optical purity >99.9% *ee*. The *ee*-value of **1a** was determined by chiral HPLC analysis [column, Chiralpak AD (4.6ϕ×250 mm); eluent, 85:15 *n*-hexane:2-propanol mixture; flow rate, 1.0 ml/min; $t_R(R)$=12.5 min, $t_R(S)$=19.8 min]. Mp 90–91°C. $[\alpha]_D^{25}$ +19.2 (*c* 1.0; MeOH); IR (KBr): 3261, 3098, 1471, 1383, 1085, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (1H, d, J=2.1 Hz), 7.48 (1H, d, J=8.2 Hz), 7.24 (1H, dd, J=8.2, 2.1 Hz), 3.76 (1H, ddd, J=11.7, 3.3, 3.3 Hz), 3.66 (1H, ddd, J=11.7, 9.5, 3.3 Hz), 3.58 (2H, dd, J=6.0, 6.0 Hz), 3.36 (1H, d, J=13.2 Hz), 3.11 (1H, d, J=13.2 Hz), 2.97 (1H, ddd, J=12.8, 9.5, 3.3 Hz), 2.79 (1H, ddd, J=12.8, 3.3, 3.3 Hz), 2.15 (1H, ddd, J=14.4, 6.0, 6.0 Hz), 1.79 (1H, ddd, J=14.4, 6.0, 6.0 Hz); MS (EI) *m/z*: 275

(M^+). Anal. calcd for $C_{12}H_{15}NO_2Cl_2$: C, 52.19; H, 5.48; N, 5.07; Cl, 25.68. Found: C, 52.13; H, 5.48; N, 5.09; Cl, 25.67.

3.27. 2-[(2R)-(4-Chlorophenyl)morpholin-2-yl]ethanol *1b*

According to a similar procedure for the preparation of **1a**, **1b** (53 mg) was prepared in 68% yield from **8b** (148 mg, 0.32 mmol) as white crystals of optical purity >99.9% *ee*. The *ee*-value of **1b** was determined by chiral HPLC analysis [column, Chiralpak AD (4.6ϕ×250 mm); eluent, 85:15 *n*-hexane:2-propanol mixture; flow rate, 1.0 ml/min; $t_R(R)$=9.8 min, $t_R(S)$=11.6 min]. Mp 170–171°C. $[\alpha]_D^{25}$ +28.0 (*c* 1.0; MeOH); IR (KBr): 3270, 3085, 2913, 1484, 1364, 1083, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (2H, d, *J*=8.7 Hz), 7.35 (2H, d, *J*=8.7 Hz), 3.73 (1H, ddd, *J*=11.6, 3.4, 3.4 Hz), 3.65 (1H, ddd, *J*=11.6, 9.6, 3.0 Hz), 3.57 (2H, m), 3.42 (1H, d, *J*=13.3 Hz), 3.12 (1H, d, *J*=13.3 Hz), 2.97 (1H, ddd, *J*=12.8, 9.6, 3.4 Hz), 2.77 (1H, ddd, *J*=12.8, 3.4, 3.0 Hz), 2.11 (1H, ddd, *J*=14.5, 7.0, 5.1 Hz), 1.77 (1H, ddd, *J*=14.5, 6.2, 4.8 Hz); MS (EI) *m/z*: 241 (M^+). Anal. calcd for $C_{12}H_{16}NO_2Cl$: C, 59.63; H, 6.67; N, 5.80; Cl, 14.67. Found: C, 59.25; H, 6.72; N, 5.66; Cl, 14.63.

3.28. 2-[(2R)-(3,4-Difluorophenyl)morpholin-2-yl]ethanol *1c*

According to a similar procedure for the preparation of **1a**, **1c** (6.90 g) was prepared in 81% yield from **8c** (16.0 g, 35.0 mmol) as white crystals of optical purity >99.9% *ee*. The *ee*-value of **1c** was determined by chiral HPLC analysis [column, Chiralpak AD (4.6ϕ×250 mm); eluent, 85:15 *n*-hexane:2-propanol mixture; flow rate, 1.0 ml/min; $t_R(R)$=12.6 min, $t_R(S)$=18.5 min]. Mp 133–134°C. $[\alpha]_D^{25}$ +22.6 (*c* 1.0; MeOH); IR (KBr): 3264, 3078, 1608, 1518, 1275, 1121 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.1–7.3 (3H, m), 3.75 (1H, ddd, *J*=11.7, 3.5, 3.5 Hz), 3.67 (1H, ddd, *J*=11.7, 9.5, 3.1 Hz), 3.58 (2H, m), 3.36 (1H, d, *J*=13.2 Hz), 3.11 (1H, d, *J*=13.2 Hz), 2.97 (1H, ddd, *J*=12.6, 9.5, 3.5 Hz), 2.78 (1H, ddd, *J*=12.6, 3.5, 3.1 Hz), 2.14 (1H, ddd, *J*=14.3, 6.6, 5.8 Hz), 1.78 (1H, ddd, *J*=14.3, 5.7, 5.2 Hz); MS (EI) *m/z*: 243 (M^+). Anal. calcd for $C_{12}H_{15}NO_2F_2$: C, 59.25; H, 6.22; N, 5.76; F, 15.62. Found: C, 59.21; H, 6.25; N, 5.71; F, 15.37.

3.29. 2-[(2R)-(4-Fluorophenyl)morpholin-2-yl]ethanol *1d*

According to a similar procedure for the preparation of **1a**, **1d** (1.34 g) was prepared in 78% yield from **8d** (3.36 g, 7.65 mmol) as white crystals of optical purity >99.9% *ee*. The *ee*-value of **1d** was determined by chiral HPLC analysis [column, Chiralpak AD (4.6ϕ×250 mm); eluent, 85:15 *n*-hexane:2-propanol mixture; flow rate, 1.0 ml/min; $t_R(R)$=15.0 min, $t_R(S)$=18.7 min]. Mp 139–140°C. $[\alpha]_D^{25}$ +33.6 (*c* 1.0; MeOH); IR (KBr): 3268, 3080, 1509, 1225, 1160, 1081, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (1H, d, *J*=8.7 Hz), 7.37 (1H, d, *J*=8.7 Hz), 7.11 (1H, d, *J*=8.7 Hz), 7.09 (1H, d, *J*=8.7 Hz), 3.73 (1H, ddd, *J*=11.6, 3.4, 3.1 Hz), 3.66 (1H, ddd, *J*=11.6, 9.8, 3.1 Hz), 3.56 (2H, m), 3.42 (1H, d, *J*=13.4 Hz), 3.11 (1H, d, *J*=13.4 Hz), 2.96 (1H, ddd, *J*=13.0, 9.8, 3.4 Hz), 2.76 (1H, ddd, *J*=13.0, 3.1, 3.1 Hz), 2.11 (1H, ddd, *J*=14.6, 7.1, 4.9 Hz), 1.78 (1H, ddd, *J*=14.6, 6.5, 4.5 Hz); MS (EI) *m/z*: 225 (M^+). Anal. calcd for $C_{12}H_{16}NO_2F$: C, 63.98; H, 7.16; N, 6.22; F, 8.43. Found: C, 63.86; H, 7.19; N, 6.12; F, 8.27.

Acknowledgements

We are grateful to Mr. Yoji Furukawa for the X-ray analysis.

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11. Crystal data of (*R*)-MTPA amide of (*R*)-**1a**: $C_{22}H_{22}NO_4Cl_2F_3$, MW=492.3, T=298 K, CuKα radiation, λ=1.5418 Å; monoclinic, space group $P2_1$, *a*=12.462(2) Å, *b*=7.440(2) Å, *c*=13.395(2) Å, β=110.6(1) Å, *V*=1162.3(3) Å^3, Z=2, *Dc*=1.41 g/cm^3, *R*=0.043. Full X-ray crystallographic data will be deposited with the Cambridge Crystallographic Data Centre.