Catalysis Today 140 (2009) 100–104

Contents lists available at ScienceDirect

Catalysis Today

journal homepage: www.elsevier.com/locate/cattod

# A practical approach to the synthesis of enantiomerically pure 2,6-disubstituted morpholines under phase transfer catalysis conditions☆

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ARTICLE INFO

*Article history:*
Available online 11 September 2008

*Keywords:*
Phase transfer catalysis
Cyclization
Sulfonamides
Morpholines

ABSTRACT

A novel, straightforward and high yielding synthesis of enantiomerically pure 2,6-disubstituted morpholines has been developed through the regioselective cyclization of diols. Cyclization precursors have been obtained by the ring opening of commercially available chiral epoxides under solid–liquid phase transfer catalysis conditions (SL-PTC).



## 1. Introduction

Substituted morpholines have aroused great interest due to the presence of this skeleton in therapeutically and biologically active compounds [1]. 2,6-Disubstituted morpholines are also used as active ingredient in agricultural formulations for the control of disease in cereal crops [2]. Enantiomerically enriched 2-vinyl morpholines have been generated in moderate to good ees by palladium catalyzed tandem allylic substitution [3]. However, excellent ees have only been obtained by using a xylofuranose-based phosphinooxazinane as ligand [4]. Optically pure 2,6-disubstituted morpholines could also be prepared by diastereoselective alkylation of 6-substituted 3-oxo morpholines, followed by reduction of the carbonyl moiety and removal of the chiral auxiliary [5]. Moreover, $C_2$ symmetric morpholines have been used as chiral auxiliaries [6].

We recently designed a new straightforward method for the synthesis of enantiomerically pure 2,6-disubstituted morpholines **7** through assembling in a stereoselective fashion a left hand, epoxide-derived portion, with a right hand, solketal-derived portion [7]. The acid catalyzed cyclization of the epoxy alcohol **6** or epoxide **8** proceeds in a highly regioselective fashion and without racemization of the epoxide stereocenter, affording regioselectively the morpholine skeleton through a 6-*Exo-Tet* pathway (Scheme 1) [8]. The new approach is applicable to the synthesis of a variety of enantiopure 2,6-disubstituted morpholines. As a matter of fact, the 2-hydroxymethyl substituent is amenable of further functionalizations, whereas the substituent in position 6 can be chosen by selecting the opportune epoxide, readily available in an enantiopure form.

Here we report two new pathways to enantiopure morpholines avoiding limitations related to the synthesis of the solketal-derived sulfonamide **2** and sulfonate ester **5**, precursor of the *in situ* generated epoxide **6**.

The sulfonamide **2** has previously been generated through nucleophilic displacement of the mesylate **9** under solid–liquid phase transfer catalysis conditions (SL-PTC) with excess tosyl amide (5 equiv.) in order to limit the amount of undesired *bis*-alkylation product **12** (Scheme 2). Although excess reagent can be recovered by crystallization, alternatives protocols were desirable.

We found that sulfonamide **2** can be efficiently generated through nucleophilic displacement of mesylate **9** with $NaN_3$ under liquid–liquid (LL) PTC conditions without organic solvent. The reaction has been carried out by heating a heterogeneous mixture of **9** and saturated aqueous $NaN_3$ solution in the presence of catalytic amounts of $Et_3BnN^+Cl^-$ (TEBA) as a PT catalyst (Scheme 2).

High yields of azide **10** have been obtained without using toxic, anhydrous dipolar aprotic solvents such as DMF and DMSO, which have been previously employed for the same reaction and usually require a tedious work-up for product recovery [9]. Under LL-PTC conditions the azide **10** has been recovered from the reaction mixture by organic layer separation and was subsequently reduced

☆ Dedicated to Prof. Dario Landini on occasion of his 70th birthday.

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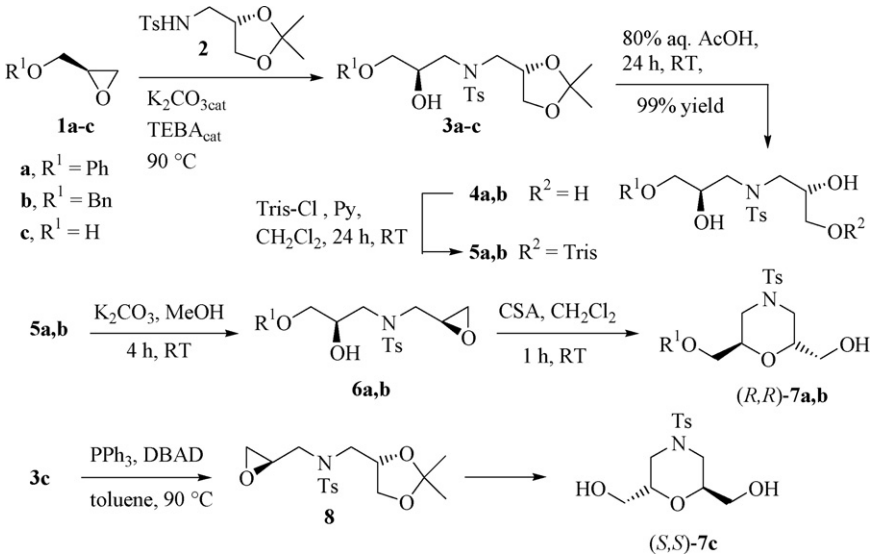
doi:10.1016/j.cattod.2008.07.005



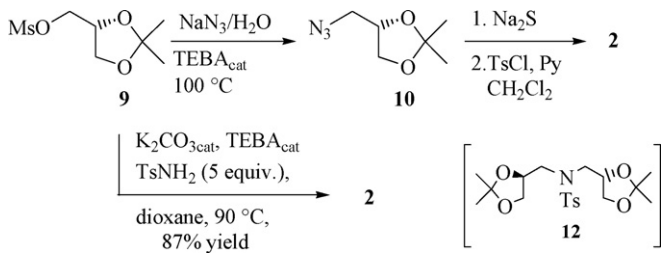

**Scheme 1.**

with aqueous $Na_2S$. The amine thus obtained was converted into the required sulfonamide **2** by standard *N*-tosylation. The whole procedure employs a low amount of organic solvent, providing high overall yield of sulfonamide **2**.

We also found that the morpholine skeleton could be more efficiently built up by converting the hydroxy group of **3b** into a good leaving group before 1,2-diol deprotection (Scheme 3).

Thus, **3b** was treated with methanesulfonyl chloride and $Et_3N$ at room temperature affording mesylate **13b** which was converted into diol **14b** in 90% overall yield by treating with 80% acetic acid. The cyclization of diol **14b** could in principle generate the desired morpholine (*S*,*S*)-**7b** along with the seven membered [1,4]-oxazepan-6-ol **15b** ring. However, cyclization is driven by substrate bias to regioselectively generate the desired morpholine (*S*,*S*)-**7b**. Indeed, 95% yield of enantiomerically pure (*S*,*S*)-**7b** was isolated when **14b** had been treated with stoichiometric amounts of NaH in THF at RT (Scheme 3). It is worth noting that morpholine (*S*,*S*)-**7b** could also been obtained in 90% yield by carrying out the cyclization in *tert*-butyl alcohol, using $K_2CO_3$ as mild and inexpensive base.

This new approach generates high yields of 2,6-disubstituted morpholines without any trace amount of the oxazepan-6-ol **15** by product. Moreover, unexpensive and nearly equimolar amount of mesyl chloride instead of excess 2,4,6-triisopropylbenzensulfonyl chloride (tris–Cl, 3 equiv.) have been used in order to insert the leaving group required for the next cyclization. Both enantiomeric morpholines can be obtained at will by choosing the proper epoxide enantiomer or from the same hydroxysulfonamide **3** by switching pathway since the cyclization, in this case, occurs through inversion of configuration of the carbon atom bearing the mesylate group.



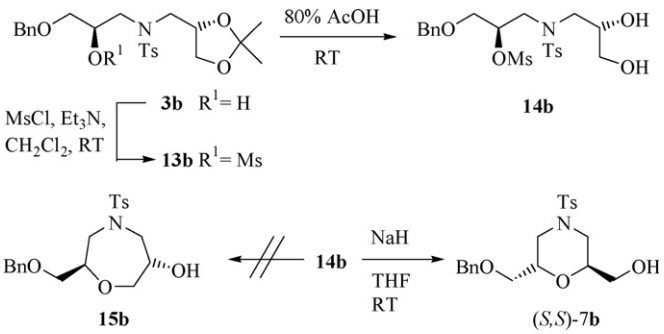

**Scheme 2.**

A complementary approach to enantiomerically pure 2,6-disubstituted morpholines has also been developed through the ring opening of chiral, nonracemic epoxides under SL-PTC conditions, followed by cyclization without protecting group chemistry.

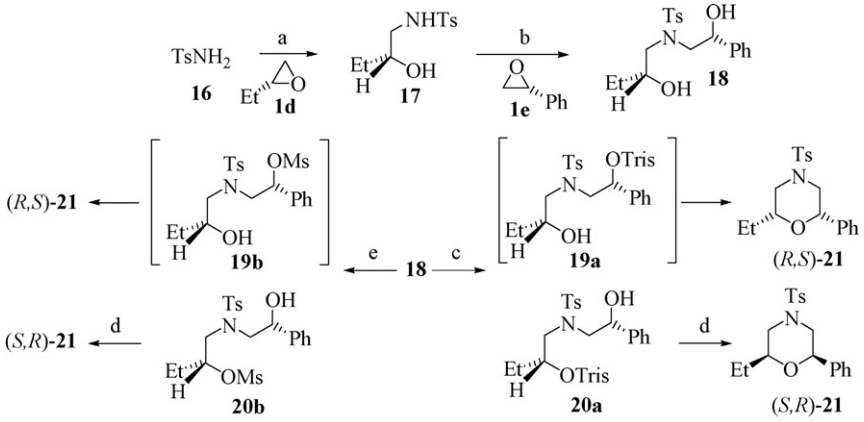
The ring opening reaction of (*R*)-epoxybutane (**1d**) with tosylamide (**16**), followed by the ring opening of (*R*)-epoxystyrene (**1e**) with the hydroxysulfonamide **17** thus obtained, generated the unsymmetrically substituted diol **18** in good yield. Both steps have been carried out under SL-PTC conditions in the presence of catalytic amounts of solid, anhydrous caesium carbonate as base and TEBA as PT catalyst (Scheme 4).

The diol **18** was converted into the corresponding oxy-dianion with sodium hydride at 0 °C and subsequently treated with tris–Cl at −78 °C. Under such reaction conditions a mixture of enantiopure sulfonate ester **20a** (72% yield) and morpholine (*R*,*S*)-**21** (21% yield) has been obtained. Morpholine (*R*,*S*)-**21** derives from cyclization of very reactive benzylic sulfonate ester **19a**. The preferential formation of sulfonate ester **20a** is likely due to the steric hindrance of the tris substituent. The sulfonyl ester **20a** could be ring closed to enantiopure morpholine (*S*,*R*)-**21** by further treating with NaH at room temperature.

The steric hindrance of the 2,4,6-triisopropylbenzensulfonyl moiety was optimal in order to prevent *in situ* cyclization of **20a** causing erosion of ee of the morpholine **21**. In fact, when sterically unhindered methanesulfonyl chloride was used, 50% of sulfonate ester **20b** has been isolated along with 29% of morpholine (*R*,*S*)-**21**




**Scheme 3.**




a) **16** (2.5 mol), **1d** (1 mol), $Cs_2CO_3$ (0.1 mol), TEBA (0.1 mol), dioxane, 55 °C, 3 d, **17** (77%); b) **17** (2 mol), **1e** (1 mol), $Cs_2CO_3$ (0.1 mol), TEBA (0.1 mol), dioxane, 80 °C, 24 h, **18** (76%); c) **18** (1 mol), Tris-Cl (1 mol), NaH (3 mol), THF, -78 °C, 75 min, **20a** (72%, ee 99%), (*R,S*)-**21** (21%, ee 95%); d) NaH (1.5 mol), THF, 0 – 25 °C, 5 h (*S,R*)-**21** (86%, ee 99%); e) **18** (1 mol), MsCl (1 mol), NaH (3 mol), THF, -78 °C, 4 h, **20b** (50%), (*R,S*)-**21** (29%, ee 65%).

**Scheme 4.**

(65% ee) deriving from cyclization of reactive sulfonate ester **19b** and partial *in situ* cyclization of sulfonyl ester **20b**.

In summary, we developed new straightforward methods for the synthesis of enantiomerically pure 2,6-disubstituted morpholines through cyclization of diol **14**. Moreover, an efficient and high yielding synthesis of sulfonamide **2** has been carried out through the nucleophilic displacement of mesylate **9** with aqueous $NaN_3$ without organic solvent under LL-PTC conditions, followed by standard high yielding transformations. A complementary approach to enantiopure 2,6 disubstituted morpholines has also been achieved through regioselective functionalization of diol **18** with tris–Cl.

## 2. Experimental section

### 2.1. General remarks

Melting points were determined on a BÜCHI 535 and are corrected. Infrared (IR) spectra were recorded on a PerkinElmer 1725 X FT-IR spectrometer. NMR spectra were recorded on a Bruker AC 300 or AC 200 spectrometers, operating at 300.13 or 200.13 MHz for $^1$H NMR and 75.3 or 50 MHz for $^{13}$C NMR. Coupling constants *J* are in Hz. Chemical shifts were reported by using $CHCl_3$ as external standards (7.24 ppm for $^1$H NMR and 77.0 for $^{13}$C NMR). APT experiments were used in the assignment of carbon spectra. Optical rotations were measured with a PerkinElmer 241 polarimeter; the $[\alpha]_D$ values are reported in $10^{-1}$ deg cm$^{-2}$ g$^{-1}$, concentration (*c*) is reported in g per 100 mL. Mass spectra (ESI and APCI) were measured on 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 a Agilent HP 1100 apparatus, equipped with a diode array detector, using mixtures of hexane/2-propanol as eluent, detection at 230 nm unless otherwise stated. The flux was set to 1 mL min$^{-1}$ unless otherwise stated and the volume of injection was 20 μL. Petroleum ether (PE) refers to the fraction boiling in the range of 40–60 °C.

**1-Azido-2,3-propanediol isopropylidene ketal (10)**. In a round bottom flask an heterogeneous mixture of mesylate **9** (40 mmol, 8.42 g), 4.5 M aqueous $NaN_3$ solution (40 mmol, 9 mL) and $Et_3BnN^+Cl^-$ (4 mmol, 912 mg) was stirred at reflux for 8 h. The organic phase was separated affording the title compound 5.78 g, 92%, which was converted to amine **11** without further purification. $^1$H NMR ($CDCl_3$, 300 MHz) δ, 4.28 (m, 1H), 4.06 (dd, 1H, *J* = 4.6 and 8.4), 3.78 (dd, 1H, *J* = 4.6 and 8.4), 3.37 (dd, 1H, *J* = 4.6 and 12.6), 3.34 (dd, 1H, *J* = 4.6 and 12.6), 1.47 (s, 3H), 1.37 (s, 3H).

**Sulfonamide 2**. Azide **10** (2.83 g, 18 mmol) was dissolved in MeOH (4 mL), and the resulting solution added to an aqueous solution of $Na_2S{\cdot}9H_2O$ (5.52 g, 23 mmol, in 9 mL of $H_2O$). After stirring at 55 °C for 24 h the homogeneous solution was saturated with NaCl and extracted with AcOEt (5 × 15 mL). The organic solution was dried ($Na_2SO_4$), filtered, concentrated *in vacuo* to give 1.94 g of 1-amino-2,3-propanediol isopropylidene ketal (**11**) yield 82%, which was used without further purification. $^1$H NMR ($CDCl_3$, 200 MHz) δ, 4.11 (m, 1H), 4.04 (dd, 1H, *J* = 7.8 and 6.4), 3.66 (dd, 1H, *J* = 7.8 and 6.4), 2.82 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H).

The amine **11** (1.94 g, 14.8 mmol) was dissolved in $CH_2Cl_2$ (10 mL) and $Et_3N$ (2.5 mL, 17.8 mmol) was added. After cooling to 0 °C, tosyl chloride (3.43 g, 18 mmol) was added and the temperature was allowed to warm to 25 °C. After 18 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] to give 3.97 g of **2**, yield 94%, white solid, mp 91–92 °C, $[\alpha]_D^{25}$ 10.4 (*c* 1, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): δ, 1.28 (s, 3H), 1.33 (s, 3H), 2.41 (s, 3H), 2.92 (m, 1H), 3.12 (ddd, 1H, *J* = 14.3, 7.8 and 4.6), 3.66 (dd, 1H, *J* = 8.5 and 5.9), 3.98 (dd, 1H, *J* = 8.5 and 6.4), 4.15 (m, 1H), 4.78 (t, 1H, *J* = 6.1), 7.29 (d, 2H, *J* = 8.3), 7.71 (d, 2H, *J* = 8.3).

**Mesylate 13b**. In a round bottom flask **3b** (5.49 g, 12.2 mmol) was dissolved in $CH_2Cl_2$ (10 mL) and $Et_3N$ (2.1 mL, 14.7 mmol) was added. After cooling to 0 °C, methanesulfonyl chloride (1.1 mL, 14.2 mmol) was added drop-wise (20 min) and the temperature was allowed to warm to 25 °C. After 20 h the reaction mixture was made acidic with 10% aq. HCl. The organic solution was dried ($Na_2SO_4$), filtered, concentrated *in vacuo* to give 2.98 g of **13b**, yield 94%, $^1$H NMR (200 MHz, $CDCl_3$): δ = 7.67 (d, 2H, *J* = 8.4), 7.33–7.29 (m, 7H), 5.20 (m, 1H), 4.58 (m, 2H), 4.29 (m, 1H), 4.00 (m, 1H), 3.78–3.41 (m, 3H), 3.27–2.86 (m, 5H), 2.43 (s, 3H), 1.39 (s, 3H), 1.30 (s, 3H).

**Diol 14b**. Mesylate **13b** (2.98 g, mmol) was dissolved in 80% aq. $CH_3COOH$ (15 mL) and stirred at 25 °C for 24 h. After concentration *in vacuo* the residue was dissolved in AcOEt and washed with

$NaHCO_{3\ sat}$. The organic solution was dried ($Na_2SO_4$), filtered, concentrated and purified by flash column chromatography [AcOEt–PE 1:1] to give to give 2.72 g of **14b**, yield 99%, as a white solid, mp 101.2 °C, $[\alpha]_D^{25}$ 9.1 (*c* 1.0, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$, 7.68 (d, 2H, *J* = 8.4), 7.35–7.25 (m, 7H), 5.12 (m, 1H), 4.57 (s, 2 H), 3.92 (m, 1H), 3.86 (dd, 1 H, *J* = 11.4 and 3.5), 3.77 (dd, 1 H, *J* = 11.1 and 5.1), 3.65 (dd, 1 H, *J* = 11.4 and 3.9), 3.51 (dd, 1 H, *J* = 11.4 and 5.1), 3.45 (dd, 1 H, *J* = 13.5 and 4.5), 3.36 (dd, 1 H, *J* = 14.7 and 6.3), 3.20 (dd, 1 H, *J* = 14.9 and 4.2), 3.10 (dd, 1 H, *J* = 14.9 and 7.5), 3.04 (s, 3H), 2.43 (s, 3H), 2.20 (bs, 1H).

$^{13}$C NMR 300 MHz ($CDCl_3$) $\delta$, 144.3 (C), 137.2 (C), 134.2 (C), 130.0 (2 CH), 128.5 (CH), 128.0 (CH), 127.9 (CH), 79.7 (CH), 73.6 ($CH_2$), 70.5 (CH), 69.5 ($CH_2$), 63.9 ($CH_2$), 53.9 ($CH_2$), 51.9 ($CH_2$), 38.4 ($CH_3$), 21.5 ($CH_3$).

### 2.2. (2S,6S)-N-tosyl-2-hydroxymethyl-6-benzyloxymethyl-morpholine (7b)

In a flame-dried round flask under Ar, the solution of diol **13b** (488 mg, 1 mmol) in anhydrous THF (3 ml) was added drop-wise (10 min) to 60% NaH (60 mg, 1.5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C until hydrogen evolution was not longer detectable (30 min), After 5 h the reaction was quenched by addition of saturated $NH_4Cl$ solution. The crude was diluted with $CH_2Cl_2$ and filtered through a celite pad. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (AcOEt–hexane, 1:1) to give 372 mg of **7b**, yield 95% as a colourless syrup, $[\alpha]_D^{25}$ 3.50 (*c* 1.1, $CHCl_3$). HPLC (Chiralpak AD, *i*PrOH–hexane 20–80) $t_R$ (*2R,6R*) 19.9 min, $t_R$ (*2S,6S*) 15.9 min, $t_R$ (*2R,6S + 2S,6R*) 11.8, 15.6 min; ee 99%. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.43 (s, 3H), 2.74 (dd, 1H, *J* = 11.5, 7.2), 2.89 (dd, 1H, *J* = 11.5, 3.6), 3.09–3.20 (m, 2H), 3.60–3.68 (m, 4H), 3.85 (m, 1H), 4.04 (m, 1H), 4.54 (AB q, 2H, *J* = 12.0), 7.25–7.33 (m, 7H), 7.60 (d, 2H, *J* = 8.2). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 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). APCI-MS *m*/*z* 392 $[M+H]^+$.

### 2.3. Synthesis of hydroxysulfonamide 17

In a dry screw cap vial, a solution of (*R*)-1,2-epoxybutane (**1d**) (1.44 g, 20 mmol) in dioxane (5 mL) was added at 25 °C to a heterogeneous mixture of tosylamide (8.56 g, 50 mmol), TEBA (0.46 g, 2 mmol) and anhydrous caesium carbonate (0.65 g, 2 mmol) in anhydrous dioxane (10 mL). The reaction mixture was stirred at 85 °C for 3 d, the crude was diluted with $CH_2Cl_2$ and filtered through a celite pad. The solvent was distilled under vacuum and the residue was purified by flash chromatography (AcOEt–hexane, 1:1) to give 3.76 g of **17**, yield 77%, as a white solid, mp 75.4–76.7 °C, $[\alpha]_D^{20}$ 24.4 (*c* 1, $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$, 7.74 (d, 2H, *J* = 8.3), 7.31 (d, 2H, J = 8.3), 4.82 (t, 1H, *J* = 0.9), 3.61 (m, 1H), 3.08 (m, 1H), 2.78 (m, 1H), 2.42 (s, 3H), 1.90 (d, 1H, *J* = 4.5), 1.56–1.41 (m, 2H), 0.90 (t, 3H, *J* = 7.5). $^{13}$C NMR ($CDCl_3$, 300 MHz) $\delta$, 143.9 (C), 137.1 (C), 130.2 (CH), 127.5 (CH), 72.2 (CH), 48.8 ($CH_2$), 56.6 ($CH_2$), 27.9 ($CH_2$), 21.9 ($CH_3$), 10.2 ($CH_3$).

### 2.4. Synthesis of diol 18

In a screw cap vial, a solution of (*R*)-epoxystyrene (**1e**) (180 mg, 1.5 mmol) in dioxane (0.5 mL) was added to a heterogeneous mixture of amido alcohol **17** (730 mg, 3 mmol), tetrabutylammonium bromide (48 mg, 0.15 mmol) and anhydrous caesium carbonate (49 mg, 0.15 mmol) in anhydrous dioxane (1.5 mL). The reaction mixture was stirred at 80 °C for 20 h (TLC analysis; AcOEt–hexane, 1:1), then the crude was diluted with $CH_2Cl_2$ and filtered through a celite pad. The solvent was distilled under vacuum and the residue was purified by flash chromatography (AcOEt–hexane, 1:3) to give 482 mg of **18**, yield 88%, as a white solid, mp 116–117 °C, $[\alpha]_D^{20}$ 72.6 (*c* 1, $CHCl_3$). $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$, 7.69 (d, 2H, *J* = 8.2 Hz), 7.38–7.26 (m, 7H), 5.14 (dd, 1 H, *J* = 8.3, 4.6), 3.87 (m, 1H), 3.43 (bs, 1H), 3.25–3.13 (m, 3H), 2.98 (dd, 1H, *J* = 14.0 and 2.6), 2.41 (s, 3H), 1.60–1.45 (m, 3H), 1.00 (t, 3H, *J* = 7.3). $^{13}$C NMR ($CDCl_3$, 300 MHz) $\delta$, 144.2 (C), 141.8 (C), 135.4 (C), 130.2 (CH), 129.0 (CH), 128.3 (CH), 127.9 (CH), 126.4 (CH), 73.3 (CH), 71.6 (CH), 58.5 ($CH_2$), 56.6 ($CH_2$), 27.8 ($CH_2$), 21.9 ($CH_3$), 10.4 ($CH_3$).

### 2.5. Reaction of diol 18 with tris–chloride

In a flame-dried round flask under Ar, the solution of diol **18** (364 mg, 1 mmol) in anhydrous THF (3 mL) was added drop-wise (30 min) by syringe to 50% NaH (144 mg, 3 mmol) at 0 °C. The reaction mixture was stirred at 0 °C until hydrogen evolution was not longer detectable (30 min), then it was cooled to −80 °C and a solution of tris–chloride **5** (303 mg, 1 mmol) in THF (2 mL) was added drop-wise (30 min) by syringe. After 75 min, the reaction was quenched by addition of saturated $NH_4Cl$ solution. The crude was diluted with $CH_2Cl_2$ and filtered through a celite pad. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (AcOEt–hexane, 1:7–1:4) to give:

**Sulfonate ester 20**: clear oil (454 mg, 72%), $[\alpha]_D^{20}$ + 13.0 (*c* 1, $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$, 7.69 (d, 2H, *J* = 8.3), 7.36–7.25 (m, 9H), 4.97 (m, 1H), 4.88 (m, 1H), 4.16–4.07 (m, 2H), 3.59 (dd, 1H, *J* = 14 and 6.9), 3.42–3.27 (m, 2H), 3.12 (m, 1H), 2.90 (m, 1H), 2.41 (s, 3H), 1.80–1.55 (m, 3H), 1.27–1.16 (m, 18H), 0.82 (t, 3H, *J* = 7.4). $^{13}$C NMR ($CDCl_3$, 300 MHz) $\delta$, 153.7 (C), 150.3 (C), 144.0 (C), 141.3 (C), 135.2 (C), 129.9 (2 CH), 128.6 (2 CH), 127.9 (CH), 127.6 (CH), 125.9 (CH), 123.7 (CH), 81.5 (CH), 72.6 (CH), 58.6 ($CH_2$), 53.4 ($CH_2$), 34.2 (CH), 29.7 (CH), 25.0 ($CH_2$), 24.8 ($CH_3$), 24.5 ($CH_3$), 23.5 ($CH_3$), 21.5 ($CH_3$), 9.0 ($CH_3$).

**Morpholine (R,S)-21**: white solid (73 mg, 21%) mp 119–120 °C, $[\alpha]_D^{20}$ + 130.1 (*c* 1, $CHCl_3$). HPLC (CHIRALPAK AD, *i*-PrOH/hexane 95:5), 0.6 mL/min, $t_R$ (*S,R*)-**21** 14.3, $t_R$ (*R,S*)-**21** 15.3, ee 95%; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$, 7.65 (d, 2H, *J* = 10.0), 7.35 (d, 2H, *J* = 10.0), 7.38–7.29 (m, 5H), 4.67 (dd, 1H, *J* = 10.5 and 2.5), 3.82 (dd, 1H, *J* = 11 and 2.5), 3.74–3.68 (m, 2H), 2.45 (s, 3H), 2.81 (t, 1H, *J* = 11.0), 2.12 (t, 1H, *J* = 10.5), 1.66–1.53 (m, 2H), 1.02 (t, 3H, *J* = 7.5). $^{13}$C NMR ($CDCl_3$, 300 MHz) $\delta$, 143.2 (C), 138.4 (C), 131.7 (C), 129.1 (CH), 127.8 (CH), 127.4 (CH), 127.1 (CH), 125.3 (CH), 76.4 (CH), 76.1 (CH), 51.0 ($CH_2$), 48.9 ($CH_2$), 25.6 ($CH_2$), 20.8 ($CH_3$), 9.0 ($CH_3$).

### 2.6. Morpholine (S,R)-21

In a flame-dried round bottom flask under Ar, the solution of sulfonate ester **20** (630 mg, 1 mmol) in anhydrous THF (5 mL) was added drop-wise (30 min) to 50% NaH (96 mg, 2 mmol) at 0 °C. The heterogeneous mixture was stirred at 0 °C for 6 h (TLC, AcOEt–hexane, 1:4). After addition of saturated $NH_4Cl$ solution the crude was diluted with $CH_2Cl_2$ and filtered through a celite pad. The solvent was distilled under vacuum and the residue was purified by flash column chromatography (AcOEt–hexane, 1:5) to give 296 mg of morpholine (*S,R*)-**21**, white solid (83%); mp 119.5–120.2 °C, $[\alpha_D]^{20}$ 143.2 (*c* 1, $CHCl_3$). HPLC (CHIRALPAK AD, *i*-PrOH/hexane 95:5), 0.6 mL/min, $t_R$ (*S,R*)-**21** 14.3, $t_R$ (*R,S*)-**21** 15.3, ee > 99%. $^1$H and $^{13}$C NMR spectra are identical to those described above for morpholine (*R,S*)-**21**.

## Acknowledgments

Financial support from MIUR (Sintesi e Stereocontrollo di molecole organiche per lo sviluppo di metodologie innovative di

interesse applicativo, PRIN 2005) and CNR is gratefully acknowledged.

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