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Synthesis of novel C_2-symmetric ligands based on (*R*,*R*)- and (*S*,*S*)-diphenyl-1,3-propanediol

Gregory H. P. Roos [a,*] and A. Richard Donovan [b]

[a] *Chemistry Department, College of Science, Sultan Qaboos University, Box 36, Al-Khod, Sultanate of Oman 123*
[b] *Department of Chemistry, Division of Science, Murdoch University, Perth, Australia 6150*

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Abstract

A range of novel C_2-symmetric dioxygen and dinitrogen ligands can readily be obtained through the interconversion of the parent 1,3-diphenyl-1,3-propanediol enantiomers which are, in turn, accessed in good yields via a Sharpless asymmetric epoxidative resolution.

1. Introduction

C_2-Symmetric diols have long been employed in a wide range of key asymmetric transformations and generally operate through their modification of a variety of transition metals.[1,2] Since the majority of these ligands are derived from tartrate sources which can afford 1,2- and 1,4-diols, they lead to either 5- or 7-membered rings when chelated with a metal.[3,4] With few exceptions, there appears to be a significant lack of bidentate ligands that form 6-membered rings when chelated to metals. Such diols have shown promise as chiral derivatising agents and synthetic intermediates.[5–8] We herein report ready access to the enantiomerically pure enantiomeric (*R*,*R*)-(+)- and (*S*,*S*)-(−)-1,3-diphenyl-1,3-propanediols and a range of dinitrogen-containing C_2-symmetric bidentate ligands derived therefrom.[9]

An initial literature search surprisingly revealed that little had been reported on provision of facile entry to the parent diols. In fact, the absolute configuration of the (−)-enantiomer had only recently been assigned as (*S*,*S*).[10] This (*S*,*S*)-enantiomer was first prepared in low yield (20%) via asymmetric hydrogenation of the diketone over a modified Raney nickel catalyst.[11] Related preparations using binap[12] and bihemp[10] complexes of ruthenium have appeared more recently. Aside from these small-scale, moderate-yielding microbial (40%)[13] and formal synthetic (49%)[14] routes have been reported.

* Corresponding author.

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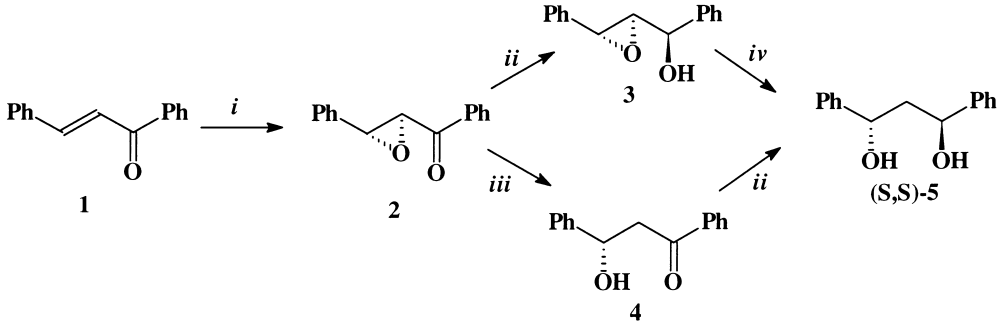
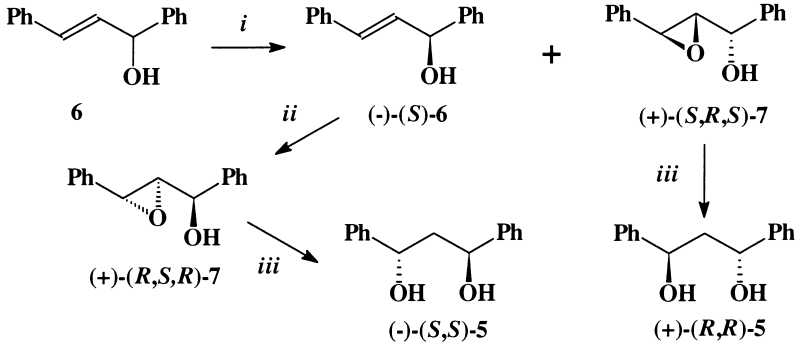
2. Discussion and results

An initial route to the parent diols sought to exploit the success (up to 93% ee) reported by Julia and co-workers in their asymmetric epoxidation of chalcone **1** under the influence of a poly-(*S*)-alanine catalyst to give epoxyketone **2**.[15] There was literature support for further conversion through either the epoxy-alcohol **3** (reduction[16]/hydride displacement[17]) or hydroxyketone **4** (hydride displacement[18]/reduction[16]) to the (*S*,*S*)-diol **5** as outlined in Scheme 1. Subsequent oxidation of chalcone **1**, both with commercial catalyst and material prepared by us, afforded epoxyketone **2** with enantiomeric excess of only 67–78%.[19]



Scheme 1. Reagents and conditions: (i) poly-(*S*)-alanine, H_2O_2; (ii) $ZnBH_4$; (iii) Red-Al®; (iv) Zn, NH_4Cl

Given the unsatisfactory nature of the above result, we therefore pursued an alternative route (Scheme 2) based on a Sharpless epoxidative kinetic resolution of hydroxyalkene **6**, available in high yield from commercial *trans*-chalcone **1** by borohydride reduction.[20] Optimisation of the reaction time to 3 h using standard Sharpless conditions (10 mol% of titanium isopropoxide, 12 mol% of L-(+)-DIPT and 70 mol% of TBHP at −20°C) and work up, gave (−)-(*S*)-3-hydroxy-1,3-diphenylpropene **6** in 42% yield (>99% ee) and (+)-(*S*,*R*,*S*)-epoxyalcohol **7** in 52% yield (89.6% ee).[21] Enantiomerically pure **7** could be obtained by a single recrystallisation from ether–light petroleum. The enantiomerically enriched (*S*)-hydroxyalkene was re-subjected to Sharpless conditions using D-(−)-DIPT to generate the alternative (*R*,*S*,*R*)-enantiomer in 68% yield.

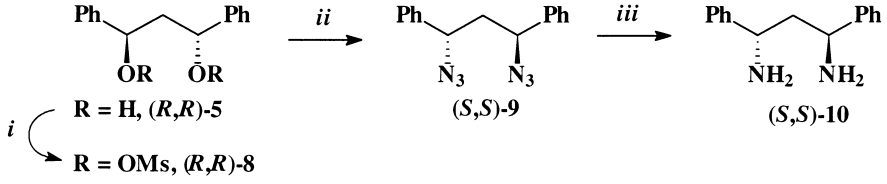


Scheme 2. Reagents and conditions: (i) L-(+)-DIPT, Ti(O-*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, −20°C, 3 h; (ii) D-(−)-DIPT, Ti(O-*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, −20°C, 3 h; (iii) Red-Al®, DME, 16 h

Epoxides **7** are activated at the C3 position by the presence of the phenyl group, the benzylic nature of this site making intermolecular C3 hydride attack more favourable than with non-activated substrates. Employing a reverse addition of Red-Al® and suitably modified work up, both the (*R*,*R*)- and (*S*,*S*)-diols **5** could be synthesised from the appropriate epoxide in 89% and 92% yield respectively.[22] There was no evidence of the alternative 1,2-diol (from C_2 hydride attack) or any of the stereoisomers of the 1,3-diol,

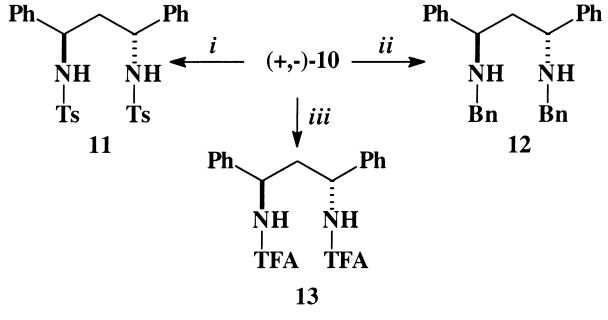
thus giving an overall combined yield of the diols **5** of 73% from the single chalcone-starting material. Enantiomeric and chemical purity were confirmed by both chiral HPLC and NMR (using the Eu[hfc]$_3$ shift reagent). As a final confirmation of the stereochemistry, crystal structures of both the (*R*,*R*)- and (*S*,*S*)-diols **5** have been obtained.[23]

In addition to the C_2-symmetric diols, we felt that the corresponding parent diamines **10** represented valuable synthetic targets and should be accessible via suitable stereocontolled displacement (Scheme 3; for convenience only one enantiomer is depicted). Activation of the diol (*R*,*R*)-**5** as the bismesylate **8** followed by displacement with sodium azide gave the diazide (*S*,*S*)-**9** and subsequent $LiAlH_4$ reduction provided the free amine (*S*,*S*)-**10** in excellent overall yield. The enantiomeric (*R*,*R*)-**10** was isolated in similar yield from the diol (*S*,*S*)-**5**.



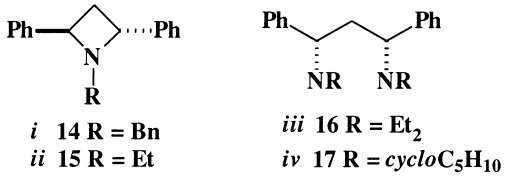
Scheme 3. Reagents and conditions: (i) NEt_3, MsCl, 0°C, 14 h; (ii) NaN_3, DMF, 14 h, 91% for 2 steps; (iii) LAH, THF, 0°C 1 h, rt 3 h, 70%

To further extend the potential utility of the parent diphenyl diamines **10**, these compounds were converted to a variety of potentially more useful derivatives (Scheme 4). Since racemisation did not present any problem, these transformations were performed on the racemic diamine, readily available from the racemic diol **5**.[24] This diamine was subsequently converted into the tosyl **11**, benzyl **12**, and trifluoroacetate **13** derivatives in good yields using standard conditions.



Scheme 4. Reagents and conditions: (i) TsCl, NEt_3, THF, 0°C, 66%; (ii) (a) PhCHO, MeOH, (b) $NaBH_4$, toluene, 75% over 2 steps; (iii) TFA, pyridine, CH_2Cl_2, 0°C, 74%

In order to prepare the benzyl derivative **12** above, we had found it necessary to effect alkylation via a condensation/reduction sequence. This was prompted by our earlier observations that when, in attempts to gain direct access to substituted diamines, the racemic mesylate **8** was treated with a number of primary amines (benzylamine and ethylamine) and secondary amines (diethylamine and piperidine) (Scheme 5), in the former case C_2-symmetric azetidines **14**, **15** were formed, while in the latter case only the *meso* diamines **16**, **17** were produced. Evidence for the formation of the latter *meso* products was the presence of a geminal coupling constant in the ^{1}H NMR spectra for the methylene group (13.6 and 13.8 Hz, respectively). In both instances a pathway involving an initial substitution followed by intramolecular attack to generate the 4-membered heterocycle seems most likely. Subsequent ring opening of the azetidinium species with accompanying inversion then leads to the *meso* diamines **16**, **17**.



i **14 R = Bn**
ii **15 R = Et**
iii **16 R = Et_2**
iv **17 R = *cyclo*C_5H_{10}**

Scheme 5. Reagents and conditions: (i) H_2NEt, 16 h, 80%; (ii) H_2NBn, DMF, 16 h, 63%; (iii) $HNEt_2$, 16 h, 81%; (iv) piperidine, DMF, 16 h, 85%

In conclusion, we have reported a high-yielding access to the enantiomerically pure C_2-symmetric 1,3-diphenyl-1,3-propanediol and 1,3-diphenyl-1,3-propanediamine enantiomers and several derivatives thereof. These species represent compounds which have potential as ligands in further asymmetric transformations, and are the subject of current studies in our laboratory.

3. Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-300 at 300 and 75.5 MHz, respectively, in $CDCl_3$ at ambient temperature with tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a Perkin–Elmer ITD Ion Trap Detector spectrometer in the electron impact mode at an emission current of 55 μA and an electron multiplier voltage of 2000 V. High resolution mass spectra (HRMS) were measured on a VG Autospec Mass Spectrometer. High pressure liquid chromatography (HPLC) was performed on a GBC LC 1150 using either a standard phase Alltech Econosil C18 column or a Chiracell OD column for determination of enantiomeric excess. The detector used was either a Polymer Laboratories PL-EMD 950 evaporative mass detector or a Knauer variable wavelength monitor set at 254 nm. IR spectra were recorded on a Perkin–Elmer 1720-X Fourier Transform Spectrometer. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Optical rotations were recorded at 20°C using an Optical Activity PolAAr 2001 polarimeter. Column chromatography refers to columns prepared as slurries of Merck silica gel 60 (70–230 mesh) in the eluent. Pre-adsorption was carried out on Merck silica gel 60 (35–70 mesh). Radial chromatography was performed using Merck silica gel 60 PF_{254}, while thin-layer chromatography was carried out on aluminium plates coated with Merck Kieselgel 60 F_{254}. 3-Hydroxy-1,3-diphenylpropene **6** was prepared in essentially quantitative yield according to the reported method.[20]

*3.1. (−)-(S)-3-Hydroxy-1,3-diphenylpropene **6** and (+)-(S,R,S)-1-hydroxy-2,3-epoxy-1,3-diphenylpropane **7***

Following the method of Sharpless and co-workers, L-(+)-DIPT (0.669 g, 2.86 mmol) was added to a 3-necked round bottom flask containing dichloromethane (230 ml) at room temperature.[20] Racemic hydroxyalkene **6** (5.00 g, 23.8 mmol) and activated powdered 3 Å molecular sieves (2.50 g) were added and the reaction mixture cooled to −20°C before the addition of titanium(IV) isopropoxide (0.71 ml, 2.38 mmol). The reaction mixture was stirred at this temperature for 0.5 h before the introduction of a pre-dried solution of *t*-butyl hydroperoxide in nonane (6.19 M, 2.69 ml). The reaction was stirred at this temperature for 3 h and then ether (23 ml) and 30% sodium hydroxide in saturated brine (1.9 ml) were added. The reaction mixture was allowed to warm to 10°C, stirred for a further 10 min and then treated with $MgSO_4$ (1.9 g) and Celite (0.24 g). After a final 15 min of stirring, the reaction mixture was filtered through a Celite pad before reduction in vacuo yielded a bright yellow oil. The crude products were separated by column chromatography (5% ethyl acetate–light petroleum eluent) to furnish, firstly, (−)-

(*S*)-3-hydroxy-1,3-diphenylpropene **6** (2.09 g, 9.95 mmol 41.8%, >99% ee determined by HPLC using a Chiralcel OD column with 5% 2-propanol–light petroleum as the eluent) which was recrystallised from ether–light petroleum as fine white needles, mp 46–47.5°C. $[\alpha]_D$ −32.1 (*c* 0.5, $CHCl_3$, >99% ee); lit.[25] $[\alpha]_D$ −24.8 (*c* 2.5, $CHCl_3$, 71% ee). This was followed by the (+)-(*S*,*R*,*S*)-epoxide **7** (2.79 g, 12.34 mmol, 51.9%, 89.6% ee determined by ^{1}H NMR analysis with Eu[hfc]$_3$) which was recrystallised from ether–light petroleum as fine white granules, mp 81.5–83°C; lit.[15b] (rac.) 69–70°C. $[\alpha]_D$ +16.3 (*c* 0.5, $CHCl_3$, >99% ee); lit.[15b] $[\alpha]_D$ −8.7 (CH_2Cl_2, 90% ee).[26] ^{1}H NMR δ 2.97 (1H, s, OH), 3.24 (1H, dd, *J*=3.0 and 2.3 Hz, *H*CCOH), 4.10 (1H, d, *J*=2.3 Hz, PhCH), 4.91 (1H, d, *J*=2.9 Hz, PhC*H*OH) and 7.15–7.47 (10H, m, Ph).

3.2. (+)-(R,R)-1,3-Diphenyl-1,3-propanediol 5

The (*S*,*R*,*S*)-epoxide (1.0 g, 4.42 mmol) in dry DME (20 ml) was cooled to 0°C with stirring under a nitrogen atmosphere. Red-Al® (65%, 2.84 ml, 8.85 mmol) was added slowly dropwise and the reaction mixture allowed to rise to room temperature and stirred overnight. The mixture was diluted with ether (30 ml) and an aqueous solution of sodium hydroxide (5%, 0.7 ml) was added. Stirring continued for 20 min, before drying with $MgSO_4$, filtration and reduction in vacuo yielded the crude product (*R*,*R*)-**5** (0.902 g, 3.96 mmol, 89.4%) which was recrystallised from chloroform as white needles, mp 151.5–153°C; lit.[14] 146.5–147.5°C. $[\alpha]_D$ +67.5 (*c* 0.3, EtOH); $[\alpha]_D$ +56.3 (*c* 0.2, $CHCl_3$); lit.[14] $[\alpha]_D$ +52 (*c* 0.5 $CHCl_3$); ^{1}H NMR δ 2.17 (2H, t, *J*=5.8 Hz, CH_2), 2.88 (2H, d, *J*=4.1 Hz, OH), 4.96 (2H, dt, *J*=5.5 and 4.5 Hz, PhC*H*OH) and 7.16–7.40 (10H, m, Ph); ^{13}C NMR δ 37.6 (CH_2), 71.7 (CH), 125.6, 125.9, 127.5 and 128.5 (C2–6) and 144.1 (C1).

3.3. (−)-(R,S,R)-1-Hydroxy-2,3-epoxy-1,3-diphenylpropane 7

D-(−)-DIPT (559 mg, 1.99 mmol) was added to a 3-necked round bottom flask containing dry dichloromethane (200 ml) under a nitrogen atmosphere. (*S*)-3-Hydroxy-1,3-diphenylpropene (2.09 g, 9.95 mmol) and activated powdered 3 Å molecular sieves (2.50 g) were added and the reaction mixture cooled to −20°C before the addition of titanium(IV) isopropoxide (0.59 ml, 1.98 mmol). The reaction mixture was stirred at this temperature for 0.5 h before the introduction of a pre-dried solution of *t*-butyl hydroperoxide in nonane (6.19 M, 2.25 ml). The reaction mixture was stirred at this temperature overnight and then ether (20 ml) and 30% sodium hydroxide in saturated brine (1.9 ml) added. The reaction mixture was allowed to warm to 10°C and stirred for a further 10 min before the addition of $MgSO_4$ (1.9 g) and Celite (0.24 g). After a final 15 min of stirring, the reaction mixture was filtered through a Celite pad before reduction in vacuo yielded a bright yellow oil. The crude product was purified by column chromatography (20% ethyl acetate–light petroleum eluent) to furnish product **7** (1.53 g, 6.77 mmol, 68.0%) which was recrystallised from ether–light petroleum as fine white needles, mp 81–82°C. $[\alpha]_D$ −16.7 (*c* 0.6, $CHCl_3$). Spectral data were identical to those of the (*S*,*R*,*S*)-enantiomer.

3.4. (S,S)-1,3-Diphenyl-1,3-propanediol 5

Using the (*R*,*S*,*R*)-epoxide **7** (1.0 g, 4.42 mmol) and the method described above for (*R*,*R*)-**5** afforded (*S*,*S*)-**5** (0.922 g, 4.04 mmol, 91.5%), which was recrystallised from chloroform as white needles, mp 149.5–151.5°C; lit.[27] 145–147°C; $[\alpha]_D$ −67.5 (*c* 0.3, EtOH); lit.[27] $[\alpha]_D$ −72.7 (*c* 10, EtOH); $[\alpha]_D$ −56.5 (*c* 0.2, $CHCl_3$); lit.[28] $[\alpha]_D$ −55.2 ($CHCl_3$). Spectral data were identical to those of the (*R*,*R*)-enantiomer.

3.5. (±)-1,3-Diphenyl-1,3-propanediazide **9**

The racemic diol **5** (0.150 g, 0.664 mmol) and triethylamine (0.205 g, 2.03 mmol) were stirred in THF (5 ml) at 0°C and methanesulfonyl chloride (0.102 ml, 1.33 mmol) was added dropwise via syringe. The reaction mixture was stirred at this temperature overnight. Precipitated triethylamine hydrochloride was filtered off and the filtrate washed with further portions (3×2 ml) of THF. The THF was removed in vacuo at 0°C and DMF (2 ml) and sodium azide (0.135 g, 2.08 mmol) added. The reaction mixture was stirred at room temperature overnight and the DMF removed in vacuo. Ether (25 ml) and water (25 ml) were added and the partitioned water layer washed with a further portion of ether (25 ml). The combined organic fractions were washed with brine (20 ml), dried ($MgSO_4$), and the solvents removed in vacuo to reveal product **9** (153 mg, 0.550 mmol, 82.9%) which was recrystallised from ether–light petroleum as fine white needles, mp 58–59°C; IR ν_{max} 3082 (CH Ar), 3029 (CH Ar), 2956 and 2924 (CH), 2107 (N_3) and 1496 and 1452 (C=C Ar); ^{1}H NMR δ 2.07 (2H, t, *J*=7.2 Hz, CH_2), 4.68 (2H, t, *J*=7.2 Hz, CH) and 7.27–7.44 (10H, m, Ph); ^{13}C NMR δ 43.5 (CH_2), 63.4 (CH), 127.3 (C3 and 5), 129.0 (*c* 4), 129.4 (C2 and 6) and 139.3 (C1); MS m/z 250 (M^+-N_2, 3%), 206 (37), 118 (40), 104 (37) and 91 (100). Anal. calcd for $C_{15}H_{14}N_6$: C, 64.7; H, 5.1; N, 30.2. Found: C, 64.6; H, 5.2; N, 30.0.

3.6. (−)-(S,S)-1,3-Diphenyl-1,3-propanediazide **9**

Using the (*R*,*R*)-diol **5** and the above method, the (*S*,*S*)-diazide was obtained in 90.7% yield and recrystallised from ether–light petroleum as fine white needles, mp 77–78.5°C. $[\alpha]_D$ −205.6 (*c* 0.1, $CHCl_3$). Spectral data were identical to those of the racemate.

3.7. (+)-(R,R)-1,3-Diphenyl-1,3-propanediazide **9**

Using the (*S*,*S*)-diol **5** and the above method, the (*R*,*R*)-diazide was obtained in 94.0% yield and recrystallised from ether–light petroleum as fine white needles, mp 77.5–79°C. $[\alpha]_D$ +203.7 (*c* 0.15, $CHCl_3$). Spectral data were identical to those of the racemate.

3.8. (±)-1,3-Diphenyl-1,3-propanediamine **10**

The racemic diazide **9** (0.106 g, 0.381 mmol) was dissolved in THF (5 ml) at 0°C with stirring. $LiAlH_4$ (0.028 g, 0.762 mmol) was added portionwise and the mixture stirred at this temperature for 1 h and for 3 h at room temperature. Moist ether was added and the reaction mixture stirred for a further 5 min before addition of $MgSO_4$. Filtration and removal of the solvents in vacuo revealed product **10** as a clear oil (0.083 g, 0.367 mmol, 96.3%).[24] ^{1}H NMR δ 1.74 (4H, broad s, NH_2), 2.01 (2H, t, *J*=6.9 Hz, CH_2), 3.91 (2H, t, *J*=6.8 Hz, CH) and 7.20–7.39 (10H, m, Ph); ^{13}C NMR δ 50.2 (CH_2), 55.2 (CH), 128.0 (C3 and 5), 128.7 (C4), 130.2 (C2 and 6) and 148.1 (C1).

3.9. (−)-(R,R)-1,3-Diphenyl-1,3-propanediamine **10**

Using the (*R*,*R*)-diazide **9** (0.305 g, 1.11 mmol) and the above method the (*R*,*R*)-diamine was obtained in 70.4% yield and recrystallised from chloroform as a gummy solid which hardened to white granules on standing, mp 70–73°C. $[\alpha]_D$ −24.5 (*c* 0.1, EtOH:H_2O [1:1]). Spectral data were identical to those of the racemate.

3.10. (+)-(S,S)-1,3-Diphenyl-1,3-propanediamine **10**

Using the (*S*,*S*)-diazide **9** (0.298 g, 1.08 mmol) and the above method the (*S*,*S*)-diamine was obtained in 70.5% yield and recrystallised from chloroform as a gummy solid which hardened to white granules on standing, mp 69–73°C. $[\alpha]_D$ +24.8 (*c* 0.1, EtOH:H_2O [1:1]), lit.[29] $[\alpha]_D$ +16.5 (*c* 1.97, $CHCl_3$, 96% ee). Spectral data was identical to those of the racemate.

3.11. (±)-N,N′-Ditoluenesulfonyl-1,3-diphenyl-1,3-propanediamine **11**

The racemic diamine **10** (0.060 g, 0.268 mmol), triethylamine (0.081 g, 0.804 mmol) and tosyl chloride (0.153 g, 0.804 mmol) were stirred in THF (5 ml) at 0°C overnight. Precipitated triethylamine hydrochloride was filtered off and the filtrate washed with further portions (3×2 ml) of THF. The THF was removed in vacuo and the residue chromatographed (25% ethyl acetate–light petroleum eluent) to give product **11** (0.095 g, 0.178 mmol, 66.4%) which was recrystallised from chloroform–light petroleum as white granules, mp 188–190°C; IR ν_{max} 3297 (NH), 3063 and 3030 (CH Ar), 2920 and 2859 (CH), 1597, 1493 and 1452 (C=C Ar) and 1160 (S=O); ^{1}H NMR δ 2.34 (6H, s, CH_3), 2.41 (2H, t, *J*=7.4 Hz, CH_2), 3.96 (2H, dt, *J*=7.2 and 7.1 Hz, CH), 5.15 (2H, d, *J*=7.0 Hz, NH), 6.84 (4H, dd, *J*=7.5 and 1.1 Hz, Ph), 7.05 (4H, d, *J*=8.2 Hz, C3 and 5 Ts), 7.11–7.24 (8H, m, Ph) and 7.39 (4H, d, *J*=8.3 Hz, C2 and 6 Ts); ^{13}C NMR δ 21.5 (CH_3), 43.3 (CH_2), 55.4 (CH), 127.0, 127.1, 128.0, 128.7 and 129.3 (C2–6 Ph and C2, 3, 5 and 6 Ts) 137.1 (C4 Ts), 138.8 (C1 Ph) and 143.1 (C1 Ts); HRMS $C_{29}H_{30}N_2O_4S_2$ calcd M^++1 535.1725; Found 537.1705. Anal. calcd for $C_{29}H_{30}N_2O_2S_2$: C, 65.1; H, 5.7; N, 5.2. Found: C, 64.8; H, 5.6; N, 5.2.

3.12. (±)-N,N′-Dibenzyl-1,3-diphenyl-1,3-propanediamine **12**

Following the method of Denmark[29] the racemic diamine **10** (0.083 g, 0.371 mmol) and benzaldehyde (0.094 ml, 0.928 mmol) were dissolved in dry methanol (5 ml) and the reaction mixture refluxed for 3 h.[30] After cooling and addition of dry toluene (5 ml), $NaBH_4$ (50.0 mg, 1.85 mmol) was added in portions over 20 min. Stirring was continued for 1.5 h and the solvents removed at reduced pressure, water (20 ml) and ethyl acetate (20 ml) were added and the organic layer removed, washed with brine, dried ($MgSO_4$), and the solvents removed in vacuo. The residue was purified by chromatography (20% ethyl acetate–light petroleum eluent) to reveal product **12** (0.114 g, 0.281 mmol, 75.6%) as a clear oil; ^{1}H NMR δ 2.06 (2H, t, *J*=6.6 Hz, CH_2), 2.36 (2H, broad s, NH), 3.47 (4H, ABq, *J*=13.0 Hz, CH_2Ph), 3.64 (2H, t, *J*=6.6 Hz, CH) and 7.12–7.34 (20H, m, Ph); ^{13}C NMR δ 45.5 (CH_2), 51.1 (CH_2Ph), 64.7 (CH), 126.7, 127.0, 127.9, 128.0, 128.2 and 128.2 (C2–6) and 140.0 and 143.2 (C1).

3.13. (±)-N,N′-Bis(trifluoroacetyl)-1,3-diphenyl-1,3-propanediamine **13**

The racemic diamine **10** (0.085 g, 0.379 mmol) and pyridine (0.072 g, 0.911 mmol) were stirred in dichloromethane (10 ml) at 0°C TFA (0.129 ml, 0.911 mmol) was added dropwise via syringe and the reaction mixture stirred for 3 h. Further dichloromethane (30 ml) and HCl (1 M, 20 ml) were added, the organic layer separated, washed with saturated bicarbonate solution (15 ml), water (15 ml) and brine (15 ml), then dried ($MgSO_4$) and the solvents removed in vacuo. The oily residue was purified by column chromatography (15–30% ethyl acetate–light petroleum gradient eluent) to yield product **13** (0.117 g, 0.280 mmol, 73.8%) which was recrystallised from chloroform–light petroleum as fine white needles, mp 204–205°C; IR ν_{max} 3710 (NH), 3090 (CH Ar), 2926 (CH), 1692 (C=O), 1548 and 1497 (C=C Ar)

and 1189 (CF); ^{1}H NMR δ 2.68 (2H, t, *J*=7.4 Hz, CH_2), 4.73 (2H, dt, *J*=7.4 and 7.3 Hz, CH), 6.49 (2H, d, *J*=6.5 Hz, NH), 7.22–7.28 (4H, m, Ph) and 7.36–7.46 (6H, m, Ph); ^{13}C NMR δ 38.7 (CH_2), 52.4 (CH), 115.6 (q, *J*=288.2 Hz, CF_3), 127.1 (C3 and 5), 129.2 (C4), 129.5 (C2 and 6), 137.4 (C1) and 156.4 (q, *J*=37.3 Hz, C=O); MS m/z 418 (M^+, 5%), 305 (19), 202 (49), 193 (93), 104 (73) and 69 (100); HRMS calcd for $C_{19}H_{16}N_2O_2F_6$: 418.1116. Found: 418.1106. Anal. calcd for $C_{19}H_{16}N_2O_2F_6$: C, 54.5; H, 3.9; N, 6.7. Found: C, 54.4; H, 4.1; N, 6.7.

3.14. (±)-N-*Benzyl-2,4-diphenylazetidine* ***14***

The racemic diol **5** (0.150 g, 0.664 mmol) and triethylamine (0.205 g, 2.03 mmol) were stirred in THF (5 ml) at 0°C and methanesulfonyl chloride (0.102 ml, 1.33 mmol) was added dropwise via syringe. The reaction mixture was stirred at this temperature overnight. Precipitated triethylamine hydrochloride was filtered off and the filtrate washed with further portions (3×2 ml) of THF. The THF was removed in vacuo at 0°C and DMF (2 ml) and benzylamine (0.335 g, 3.32 mmol) added. The reaction mixture was stirred at room temperature overnight, the DMF removed in vacuo and then ether (25 ml) and water (25 ml) added. The water layer was washed with a further portion of ether (25 ml), the organic fractions combined, washed with brine (20 ml), dried ($MgSO_4$) and the solvents removed in vacuo. The crude product was purified by column chromatography (20% ethyl acetate–light petroleum eluent) to give **14** (0.125 g, 0.417 mmol, 62.9%) which was recrystallised from ether–light petroleum as white cubes, mp 69–70.5°C; IR ν_{max} 3081 (CH Ar), 3028 (CH Ar), 2905 and 2851 (CH), and 1599, 1491 and 1451 (C=C Ar); ^{1}H NMR δ 2.67 (2H, t, *J*=6.8 Hz, CH_2), 2.38 (2H, ABq, *J*=14.0 Hz, CH_2Ph), 4.76 (2H, t, *J*=6.8 Hz, CH) and 7.00–7.43 (15H, m, Ph); ^{13}C NMR δ 35.1 (CH_2), 54.5 (CH_2Ph), 65.6 (CH), 126.9, 127.9, 128.3, 128.5, 128.7 and 129.0 (C2–6), 139.8 (C1 Bn) and 142.3 (C1); MS m/z 299 (M^+, 4%), 194 (17), 104 (15), 103 (11), 92 (12) and 91 (100). HRMS calcd for $C_{22}H_{21}N$: M^++1 300.1752. Found: 300.1748. Anal. calcd for $C_{22}H_{21}N$: C, 88.2; H, 7.1; N, 4.7. Found: C, 88.0; H, 7.1; N, 4.7.

3.15. (±)-N-*Ethyl-2,4-diphenylazetidine* ***15***

The racemic diol **5** (0.150 g, 0.664 mmol) and triethylamine (0.205 g, 2.03 mmol) were stirred in THF (5 ml) at 0°C and methanesulfonyl chloride (0.102 ml, 1.33 mmol) added dropwise via syringe. The reaction mixture was stirred at this temperature overnight. Precipitated triethylamine hydrochloride was filtered off and the filtrate washed with further portions (3×2 ml) of THF. The THF was removed in vacuo at 0°C and replaced with ethylamine (5 ml). The reaction mixture was stirred at room temperature overnight and the ethylamine removed in vacuo before ether (25 ml) and water (25 ml) were added. The water layer was washed with a further portion of ether (25 ml), the organic fractions combined, washed with brine (20 ml), dried ($MgSO_4$) and the solvents removed in vacuo. The product **15** was isolated by column chromatography (20% ethyl acetate–light petroleum eluent) as a clear oil (0.126 g, 0.530 mmol, 79.8%); IR ν_{max} 3082 (CH Ar), 2965, 2893 and 2815 (CH), and 1602 and 1492 (C=C Ar); ^{1}H NMR δ 0.59 (3H, t, *J*=7.2 Hz, CH_3), 2.05–2.24 (2H, m, C*H*$_2$CH$_3$), 2.56 (2H, t, *J*=6.9 Hz, CH_2), 4.62 (2H, t, *J*=6.9 Hz, CH), 7.15–7.22 (2H, m, Ph), 7.24–7.33 (4H, m, Ph) and 7.38–7.45 (4H, m, Ph); ^{13}C NMR δ 13.8 (CH_3), 34.8 (C*H*$_2$CH$_3$), 45.9 (CH_2), 65.9 (CH), 127.8 (C4), 128.3 (C3 and 5), 128.7 (C2 and 6) and 142.9 (C1); MS m/z 237 (M^+, 8%), 132 (34), 118 (32), 104 (75), 103 (29), 152 (100) and 77 (31). HRMS calcd for $C_{17}H_{19}N$: M^++1 238.1596. Found: 238.1595.

3.16. N,N′-Bis(diethyl)-1,3-diphenyl-1,3-propanediamine **16**

The racemic diol **5** (0.150 g, 0.664 mmol) and triethylamine (0.205 g, 2.03 mmol) were stirred in THF (5 ml) at 0°C and methanesulfonyl chloride (0.102 ml, 1.33 mmol) was added dropwise via syringe. The reaction mixture was stirred at this temperature overnight. Precipitated triethylamine hydrochloride was filtered off and the filtrate washed with further portions of THF (3×2 ml). The THF was removed in vacuo at 0°C, replaced with diethylamine (5 ml) and the reaction mixture stirred at room temperature overnight. The diethylamine was removed in vacuo and ether (25 ml) and water (25 ml) added, the water layer was washed with a further portion of ether (25 ml), the organic fractions combined, washed with brine (20 ml), dried ($MgSO_4$) and the solvents removed in vacuo. The product **16** was isolated by column chromatography (20% ethyl acetate–light petroleum eluent) as a clear oil (0.182 g, 0.538 mmol, 81.1%); IR ν_{max} 3061 (CH Ar), 2956, 2924 and 2853 (CH), and 1601 and 1496 (C=C Ar); ^{1}H NMR δ 0.57 (6H, t, *J*=7.1 Hz, CH_3), 2.03–2.19 (2H, m, C*H*$_2$CH$_3$), 2.50 (2H, ddd, *J*=13.8, 7.5 and 7.5 Hz, CH_2), 2.59–2.71 (2H, m, C*H*$_2$CH$_3$), 3.84 (2H, dd, *J*=7.5 and 7.5 Hz, CH) and 7.14–732 (10H, m, Ph); ^{13}C NMR δ 14.2 (CH_3), 34.8 (C*H*$_2$CH$_3$), 43.7 (CH_2), 60.4 (CH), 127.1 (C4), 128.1 (C3 and 5), 129.4 (C2 and 6) and 140.2 (C1); MS m/z 339 (M^++1, 7%), 338 (2), 265 (35), 264 (56), 174 (58), 162 (100), 132 (32) and 105 (32). Anal. calcd for $C_{23}H_{34}N_2$: C, 81.6; H, 10.1; N, 8.3. Found: C, 81.6; H, 10.2; N, 8.0.

3.17. 1,3-Diphenyl-1,3-dipiperidylpropane **17**

The racemic diol **5** (0.100 g, 0.469 mmol) and triethylamine (0.145 g, 1.43 mmol) were stirred in dichloromethane (70 ml) at 0°C and methanesulfonyl chloride (0.073 ml, 0.938 mmol) was added dropwise via syringe. The reaction mixture was stirred at this temperature overnight and then ice-water (25 ml) was added and the organic layer separated. The aqueous portion was extracted with cold dichloromethane (20 ml), and the organic fractions combined, washed with brine (25 ml) at 0°C, dried over $MgSO_4$ and reduced in vacuo at 0°C. DMF (0.5 ml) and piperidine (0.199 g, 2.34 mmol) were added, and the reaction mixture was stirred at room temperature overnight. The DMF was removed in vacuo and then ether (25 ml), saturated bicarbonate solution (10 ml) and water (15 ml) were added, then the water layer was separated and washed with a further portion of ether (25 ml). The organic fractions were combined, washed with brine (20 ml), dried ($MgSO_4$) and the solvents removed in vacuo. The product **17** was isolated by column chromatography (20% ethyl acetate–light petroleum eluent) as a pale yellow oil (0.144 g, 0.396 mmol, 84.6%); IR ν_{max} 3082 (CH Ar), 3026 (CH Ar), 2930 and 2851 (CH) and 1491 and 1466 (C=C Ar); ^{1}H NMR δ 1.14–1.31 (4H, m, C4 pip.), 1.33–1.57 (8H, m, C3 and 5 pip.), 1.89 (1H, ddd, *J*=13.6, 7.6 and 7.6 Hz, CH_2), 2.01–2.18 (4H, m, C2 and 6 pip.), 2.25–2.43 (4H, m, C2 and 6 pip.), 2.60 (1H, ddd, *J*=13.5, 7.7 and 7.6 Hz, CH_2), 3.38 (2H, dd, *J*=7.6 and 7.6 Hz, CH) and 7.01–7.24 (10H, m, Ph); ^{13}C NMR δ 25.2 (C4 pip.), 26.9 (C3 and 5 pip.), 34.6 (CH_2), 51.3 (C2 and 6 pip.), 67.3 (CH), 127.1 (C4), 128.0 (C3 and 5), 129.4 (C2 and 6) and 139.6 (C1); MS m/z 363 (M^++1, 4%), 277 (13), 186 (100), 174 (26), 104 (32) and 91 (39). HRMS calcd for $C_{25}H_{34}N_2$: M^++1 363.2800. Found: 363.2802.

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