DOI: 10.1002/ejoc.200700011

Concise Synthesis of 2,6-Disubstituted Morpholines by Cyclization of Epoxy Alcohols

Domenico Albanese,*[a] Matteo Salsa,[a] Dario Landini,[a] Vittoria Lupi,[a] and Michele Penso[b]

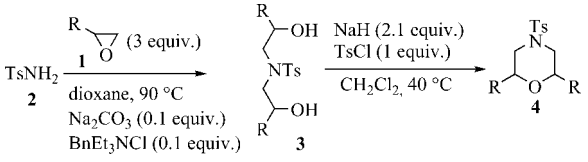
Keywords: Phase-transfer catalysis / Cyclization / Sulfonamides / Epoxy alcohols / Morpholines

A novel, straightforward and high yielding synthesis of enantiomerically pure 2,6-disubstituted morpholines was developed by acid-catalyzed cyclization of epoxy alcohols.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2007)

Introduction

Substituted morpholines have aroused great interest owing to the presence of this skeleton in therapeutically and biologically active compounds.[1] Moreover, C_2-symmetric morpholines have been used as chiral auxiliaries.[2] Palladium-catalyzed tandem allylic substitution has been used to build up enantiomerically enriched 2-vinyl morpholines in moderate-to-good *ee*'s.[3] However, excellent *ee*'s are only obtained by using a xylofuranose-based phosphanyloxazinane ligand.[4] Optically pure 2,6-disubstituted morpholines can also be prepared by diastereoselective alkylation of 6-substituted 3-oxomorpholines, followed by the reduction of the carbonyl moiety and removal of the chiral auxiliary.[5] In a previous paper, we reported the synthesis of racemic 2,6-disubstituted morpholines **4** through the phase-transfer catalyzed dialkylation of 4-methylbenzenesulfonamide (**2**) by oxiranes **1**, followed by cyclization of hydroxysulfonamides **3** thus obtained (Scheme 1).[6]



Scheme 1.

A similar approach was successfully employed for the synthesis of enantiomerically pure 2,6-disubstituted morpholines through the ring opening of enantiopure epoxides, followed by protecting group manipulations.[7] However, a new approach was designed to develop a more direct synthesis. Therefore, epoxy alcohol **5**, easily accessible by the ring opening of an epoxide with a proper nitrogen nucleophile, was envisioned as a potential precursor of 2,6-disubstituted morpholines by regioselective cyclization (Figure 1).

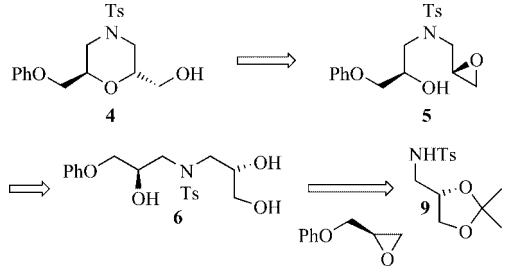


Figure 1. Retrosynthesis.

Herein we describe the concise, high-yielding synthesis of enantiopure 2,6-disubstituted morpholines by the cyclization of epoxy alcohols, which affords regioselectively the six-membered morpholine skeleton through a 6-e*xo*-*tet* pathway.[8]

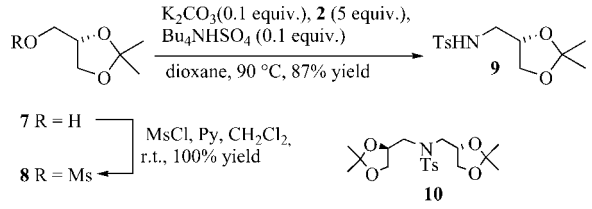
Results and Discussion

(*S*)-*N*-(2,2-Dimethyl[1,3]dioxolan-4-ylmethyl)-4-methylbenzenesulfonamide (**9**), derived from (*S*)-solketal (**7**) by hydroxy group activation, followed by nucleophilic displacement with sulfonamide **2** was chosen as the nitrogen nucleophile bearing the right-hand side of the target morpholine (Scheme 2).

[a] Dipartimento di Chimica Organica e Industriale
Via Venezian 21, 20133 Milano, Italia
Fax: +39-0250314159
E-Mail: domenico.albanese@unimi.it
[b] Istituto CNR-ISTM,
Via Golgi 19, 20133 Milano, Italia

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 2.

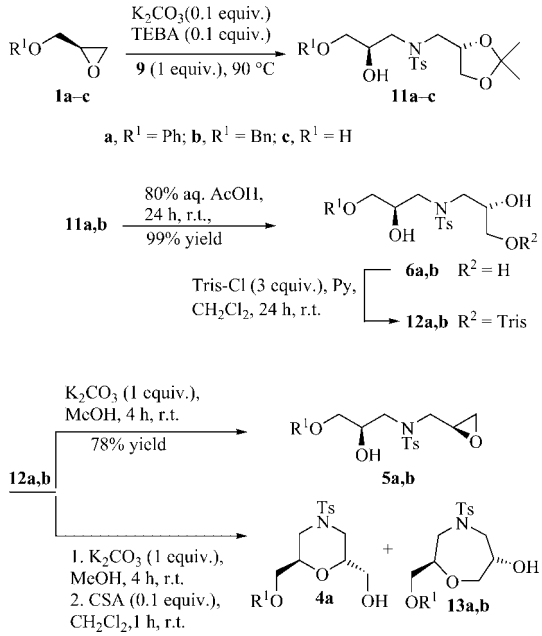
Mesylate **8** was obtained in quantitative yield by a known procedure,[9] whereas its conversion to corresponding sulfonamide **9** required optimization. The reaction was carried out under solid–liquid phase-transfer catalysis conditions (SL-PTC) at 90 °C by using solid anhydrous K_2CO_3 as the base in the presence of $Bu_4N^+HSO_4^-$ as the catalyst. An excess of sulfonamide **2** was used to minimize the formation of bisalkylation product **10**.[10] The best results were obtained by using a fivefold excess of **2**, which afforded sulfonamide **9** in 87% yield. The excess reagent was recovered by crystallization of the reaction mixture.

The ring opening of epoxides **1a**–**c** with sulfonamide **9** was carried out under SL-PTC conditions without solvent[11] by using anhydrous K_2CO_3 as the base in the presence of $BnEt_3N^+Cl^-$ (TEBA) heated at 90 °C (Scheme 3). High yields of enantiopure hydroxysulfonamides **11a**–**c** were obtained in short reaction times (Table 1).

Compound (*R*,*S*)-**11a** was chosen as a model for the investigation of the additional synthetic steps (Scheme 3).

Removal of the diol protection with 80% aqueous acetic acid followed by selective sulfonylation of the primary hydroxy group with 2,4,6-triisopropylbenzenesulfonyl chloride (Tris-Cl) afforded sulfonate ester (*R*,*S*)-**12a** in 63% overall yield. When the latter was treated with 1 equiv. of K_2CO_3 in methanol at room temperature, epoxide (*R*,*S*)-**5a** could be isolated in 78% yield along with trace amounts of cyclization products (Table 2, Entry 1).

In contrast, mixtures of morpholine **4a** and [1,4]oxazepan-6-ol **13a** were isolated in good yields, but with poor regioselectivity, through the base-promoted cyclization reaction of (*R*,*S*)-**5a** with methanolic K_2CO_3 (Table 2, Entries 2, 3). These two heterocycles are formed depending upon which of the two different epoxy ring carbon atoms undergoes nucleophilic attack during cyclization



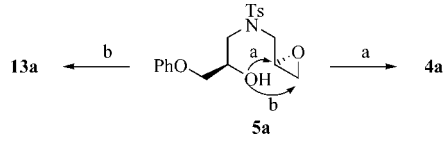
Scheme 3.

Table 1. Ring opening of epoxides **1a**–**c**.[a]

Epoxide	R	*t* [h]	Product	Yield [%]
(*R*)-**1a**	Ph	2.5	(*R*,*S*)-**11a**	89
(*R*)-**1b**	Bn	4	(*R*,*S*)-**11b**	98
(*S*)-**1c**	H	2	(*R*,*S*)-**11c**	87

[a] Reaction conditions: **9** (1 equiv.), K_2CO_3 (0.1 equiv.), TEBA (0.1 equiv.), 90 °C.

(Scheme 4). The structure of **13a** was proved by comparison with the compound prepared through an unambiguous synthetic pathway.[12]



Scheme 4.

The acid-catalyzed cyclization was addressed next. Under acidic conditions, the nucleophile is expected to attack the more highly substituted carbon atom of the epoxide

Table 2. Cyclization of sulfonate esters **12a**,**b**.[a]

Entry	Substrate	Base [equiv.]	t_1 [h][a]	Acid [equiv.]	t_2 [h][b]	Yield [%][c]	**4/13**[d]
1	(*R*,*S*)-**12a**	K_2CO_3 (1)	4	–	–	78	–[e]
2	(*R*,*S*)-**12a**	K_2CO_3 (5)	20	–	–	85	50:50
3	(*R*,*S*)-**12a**	K_2CO_3 (2)	24	–	–	78	64:36
4	(*R*,*S*)-**5a**	–	–	CSA (0.1)	1	81	91:9
5	(*R*,*S*)-**12a**	K_2CO_3 (1)	4	CSA (0.1)	1	87	96:4
6	(*R*,*S*)-**12a**	DBU (1)	5	CSA (0.1)	1	87	93:7
7	(*R*,*S*)-**12a**	K_2CO_3 (1)	4	$Sn(OTf)_2$ (0.1)	1	87	93:7
8	(*R*,*S*)-**12b**	K_2CO_3 (1)	4	CSA (0.1)	1	87	95:5
9	(*R*,*S*)-**12b**	K_2CO_3 (1)	4	$Sn(OTf)_2$ (0.1)	1	52	95:5
10	(*R*,*S*)-**12b**	K_2CO_3 (1)	4	$Yb(OTf)_3$ (0.1)	24	–[f]	–

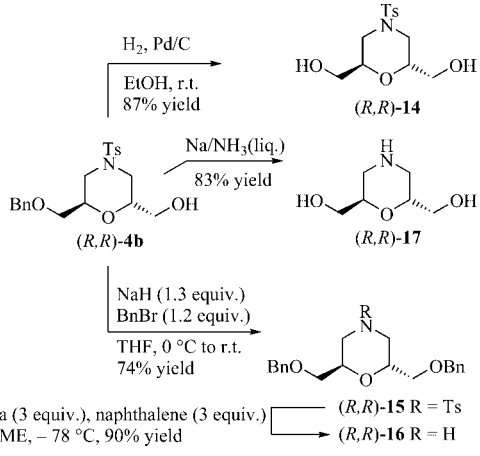
[a] Time for generation of epoxide **5**. [b] Time for acid-promoted cyclization. [c] Isolated yield. [d] Determined by HPLC. [e] Epoxide **5a**. [f] Not isolated.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

ring as it bears more of the positive charge.[13] Moreover, the acid-catalyzed cyclization of epoxy alcohols has been exploited in the synthesis of various O-heterocycles.[14]

We were pleased to find that the cyclization smoothly proceeded in a highly regioselective fashion when epoxide (*R*,*S*)-**5a** was treated with catalytic amounts of (1*S*)-(+)-camphor-10-sulfonic acid monohydrate (CSA)[15] in CH_2Cl_2 at 25 °C. In fact, a 91:9 ratio of **4a**/**13a** was obtained in an 81% yield after a reaction time of only 1 h (Table 2, Entry 4). A more practical approach was developed by generating epoxide **5a** in situ followed by the sequential acid-promoted cyclization. In the first step of the reaction, epoxide **5a** was generated from sulfonate ester **12a** by using a stoichiometric amount of solid K_2CO_3 in MeOH at room temperature. After MeOH removal, CH_2Cl_2 was added and undissolved material was filtered through a small SiO_2 pad; subsequently, a protic or Lewis acid was added to promote epoxy alcohol cyclization. Under these reaction conditions, 87% overall yield of **4a** was obtained (Table 2, Entry 5). Slightly lower regioselectivity was obtained by using DBU instead of K_2CO_3 (Table 2, Entry 6), whereas Et_3N proved to be ineffective. The cyclization of sulfonate ester (*R*,*S*)-**12b** afforded morpholine (*R*,*R*)-**4b** (Table 2, Entry 8) with high regioselectivity. Good results were also obtained by using Lewis acids such as $Sn(OTf)_2$ (Table 2, Entries 7, 9), whereas the cyclization was slower in the presence of $Yb(OTf)_3$ (Table 2, Entry 10).

C_2-Symmetric 2,6-bis(hydroxymethyl)morpholine (*R*,*R*)-**14** could be easily generated by hydrogenolysis of the benzyl moiety of morpholine (*R*,*R*)-**4b** and represents a key intermediate in the preparation of a variety of C_2-symmetric morpholines through standard functional group chemistry (Scheme 5).

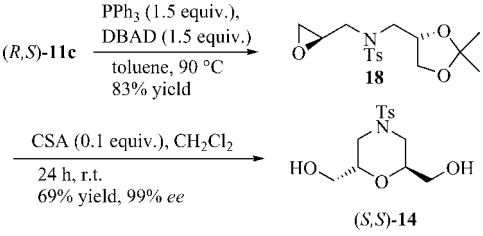


Scheme 5.

For example, (*R*,*R*)-**16** could be obtained through O-alkylation followed by detosylation, whereas fully deprotected morpholine (*R*,*R*)-**17** could be isolated upon treatment of (*R*,*R*)-**4b** with Na/NH_3 (liquid).

Morpholines **4a**,**b** were isolated in an enantiomerically pure form, as proved by chiral HPLC, which indicates that the cyclization proceeds through a clean S_N2 mechanism.

The ring opening of (*S*)-glycidol (**1c**) with sulfonamide (*S*)-**9** afforded dihydroxysulfonamide (*R*,*S*)-**11c**, which could directly generate morpholine (*S*,*S*)-**14** through acid-promoted domino ketal-removal, cyclization of epoxide **18** (Scheme 6).



Scheme 6.

Thus, diol (*R*,*S*)-**11c** was converted into epoxide **18** in good yields with *N*-tosylimidazole or *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole in the presence of NaH. However, a mixture of the two diastereoisomeric epoxides was obtained as a result of the competition of the two hydroxy groups for sulfonylation. Nevertheless, epoxide **18** (*de* 20%) was subjected to a catalytic amount of CSA in CH_2Cl_2 at room temperature to afford, after 24 h, a mixture of diastereoisomeric morpholines **14** in 67% yield. The regioselective diol-to-epoxide conversion was performed and the product was obtained in 83% yield by the Mitsunobu reaction using di-*tert*-butylazodicarboxylate (DBAD) in the presence of PPh_3 in toluene (Scheme 6).

The subsequent domino ketal-removal, cyclization reaction promoted by CSA afforded (*S*,*S*)-**14** in 69% yield as the cyclization proceeds with inversion of configuration at the epoxide stereogenic centre. Both enantiomers of morpholine **14** can thus be prepared from a single epoxide precursor by choosing the proper pathway. In fact, (*R*,*R*)-**14** was obtained from the ring opening of (*R*)-benzyl glycidol (**1b**), which is commercially available, but it is also easily prepared by benzylation of (*S*)-glycidol (**1c**).[16] The latter was used to generate morpholine (*S*,*S*)-**14** through the domino ketal-removal, cyclization approach.

In summary, we developed a new straightforward method for the synthesis of enantiomerically pure 2,6-disubstituted morpholines through assembling, in a stereoselective fashion, a left hand epoxide-derived portion with a right hand solketal-derived portion. Both starting material are widely accessible in both enantiopure forms. The acid-promoted cyclization of in situ generated epoxy alcohols **5a**,**b**, or epoxide **18**, proceeds in a highly regioselective fashion and without racemization of the epoxide stereocentre. The new approach is applicable to the synthesis of a variety of 2,6-disubstituted morpholines. As a matter of fact, the 2-hydroxymethyl substituent is amenable to further functionalization, whereas the substituent in the 6-position can be chosen by using the proper epoxide, which is readily available in an enantiopure form. Studies are now in progress to optimize the cyclization through the domino ketal-removal, cyclization of epoxide **18**.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Experimental Section

General Remarks: Melting points were determined with a BÜCHI 535 and are corrected. Infrared (IR) spectra were recorded with a Perkin–Elmer 1725 X FTIR spectrometer. NMR spectra were recorded with a Bruker AC 300 or AC 200 spectrometer. Chemical shifts are reported by using $CHCl_3$ as an external standard (δ =7.24 ppm for ^1H NMR and 77.0 for ^{13}C NMR). APT experiments were used in the assignment of carbon spectra. Optical rotations were measured with a Perkin–Elmer 241 polarimeter; the $[a]_D$ values are reported in 10^{-1} deg cm^{-2} g^{-1}, concentration (c) is reported in grams per 100 mL of solvent. Mass spectra (ESI and APCI) were measured with a LCQ Advantage Thermo-Finnigan spectrometer. Column chromatography on silica gel (230–400 mesh) was performed by the flash technique or by using MPLC. Chiral HPLC separations were performed on an Agilent HP 1100 apparatus, equipped with a diode array detector, by using mixtures of hexane/2-propanol as the eluent with detection at 230 nm, unless otherwise stated. The flux was set to 1 mL min^{-1} and the volume of injection was 20 μL. Petroleum ether (PE) refers to the fraction boiling in the range of 40–60 °C.

(*R*)-2-Phenoxymethyloxirane (**1a**) was prepared in 75% yield as described previously.[17]

(*R*)-2-Benzyloxymethyloxirane (**1b**) was prepared by O-alkylation of (*S*)-glycidol (**1c**).[18]

Synthesis of (*S*)-*N*-(2,2-Dimethyl[1,3]dioxolan-4-ylmethyl)-4-methylbenzenesulfonamide (9): A mixture of solketal-mesylate **8** (4.15 g, 19.7 mmol), $TsNH_2$ (16.9 g, 99 mmol), K_2CO_3 (5.40 g, 39.4 mmol), $Bu_4N^+HSO_4^-$ (0.67 g, 1.97 mmol) and dioxane (20 mL) was stirred at 90 °C for 48 h. After cooling, the solvent was evaporated and AcOEt (100 mL) added. The organic solution was washed with water (2 × 20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to yield 21 g of a white solid. The latter was crystallized with $CHCl_3$ (95 mL). After filtration of $TsNH_2$ (10.8 g, 76%), the crude product was concentrated and purified by MPLC (AcOEt/PE, 1:2) to provide **9** (4.85 g, 87%) along with **10** (0.23 g, 2.3%) and $TsNH_2$ (3.63 g). **9**: White solid, m.p. 91–92 °C. $[a]_D^{25}$ = –10.6 (c = 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 3 H), 1.33 (s, 3 H), 2.41 (s, 3 H), 2.92 (m, 1 H), 3.12 (ddd, J = 14.3, 7.8, 4.6 Hz, 1 H), 3.66 (dd, J = 8.5, 5.9 Hz, 1 H), 3.98 (dd, J = 8.5, 6.4 Hz, 1 H), 4.15 (m, 1 H), 4.78 (t, J = 6.1 Hz, 1 H), 7.29 (d, J = 8.3 Hz, 2 H), 7.71 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 25.1 (CH_3), 26.8 (CH_3), 45.3 (CH_2), 65.5 (CH_2), 74.0 (CH), 109.7 (C), 127.1 (CH), 129.8 (CH), 136.7 (C), 143.6 (C) ppm. IR (nujol): $\tilde{\nu}$ = 3282, 3042, 1599, 1430, 1319, 1308, 1218, 1168, 1154, 1082, 1050 cm^{-1}. MS (APCI): m/z = 286 [M + H]$^+$. $C_{13}H_{19}NO_4S$ (285.4): calcd. C 54.72, H 6.71, N 4.91; found C 54.90, H 6.73, N 4.89. **10**: Colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 6 H), 1.39 (s, 6 H), 2.43 (s, 3 H), 3.31 (dd, J = 14.7, 6.8 Hz, 2 H), 3.43 (dd, J = 14.7, 4.9 Hz, 2 H), 3.69 (dd, J = 8.4, 6.5 Hz, 2 H), 4.06 (dd, J = 8.4, 6.2 Hz, 2 H), 4.31 (m, 2 H), 7.29 (d, J = 8.3 Hz, 2 H), 7.71 (d, J = 8.3 Hz, 2 H) ppm.

General Procedure for the Ring Opening of Epoxides 1a–c: A mixture of epoxide **1** (10 mmol), **9** (10 mmol), K_2CO_3 (1 mmol) and TEBA (1 mmol) was stirred at 90 °C until the starting material was no longer detectable (TLC analysis). After cooling, the crude material was diluted with Et_2O and washed with water (2 × 5 mL). After extraction of the aqueous phase with Et_2O (2 × 10 mL), the combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography. Starting epoxide, reaction time, eluent, yield and physical and spectroscopic data of **11a–c** are as follows.

***N*-[(*R*)-2-Hydroxy-3-phenoxypropyl]-*N*-{(*S*)-2,2-dimethyl[1,3]dioxolan-4-ylmethyl}-4-methylbenzenesulfonamide (11a):** (*R*)-**1a**, 2.5 h, AcOEt/PE (1:4). Yield: 89%, colourless oil. $[a]_D^{25}$ = +17.5 (c = 0.84, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.42 (s, 3 H), 2.42 (s, 3 H), 3.04 (dd, J = 8.2, 14.9 Hz, 1 H), 3.11 (dd, J = 8.2, 14.9 Hz, 1 H), 3.57–3.70 (m, 3 H), 3.98 (m, 2 H), 4.10 (m, 1 H), 4.31 (m, 1 H), 4.49 (m, 1 H), 6.87 (d, J = 8.1 Hz, 2 H), 6.96 (t, J = 7.4 Hz, 1 H), 7.30 (m, 4 H), 7.70 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3), 25.2 (CH_3), 26.6 (CH_3), 53.9 (CH_2), 54.5 (CH_2), 67.1 (CH_2), 69.4 (CH_2), 69.7 (CH), 75.8 (CH), 110.0 (C), 114.4 (CH), 121.0 (CH), 127.3 (CH), 129.4 (CH), 129.7 (CH), 135.4 (C), 143.8 (C) ppm. IR (nujol): $\tilde{\nu}$ = 3380, 3064, 3037, 1598, 1334, 1270, 1159, 1095, 1062 cm^{-1}. $C_{22}H_{29}NO_6S$ (435.5): calcd. C 60.67, H 6.71, N 3.22; found C 60.54, H 6.70, N 3.23.

***N*-[(*R*)-3-Benzyloxy-2-hydroxypropyl]-*N*-{(*S*)-2,2-dimethyl[1,3]dioxolan-4-ylmethyl}-4-methylbenzenesulfonamide (11b):** (*R*)-**1b**, 4 h, AcOEt/PE (1:2). Yield: 98%, colourless oil. $[a]_D^{25}$ = +5.8 (c = 0.35, $CHCl_3$). HPLC (Chiralcel OD, *i*PrOH/hexane, 10:90): t_R (*R*,*S*) = 19.6 min, t_R (racemic diastereoisomeric mixture) = 19.6, 21.2, 23.3, 25.4 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.38 (s, 3 H), 2.42 (s, 3 H), 2.94–3.04 (m, 2 H), 3.51–3.63 (m, 6 H), 4.07–4.12 (m, 2 H), 4.41–4.48 (m, 1 H), 4.54 (s, 2 H), 7.25–7.33 (m, 7 H), 7.68 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3), 25.3 (CH_3), 26.6 (CH_3), 53.8 (CH_2), 54.5 (CH_2), 67.2 (CH_2), 70.1 (CH), 71.7 (CH_2), 73.4 (CH_2), 75.8 (CH), 109.9 (C), 127.3 (CH), 127.7 (CH), 128.3 (CH), 129.8 (CH), 135.6 (C), 138.0 (C), 143.7 (C) ppm. IR (neat): $\tilde{\nu}$ = 3406, 3061, 3032, 2989, 2924, 2871, 1599, 1496, 1453, 1336, 1274, 1159, 1089, 1072 cm^{-1}. $C_{23}H_{31}NO_6S$ (449.6): calcd. C 61.45, H 6.95, N 3.12; found C 61.59, H 6.97, N 3.11.

***N*-[(*R*)-2,3-Dihydroxypropyl]-*N*-{(*S*)-2,2-dimethyl[1,3]dioxolan-4-ylmethyl}-4-methylbenzenesulfonamide (11c):** (*S*)-**1c**, 2 h, AcOEt/PE (3:1). Yield: 87%, white solid, m.p. 87–88 °C. $[a]_D^{25}$ –10.4 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.41 (s, 3 H), 2.37 (s, 3 H), 2.95 (dd, J = 14.7, 8.1 Hz, 2 H), 3.43–3.70 (m, 6 H), 3.83 (br. s, 1 H), 3.97–4.03 (m, 1 H), 4.09 (dd, J = 8.7, 6.6 Hz, 1 H), 4.45 (m, 1 H), 7.32 (d, J = 8.2 Hz, 2 H), 7.68 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 25.2 (CH_3), 26.6 (CH_3), 54.2 (CH_2), 54.4 (CH_2), 63.7 (CH), 67.4 (CH), 71.1 (CH), 76.0 (CH), 110.1 (C), 127.3 (CH), 129.9 (CH), 135.1 (C), 144.0 (C) ppm. ESI-MS: m/z = 383 [M + Na]$^+$. IR (nujol): $\tilde{\nu}$ = 3349, 3054, 3042, 1599, 1335, 1253, 1214, 1161, 1108, 1058, 953 cm^{-1}. $C_{16}H_{25}NO_6S$ (359.4): calcd. C 53.46, H 7.01, N 3.90; found C 53.53, H 7.01, N 3.88.

***N*-[(*S*)-2,3-Dihydroxypropyl]-*N*-[(*R*)-2-hydroxy-3-phenoxypropyl]-4-methylbenzenesulfonamide (6a):** Compound **11a** (915 mg, 2.10 mmol) was dissolved in 80% aq. CH_3COOH (14 mL) and stirred at room temp. for 24 h. After concentration in vacuo, the residue was dissolved in AcOEt and washed with $NaHCO_3$ (satd.) The organic solution was dried (Na_2SO_4), filtered and concentrated to give **6a** (822 mg). Yield: 99%, white solid, m.p. 80.5–82.5 °C. $[a]_D^{25}$ = +17.9 (c = 1.0, $CHCl_3$). HPLC (Chiralpak AD, *i*PrOH/hexane, 20:80): t_R (*R*,*S*) = 23.1 min, t_R (*R*,*R*) = 16.1 min, *de* 98%.[3] ^1H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3 H), 3.09–3.21 (m, 2 H), 3.30–3.80 (m, 4 H), 3.96–3.99 (m, 2 H), 4.11 (m, 1 H), 4.39, (m, 1 H), 6.88 (d, J = 7.8 Hz, 2 H), 6.96 (t, J = 7.3 Hz, 1 H), 7.30 (m, 4 H), 7.70 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 54.7 (CH_2), 55.0 (CH_2), 63.9 (CH_2), 69.5 (CH_2), 70.4 (CH), 71.9 (CH), 114.5 (CH), 121.3 (CH), 127.4 (CH), 129.5 (CH), 129.9 (CH), 134.8 (C), 144.0 (C), 158.3 (C) ppm. ESI-MS: m/z = 419 [M + Na]$^+$. IR (nujol): $\tilde{\nu}$ = 3253, 1599, 1340, 1253,

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

1147, 1070, 1003 cm^{-1}. $C_{19}H_{25}NO_6S$ (395.5): calcd. C 57.70, H 6.37, N 3.54; found C 57.62, H 6.35, N 3.55.

***N*-[(*R*)-3-Benzyloxy-2-hydroxypropyl]-*N*-[(*S*)-2,3-dihydroxypropyl]-4-methylbenzenesulfonamide (6b):** Compound **11b** (4.75 g, 10.6 mmol) was dissolved in 80% aq. CH_3COOH (72 mL) and stirred at room temp. for 22 h. The same procedure described above for **6a** was followed. Yield: 4.30 g (99%), white solid, m.p. 79.1–80.7. $[a]_D^{25}$ = +15.2 (*c* = 1.0, $CHCl_3$). HPLC (Chiralpak AD, *i*PrOH/hexane, 20:80): t_R (*R*,*S*) = 21.3 min, t_R (*S*,*S*) = 16.2 min, *de* 98%.[4] ^1H NMR (300 MHz, $CDCl_3$): δ = 2.01 (br. s, 3 H), 2.42 (s, 3 H), 2.99 (d, *J* = 9.4 Hz, 1 H), 3.04 (d, *J* = 10.3 Hz, 1 H), 3.46–3.58 (m, 5 H), 3.67 (dd, *J* = 3.9, 11.7 Hz, 1 H), 4.06 (m, 1 H), 4.21 (m, 1 H), 4.54 (s, 2 H), 7.25–7.33 (m, 7 H), 7.66 (d, *J* = 8.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 54.6 (CH_2), 55.0 (CH_2), 63.9 (CH_2), 70.7 (CH), 71.8 (CH_2), 71.9 (CH), 73.4 (CH_2), 127.3 (CH), 127.8 (CH), 128.4 (CH), 129.8 (CH), 134.9 (C), 137.7 (C), 143.8 (C) ppm. ESI-MS: *m*/*z* = 842 $[2M + Na]^+$. IR (nujol): $\tilde{\nu}$ = 3290, 3068, 3027, 1599, 1338, 1151, 1087, 999 cm^{-1}. $C_{20}H_{27}NO_6S$ (409.5): calcd. C 58.66, H 6.65, N 3.42; found C 58.62, H 6.64, N 3.43.

(*R*,*S*)-Sulfonate Ester (12a): In a round-bottomed flask, **6a** (746 mg, 1.89 mmol) was dissolved in CH_2Cl_2 (6 mL) and pyridine (3.5 mL) was added. After cooling to 0 °C, 2,4,6-triisopropylbenzenesulfonyl chloride (1.78 g, 5.87 mmol) was added, and the mixture was then warmed to 25 °C. After 24 h, the reaction mixture was made acidic with 10% aq. HCl. The organic solution was dried (Na_2SO_4), filtered, concentrated in vacuo and purified by flash column chromatography [MTBE/PE, 1:1]. Yield: 788 mg (63%), white solid, m.p. 98.4–99.7 °C. $[a]_D^{25}$ = +6.1 (*c* = 0.29, $CHCl_3$). HPLC (Chiralcel OD, *i*PrOH/hexane, 10:90): t_R (*R*,*S*) = 17.0 min, t_R (*R*,*R*) = 27.5 min, *de* 99%.[5] ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.9 Hz, 12 H), 1.25 (d, *J* = 6.9 Hz, 6 H), 2.42 (s, 3 H), 2.89 (m, 1 H), 3.10–3.23 (m, 2 H), 3.51 (dd, *J* = 8.3, 14.9 Hz, 1 H), 3.56 (dd, *J* = 8.1, 15.1 Hz, 1 H), 3.94–4.18 (m, 6 H), 4.28–4.40 (m, 2 H), 6.88 (d, *J* = 7.5 Hz, 2 H), 6.96 (t, *J* = 7.4 Hz, 1 H), 7.18 (s, 2 H), 7.30 (m, 4 H), 7.70 (d, *J* = 8.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 23.5 (CH_3) 24.7 (CH_3), 29.7 (CH) 34.3 (CH), 54.7 (2 CH_2), 69.4 (CH_2), 69.5 (2 CH), 114.6 (CH), 121.3 (CH), 123.9 (CH), 127.4 (CH), 128.8 (C), 129.5 (CH), 130.0 (CH), 134.9 (C), 144.1 (C), 151.0 (C), 154.0 (C), 158.3 (C) ppm. ESI-MS: *m*/*z* = 685 $[M + Na]^+$. IR (nujol): $\tilde{\nu}$ = 3317, 3053, 3036, 1598, 1494, 1343, 1246, 1179, 1167, 1038, 915 cm^{-1}. $C_{34}H_{47}NO_8S_2$ (661.9): calcd. C 61.70, H 7.16, N 2.12; found C 61.81, H 7.17, N 2.11.

(*R*,*S*)-Sulfonate Ester (12b): In a round-bottomed flask, **6b** (1.50 g, 3.66 mmol) was dissolved in CH_2Cl_2 (24 mL) and pyridine (1.6 mL) was added. After cooling to 0 °C, 2,4,6-triisopropylbenzenesulfonyl chloride (11.0 mmol, 3.33 g) was added, and the mixture was then warmed to 25 °C. After 30 h, the reaction mixture was made acidic with 10% aq. HCl. The organic solution was dried (Na_2SO_4), filtered, concentrated in vacuo and purified by flash column chromatography [MTBE/PE, 1:1]. Yield: 1.64 g (67%), white solid, m.p. 90.5–91.5. $[a]_D^{25}$ = +2.62 (*c* = 1.0, $CHCl_3$). HPLC (Chiralcel AD, *i*PrOH/hexane, 20:80): t_R (*R*,*S*) = 8.4 min, t_R (*R*,*R*) = 12.2 min, *de* 99%.[5] ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.6 Hz, 12 H), 1.26 (d, *J* = 7.0 Hz, 6 H), 2.43 (s, 3 H), 2.89–3.05 (m, 3 H), 3.40–3.55 (m, 5 H), 4.00–4.38 (m, 7 H), 4.53 (s, 2 H), 7.18 (s, 2 H) 7.27–7.35 (m, 7 H) 7.65 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 23.5 (CH_3), 24.7 (CH_3), 29.6 (CH), 34.2 (CH), 54.6 (CH_2), 54.9 (CH_2), 69.5 (CH), 70.3 (CH_2), 70.8 (CH), 71.5 (CH_2), 73.4 (CH_2), 123.8 (CH), 127.3 (CH), 127.7 (CH), 128.4 (CH), 129.9 (CH), 134.9 (C), 137.2 (C), 143.9 (C), 150.9 (C), 153.9 (C) ppm. ESI-MS: *m*/*z* = 699 $[M + Na]^+$. IR (nujol): $\tilde{\nu}$ = 3278, 3061, 3033, 1601, 1342, 1176, 1155 cm^{-1}. $C_{35}H_{49}NO_8S_2$ (675.9): calcd. C 62.20, H 7.31, N 2.07; found C 61.99, H 7.33, N 2.06.

***N*-[(*R*)-2-Hydroxy-3-phenoxypropyl]-*N*-[(*S*)-2-oxiranylmethyl]-4-methylbenzenesulfonamide (5a):** A stirred solution of **12a** (46 mg, 0.072 mmol) was dissolved in MeOH (1 mL) and solid K_2CO_3 (10 mg, 0.072 mmol) was added. After stirring at room temp. for 4 h, the crude was purified by MPLC (MTBE/PE, 3:2). Yield: 21 mg (78%), colourless oil. $[a]_D^{25}$ = +9.1 (*c* = 0.60, $CHCl_3$). HPLC (Chiralcel AD, *i*PrOH/hexane, 20:80): t_R (*R*,*S*) = 20.0 min, t_R (*R*,*R*) = 21.1 min.[6] ^1H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 2.65 (dd, *J* = 3.9, 6.9 Hz, 1 H), 2.82 (t, *J* = 6.3 Hz, 1 H), 3.02–3.70 (m, 6 H), 4.03 (d, *J* = 7.8 Hz, 2 H), 4.25 (m, 1 H), 6.88–7.03 (m, 3 H), 7.25–7.32 (m, 4 H), 7.72 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (CH_3), 45.7 (CH_2), 51.1 (CH), 52.1 (CH_2), 53.0 (CH_2), 69.0 (CH), 69.3 (CH_2), 114.5 (CH), 121.2 (CH), 127.3 (CH), 129.5 (CH), 130.1 (CH), 135.5 (C), 143.9 (C), 158.3 (C) ppm. ESI-MS: *m*/*z* = 378 $[M + H]^+$. IR (nujol): $\tilde{\nu}$ = 3391, 3068, 3033, 1735, 1599, 1497, 1341, 1243, 1160, 1093, 1044 cm^{-1}. $C_{19}H_{23}NO_5S$ (377.5): calcd. C 60.46, H 6.14, N 3.71; found C 60.41, H 6.13, N 3.72.

(*R*,*R*)-2-Hydroxymethyl-6-phenoxymethyl-4-tosylmorpholine (4a): In a screw cap vial, **12a** (331 mg, 0.50 mmol) was dissolved in MeOH (20 mL) and K_2CO_3 (69 mg, 0.50 mmol) was added. The resulting solution was stirred at room temp. for 4 h. After evaporation of MeOH, CH_2Cl_2 (20 mL) was added, and the mixture was filtered through a small pad of SiO_2. After concentration to 20 mL, (1*S*)-(+)-camphor-10-sulfonic acid monohydrate (CSA) (12 mg, 0.05 mmol) was added, and the solution was stirred at room temp. for 1 h. The crude product (**4a**/**13a** 96:4) was purified by MPLC (MTBE/PE, 2:1). Yield: 164 mg (87%) of **4a** as a colourless syrup along with a trace amount of **13a** (**4a**/**13a** 99:1). Data for **4a**: HPLC (Chiralcel AD, *i*PrOH/hexane, 20:80): t_R (2*R*,6*R*) = 24.0 min, t_R (**13a**) = 16.2 min. Other morpholine stereoisomers were absent: t_R (2*S*,6*S*) = 16.6 min, t_R (2*R*,6*S*) = 15.3 min, t_R (2*S*,6*R*) = 13.1 min. $[a]_D^{25}$ = +3.96 (*c* = 0.63, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.83 (dd, *J* = 11.5, 7.2 Hz, 1 H), 3.05 (dd, *J* = 11.7, 3.1 Hz, 1 H), 3.15–3.24 (m, 2 H), 3.74 (d, *J* = 5.2 Hz, 2 H), 3.94–3.97 (m, 1 H), 4.07 (dd, *J* = 9.1, 5.8 Hz, 1 H), 4.18–4.29 (m 2 H), 6.90 (d, *J* = 8.1 Hz, 2 H), 6.97 (t, *J* = 7.3 Hz, 1 H) 7.25–7.34 (m, 4 H), 7.64 (d, *J* = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 46.3 (CH_2), 46.6 (CH_2), 62.0 (CH_2), 66.4 (CH_2), 69.4 (CH), 70.6 (CH), 114.7 (CH), 121.4 (CH), 127.8 (CH), 129.5 (CH), 129.9 (CH), 132.0 (C), 144.1 (C), 158.3 (C) ppm. APCI-MS: *m*/*z* = 378 $[M + H]^+$. IR (nujol): $\tilde{\nu}$ = 3407, 3054, 3023, 1741, 1598, 1494, 1346, 1168, 1041 cm^{-1}. $C_{19}H_{23}NO_5S$ (377.5): calcd. C 60.46, H 6.14, N 3.71; found C 60.51, H 6.13, N 3.72.

(*R*,*R*)-2-Hydroxymethyl-6-benzyloxymethyl-4-tosylmorpholine (4b): In a screw cap vial, **12b** (1.40 g, 2.07 mmol) was dissolved in MeOH (30 mL) and K_2CO_3 (286 mg, 2.07 mmol) was added. The resulting solution was stirred at room temp. for 4 h. After evaporation of MeOH, CH_2Cl_2 (40 mL) was added, and the mixture was filtered through a small pad of SiO_2. After concentration, CSA (52 mg, 0.21 mmol) was added, and the solution was stirred at room temp. for 1 h. The crude product was purified by MPLC (AcOEt/PE, 1:1). Yield: 710 mg (87%), colourless syrup. $[a]_D^{25}$ = +3.59 (*c* = 1.1, $CHCl_3$). HPLC (Chiralcel AD, *i*PrOH/hexane, 20:80): t_R (2*R*,6*R*)-**4b** = 19.9 min, t_R (**13b**) = 14.7 min (**4b**/**13b** 95:5), t_R (2*S*,6*S*) = 15.9 min, t_R (2*R*,6*S* + 2*S*,6*R*) = 11.8, 15.6 min, *ee* 99%, *de* 95%. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.74 (dd, *J* = 11.5, 7.2 Hz, 1 H), 2.89 (dd, *J* = 11.5, 3.6 Hz, 1 H), 3.09–3.20 (m, 2 H),

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

3.60–3.68 (m, 4 H), 3.85 (m, 1 H), 4.04 (m, 1 H), 4.54 (AB_q, J = 12.0 Hz, 2 H), 7.25–7.33 (m, 7 H), 7.60 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 46.0 (CH_2), 46.3 (CH_2), 61.3 (CH_2), 68.3 (CH_2), 69.3 (CH), 70.5 (CH), 73.2 (CH_2), 127.5 (CH), 128.2 (CH), 129.6 (CH), 132.1 (CH), 136.4 (C), 143.8 (C) ppm. APCI-MS: m/z = 392 $[M + H]^+$. IR (neat): $\tilde{\nu}$ = 3435, 3063, 3031, 1598, 1495, 1343, 1308, 1168, 1114, 1091 cm^{-1}. $C_{20}H_{25}NO_5S$ (391.5): calcd. C 61.36, H 6.44, N 3.58; found C 61.41, H 6.46, N 3.57.

(*R*,*R*)-2,6-Bis(hydroxymethyl)-4-tosylmorpholine (14): Morpholine (*R*,*R*)-**4b** (100 mg, 0.255 mmol) was dissolved in EtOH (5 mL), 10% Pd/C (27 mg) was added and the mixture was subjected to hydrogenation under atmospheric pressure after three vacuum/H_2 cycles to remove air from the reaction vessel. After 1 h, the mixture was filtered through a pad of Celite and the filtrate evaporated. The residue was purified by flash chromatography by using AcOEt/PE (3:1). Yield: 67 mg (87%), white solid, m.p. 103.5–106.5. $[\alpha]_D^{25}$ –10.9 (c = 1.06, $CHCl_3$). HPLC (Chiralcel AD, *i*PrOH/hexane, 20:80): t_R (*R*,*R*) = 19.3 min, t_R (*S*,*S*) = 16.0 min, t_R (*meso*) = 12.0 min, *ee* 99%, *de* 96%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.90 (dd, J = 5.8, 11.5 Hz, 2 H), 3.01 (dd, J = 3.4, 11.5 Hz, 2 H), 3.71 (dd, J = 5.0, 11.6 Hz, 1 H), 3.79 (dd, J = 6.5, 11.6 Hz, 1 H), 3.90–4.00 (m, 2 H), 7.34 (d, J = 8.2 Hz, 2 H), 7.60 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 46.1 (CH_2), 61.4 (CH_2), 70.8 (CH), 127.8 (CH), 129.9 (CH), 131.9 (C), 144.2 (C) ppm. APCI-MS: m/z = 302 $[M + H]^+$. IR (nujol): $\tilde{\nu}$ = 3388, 3068, 3037, 1743, 1599, 1342, 1162, 1054 cm^{-1}. $C_{13}H_{19}NO_5S$ (301.4): calcd. C 51.81, H 6.35, N 4.65; found C 51.91, H 6.37, N 4.66.

***N*-[(*S*)-2,2-Dimethyl[1,3]dioxolan-4-ylmethyl]-*N*-[(*R*)-2-oxiranylmethyl]-4-methylbenzenesulfonamide (18):** PPh_3 (176 mg, 0.67 mmol) and di-*tert*-butylazodicarboxylate (154 mg, 0.67 mmol) were added to a stirred solution of **11c** (162 mg, 0.45 mmol) in toluene (4 mL). After stirring at 90 °C for 24 h, the solvent was removed, and the residue was purified by flash chromatography (AcOEt/PE, 1:2). Yield: 128 mg (83%), colourless oil. $[\alpha]_D^{25}$ –1.3 (c = 1, $CHCl_3$). HPLC (Chiralpak IB, EtOH/hexane, 5:95, flow 0.6 mL min^{-1}): t_R (*S*,*R*) 21.6, t_R (*S*,*S*) 20.3 min, *de* 95%.[7] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 3 H), 1.38 (s, 3 H), 2.41 (s, 3 H), 2.55 (dd, J = 2.6, 4.8 Hz, 1 H), 2.78 (t, J = 4.4 Hz, 1 H), 2.99 (dd, J = 14.9, 6.3 Hz, 1 H), 3.07–3.15 (m, 2 H), 3.52 (dd, J = 14.4, 5.5 Hz, 1 H), 3.67 (dd, J = 14.9, 3.7 Hz, 1 H), 3.78 (dd, J = 8.5, 6.3 Hz, 1 H), 4.09 (dd, J = 8.5, 6.2 Hz, 1 H), 4.34 (m, 1 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.70 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 25.3 (CH_3), 26.8 (CH_3), 45.7 (CH_2), 50.4 (CH), 51.7 (CH_2), 52.0 (CH_2), 67.5 (CH_2), 74.7 (CH), 109.6 (C), 127.2 (CH), 129.8 (CH), 136.2 (C), 143.7 (C) ppm. ESI-MS: m/z = 365 $[M + Na]^+$. IR (neat): $\tilde{\nu}$ = 3062, 2985, 2933, 2879, 1597, 1452, 1371, 1342, 1253, 1213, 1160, 1090, 1068, 1020 cm^{-1}. $C_{16}H_{23}NO_5S$ (341.4): calcd. C 56.29, H 6.79, N 4.10; found C 56.15, H 6.77, N 4.11.

(*S*,*S*)-2,6-Bis(hydroxymethyl)-4-tosylmorpholine (14): CSA (11 mg, 0.043 mmol) was added to a stirred solution of **18** (109 mg, 0.432 mmol) in CH_2Cl_2 (6 mL). After 22 h at room temp., the solvent was removed, and the residue was purified by flash chromatography (AcOEt/PE, 1:3). Yield: 90 mg (69%), white solid, m.p. 102–104 °C. $[\alpha]_D^{25}$ = +11.7 (c = 1, $CHCl_3$). HPLC (Chiralcel AD, *i*PrOH/hexane, 20:80): t_R (*S*,*S*) = 16.0 min, t_R (*meso*) = 12.0 min, t_R (*R*,*R*) = 19.4 min, *ee* 99%, *de* 96%. ^{1}H- and ^{13}C NMR spectroscopic data were identical to that of (*R*,*R*)-**14**.

(*R*,*R*)-2,6-Bis(benzyloxymethyl)-4-tosylmorpholine (15): In a two-necked flask under a nitrogen atmosphere, NaH (60% mineral oil, 8 mg, 0.33 mmol) was added at 0 °C to a stirred solution of (*R*,*R*)-**4b** (102 mg, 0.26 mmol) in anhydrous THF (1 mL). After 30 min, benzyl bromide (37 μL, 0.31 mmol) was added and the temperature was allowed to increase to 25 °C. After 5 h, excess NaH was quenched by the careful addition of water, and dichloromethane was added. The organic phase was washed with satd. NH_4Cl and water. The resulting organic solution was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (AcOEt/PE, 1:3). Yield: 93 mg (74%), white solid, m.p. 76–79 °C. $[\alpha]_D^{25}$ = +19.6 (c = 0.8, $CHCl_3$). HPLC (Chiralpak AD, *i*PrOH/hexane, 20:80): t_R (*meso*) = 14.0 min, t_R (*S*,*S*) = 16.1 min, t_R (*R*,*R*) = 23.2 min, *ee* 96%, *de* 96%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.92 (dd, J = 12.0, 6.0 Hz, 2 H), 3.04 (dd, J = 12.0, 11.4 Hz, 2 H), 3, 60 (m, 4 H), 3.99 (m, 2 H), 4.53 (dd, J = 14.2, 12.1 Hz, 2 H), 7.28–7.35 (m, 7 H), 7.61 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 46.7 (2 CH_2), 68.8 (CH_2), 69.7 (CH_2), 73.5 (CH), 127.7 (CH), 127.9 (CH), 128.4 (CH), 129.7 (CH), 132.1 (C), 137.8 (C), 143.9 (C) ppm. APCI-MS: m/z = 482 $[M + H]^+$. IR (neat): $\tilde{\nu}$ = 3435, 3063, 3031, 1598, 1495, 1343, 1308, 1168, 1114, 1091 cm^{-1}. $C_{27}H_{31}NO_5S$ (481.6): calcd. C 67.34, H 6.49, N 2.91; found C 67.57, H 6.50, N 2.92.

(*R*,*R*)-2,6-Bis(benzyloxymethyl)morpholine (16): In a two-necked flask under a nitrogen atmosphere, Na (138 mg, 6.0 mmol) was added at room temperature to a stirred solution of naphthalene (769 mg, 6 mmol) in DME (8 mL). The freshly prepared sodium naphthalenide solution (0.81 mL, 0.61 mmol) was added to a stirred solution of (*R*,*R*)-**15** (101 mg, 0.21 mmol) in DME (5 mL) under a nitrogen atmosphere at –78 °C. After stirring for 1 h at –78 °C, the reaction mixture was quenched with water, the temperature was allowed to rise to 25 °C and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2/PE, 95:5). Yield: 62 mg (90%), colourless oil. $[\alpha]_D^{25}$ = +5.6 (c = 1.2, $CHCl_3$). HPLC (Chiralcel OJ-H, *i*PrOH/hexane, 20:80, 220 nm): t_R (*R*,*R*) = 20.3 min, t_R (*S*,*S*) = 23.0 min, t_R (*meso*) = 23.6 min, *ee* 99%, *de* 96%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (br. s, 1 H), 2.18 (br. s, 1 H), 2.87 (dd, J = 5.9, 12.5 Hz, 2 H), 3.03 (dd, J = 3.7, 12.5 Hz, 2 H), 3.62 (m, 4 H), 3.94–4.01 (m, 2 H), 4.55 (s, 4 H), 7.28–7.33 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.2 (2 CH_2), 69.7 (CH), 70.6 (CH_2), 73.5 (CH_2), 127.7 (CH), 127.8 (CH), 128.4 (CH), 137.8 (C) ppm. APCI-MS: m/z = 328 $[M + H]^+$. IR (neat): $\tilde{\nu}$ = 3346, 3085, 3061, 3028, 1495, 1366, 1207, 1099 cm^{-1}. $C_{20}H_{25}NO_3$ (327.4): calcd. C 73.37, H 7.70, N 4.28; found C 73.56, H 7.72, N 4.26.

(*R*,*R*)-2,6-Bis(hydroxymethyl)morpholine (17): In a two-necked flask, ammonia (10 mL) was condensed at –78 °C and Na (120 mg, 5.2 mmol) was added. A solution of (*R*,*R*)-**4b** (340 mg, 0.87 mmol) in THF (3 mL) was added, and the reaction was heated at reflux for 45 min. Ammonia was evaporated under a nitrogen atmosphere, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (MeOH/CH_2Cl_2, 80:20). Yield: 106 mg (83%), colourless oil. $[\alpha]_D^{25}$ –24.3 (c = 1, H_2O). HPLC (Chiralcel OJ-H, *i*PrOH/hexane, 7:93, 210 nm): t_R (*R*,*R*) = 42.7 min, t_R (*S*,*S* + *meso*) = 36.1, 38.4, *ee* 99%, *de* 99%. ^{1}H NMR (300 MHz, CD_3OD): δ = 2.71 (dd, J = 12.8, 5.6 Hz, 2 H), 2.90 (dd, J = 3.5, 12.8 Hz, 2 H), 3.58 (dd, J = 4.3, 10.7 Hz, 2 H), 3.71–3.82 (m, 4 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 47.6 (CH_2), 63.8 (CH_2), 73.5 (CH) ppm. APCI-MS: m/z = 148 $[M + H]^+$. IR (neat): $\tilde{\nu}$ = 3250, 2921, 1111, 1037, 936 cm^{-1}. $C_6H_{13}NO_3$ (147.2): calcd. C 48.97, H 8.90, N 9.52; found C 48.81, H 8.93, N 9.48.

Supporting Information (see footnote on the first page of this article): Experimental procedures and full characterization of new

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

compounds towards an unambiguous synthesis of **13a** along with copies of ^{1}H and ^{13}C NMR spectra.

Acknowledgments

Financial support from MIUR (Nuovi metodi catalitici stereoselettivi e sintesi stereoselettiva di molecole funzionali) and CNR is gratefully acknowledged.

[1] For recent examples, see: a) B. A. Lanman, A. G. Myers, *Org. Lett.* **2004**, *6*, 1045–1047; b) K. Audouze, Ø. E. Nielsen, D. Peters, *J. Med. Chem.* **2004**, *47*, 3089–3104; c) R. Wijtmans, M. K. S. Vink, H. E. Schoemaker, F. L. van Delft, R. H. Blaauw, F. P. J. T. Rutjes, *Synthesis* **2004**, 641–662.

[2] a) D. Enders, O. Meyer, G. Raabe, J. Runsink, *Synthesis* **1993**, 66–72; b) C. Baldoli, P. Del Buttero, E. Licandro, S. Maiorana, A. Papagni, A. Zanotti Gerosa, *J. Organomet. Chem.* **1995**, *486*, 279–282; c) E. Licandro, S. Maiorana, L. Capella, R. Manzotti, A. Papagni, M. Pryce, C. Graiff, A. Tiripicchio, *Eur. J. Org. Chem.* **1998**, 2127–2133; d) R. Dave, N. A. Sasaki, *Org. Lett.* **2004**, *6*, 15–18.

[3] a) Y. Uozumi, A. Tanahashi, T. Hayashi, *J. Org. Chem.* **1993**, *58*, 6826–6832; b) A. Yamazaki, K. Achiwa, *Tetrahedron: Asymmetry* **1995**, *6*, 1021–1024; c) K. Ito, Y. Imahayashi, T. Kuroda, S. Eno, B. Saito, T. Katsuki, *Tetrahedron Lett.* **2004**, *45*, 7277–7281; d) M. Massacret, R. Lakhmiri, P. Lhoste, C. Nguefack, F. B. B. Abdelouahab, R. Fadel, D. Sinou, *Tetrahedron: Asymmetry* **2000**, *11*, 3561–3568; e) M. C. Wilkinson, *Tetrahedron Lett.* **2005**, *46*, 4773–4775.

[4] H. Nakano, J.-i. Yokoyama, R. Fujita, H. Hongo, *Tetrahedron Lett.* **2002**, *43*, 7761–7764.

[5] E. Bouron, G. Goussard, C. Marchand, M. Bonin, X. Pannecoucke, J.-C. Quirion, H.-P. Husson, *Tetrahedron Lett.* **1999**, *40*, 7227–7230.

[6] V. Lupi, D. Albanese, D. Landini, D. Scaletti, M. Penso, *Tetrahedron* **2004**, *60*, 11709–11718.

[7] This work will be published elsewhere.

[8] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.

[9] F. S. Gibson, M. Sook Park, H. Rapoport, *J. Org. Chem.* **1994**, *59*, 7503–7507.

[10] When stoichiometric amounts of **2** were used, 39% of **10** was isolated along with 48% of **9**.

[11] D. Albanese, D. Landini, M. Penso, *Chem. Commun.* **1999**, 2095–2096.

[12] The synthesis of **13a** is fully described in the Supporting Information.

[13] R. E. Parker, N. S. Isaacs, *Chem. Rev.* **1959**, *59*, 737–799.

[14] a) K. C. Nicolaou, C. V. C. Prasad, P. K. Somers, C.-K. Hwang, *J. Am. Chem. Soc.* **1989**, *111*, 5330–5334; b) K. C. Nicolaou, C. V. C. Prasad, P. K. Somers, C.-K. Hwang, *J. Am. Chem. Soc.* **1989**, *111*, 5335–5340.

[15] The same results were obtained by using anhydrous (±)-CSA.

[16] B. Tse, *J. Am. Chem. Soc.* **1996**, *118*, 7094–7100.

[17] V. Waagen, I. Hollingster, V. Partali, O. Thorstad, T. Anthonsen, *Tetrahedron: Asymmetry* **1993**, *4*, 2265–2274.

[18] See ref.[16] Compound (*R*)-**1b** is also commercially available.

Received: January 5, 2007
Published Online: March 13, 2007

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim