Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 2485–2490

TETRAHEDRON: *ASYMMETRY*

Dynamic kinetic resolution–asymmetric transfer hydrogenation of 1-aryl-substituted cyclic ketones

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Received 24 September 2002; accepted 10 October 2002

Abstract—A range of 1-aryl-2-tetranols, and 1-phenyl-2-indanol, have been generated in high yield and enantiomeric excess from the corresponding racemic ketones, via a dynamic kinetic resolution–transfer hydrogenation process, using Ru(II)-TsDPEN in formic acid/triethylamine (5:2). This provides a potential entry to an asymmetric total synthesis of benzazepines such as Sch 39166.

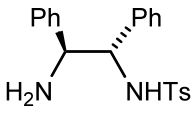
1. Introduction

The benzazepine dopamine D1 antagonist Sch 39166 **1** has been the subject of several recent synthetic studies due to its potential as a treatment for Parkinson's disease and other neurological disorders.[1] Several efficient syntheses of this material, and related compounds, have been published. However, in most of the known routes, the absolute stereochemistry is introduced by the use of enantiomerically pure starting materials, or through the use of chiral auxiliaries. The favoured route involves the use of a Jacobsen epoxidation coupled with resolution.[1]

2. Results and discussion

The structure of the benzazepine core suggests that a viable synthetic approach to the material might be via a dynamic kinetic resolution (DKR) process based upon asymmetric reduction of the carbonyl group of an appropriate ketone (**2**, Scheme 1). For such an approach to be successful, the rate of epimerisation at the benzylic centre would have to be much faster than that of the asymmetric reduction. Given the stabilisation of the enolic form of the substrate **2** by the two adjacent aromatic rings, we considered that there was a strong possibility that this would be the case. The synthesis could then be completed by tosylation of the alcohol and deprotection of the amine in the product **3** to give **4**, followed by intramolecular cyclisation and deprotection. The sequence could also be modified, if required to incorporate introduction of the 2-amino group through azide displacement of the tosylate followed by an alternative cyclisation sequence.[2]

In order to develop the underlying methodology for the synthesis of Sch 39166 and related compounds, we chose to investigate the use of asymmetric transfer hydrogenation for the dynamic kinetic resolution–reduction of 1-aryl-β-tetralones. This methodology has been the subject of ongoing studies in this research group.[3] Although we have focused primarily on the use of amino alcohol ligands for this application, catalytic transfer hydrogenation in 5:2 formic acid/triethylamine, using Noyori's catalyst, [Ru(II)(*p*-cymene)-TsDPEN], (TsDPEN = *N*-tosyl-1,2-diphenylethylenediamine **5**), has become one of the most important methods for the enantioselective reduction of ketones.[4,5] In particular the method benefits from practical simplicity and cost effectiveness due to the low catalyst loading.



(*S,S*)-TsDPEN **5**

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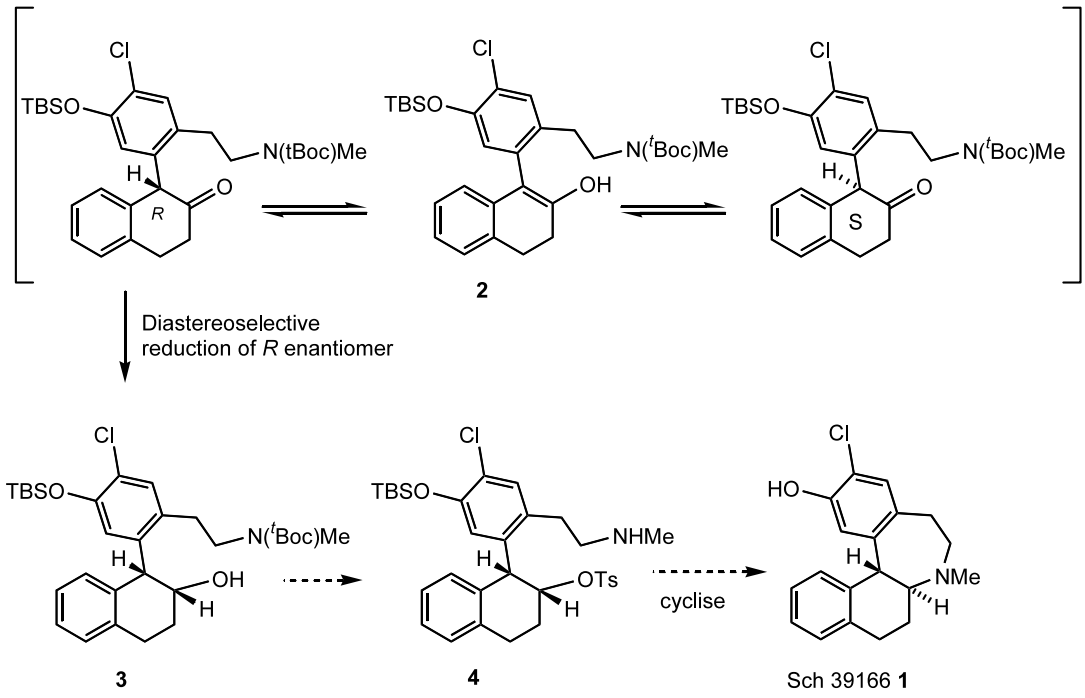
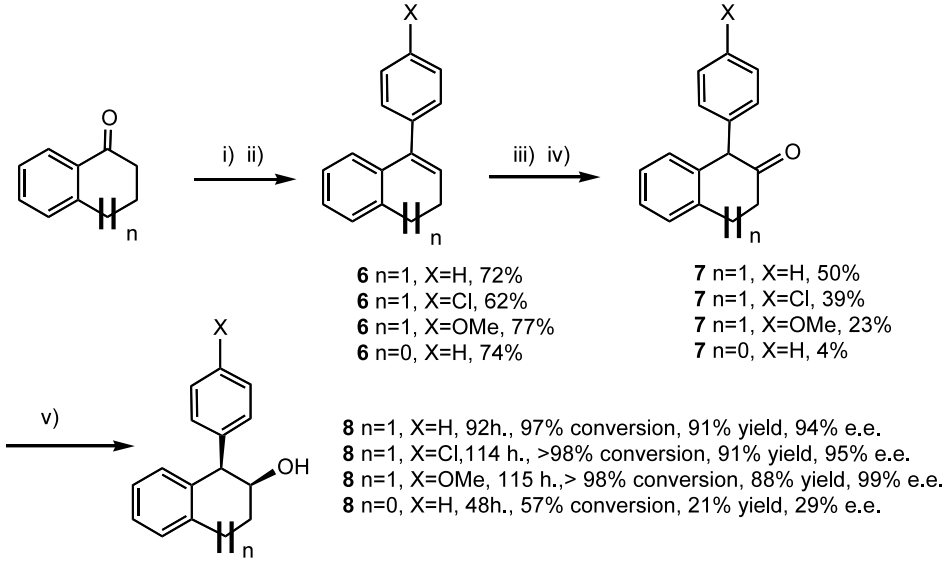
PII: S0957-4166(02)00648-1



Scheme 1. Dynamic kinetic resolution approach to Sch 39166 **1**.

DKR is attracting increasing levels of interest and research.[6] DKR has the advantage of a maximum 100% theoretical yield, over a classical resolution in which the yield is limited to 50%. The main drawback of such processes is that since an efficient racemisation of the stereogenic centre is needed, the substrate range is limited. While there are many examples of DKR's in the literature, there are very few examples to our knowledge where this process has been coupled to transfer hydrogenation. Excellent known examples include Noyori's reduction of benzils to hydrobenzoins (100% e.e.)[7] Cossy's reduction of 1,3-diketones[8] and Mioskowski's reduction of β-(3,4-dimethoxyphenyl)serine methyl ester derivatives (quantitative conversions, >99% e.e. for the major diastereoisomer).[9]

We wished to examine the use of transfer hydrogenation–DKR to the 1-aryl-2-tetralone system, a novel substrate for this application, in the belief that the ketone substrate would be able to epimerise under these conditions, and that transfer hydrogenation would (a) react preferentially with one enantiomer of ketone **2** and (b) form the *cis* product with diastereoselectivity. Towards this end, a range of 1-aryl-2-tetralones **7** were prepared from 1-tetralone and the corresponding Grignard reagents via the general method of Jensen (Scheme 2).[10] This required an elimination reaction of tertiary



Scheme 2. Synthesis and dynamic kinetic resolution–transfer hydrogenation of cyclic ketones. *Reagents and conditions*: (i) XC_6H_4MgBr, THF, 17 h; (ii) toluene *p*-TSA, 1 h; (iii) *m*-CPBA, DCM/water, 1 h, rt; (iv) ZnI_2, 120°C, 1 h; (v) [Ru(*p*-cymene)(*S*,*S*)-TsDPEN], HCO_2H:Et_3N 5:2, 92 h, rt.

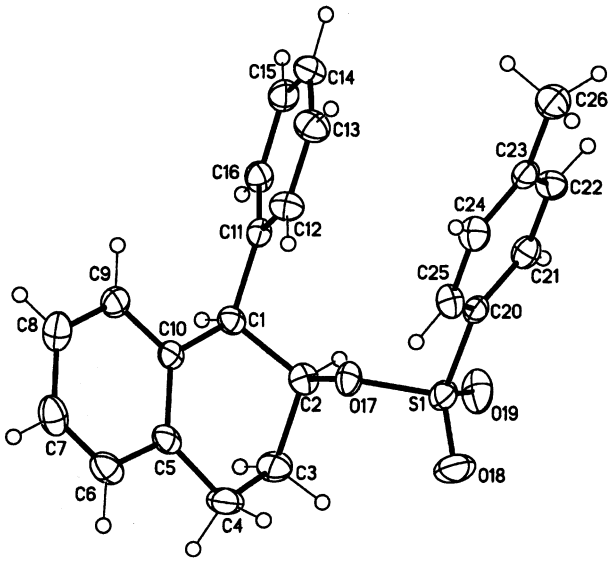
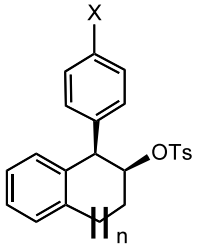


Figure 1. X-Ray crystal structure of **9**.

alcohols which generally proceeded smoothly to give intermediate alkenes **6**. The conversion of the tertiary alkenes to the 2-tetralones required the use of *m*-CPBA followed by isomerisation to the ketones. Only poor to moderate yields were obtained over the final two steps for this process. 1-Phenyl-2-indanone was prepared by the same general method however the last stage proceeded in very low yield. Although this would obviously preclude the use of the sequence in a synthetically viable approach to the alcohol targets, we were able to secure sufficient quantities of material to test the DKR-reduction reaction.

In the key step of this investigation, the racemic ketones **7** were reduced in a 5:2 formic acid/triethylamine system, using 0.5 mol% [Ru(II)(*p*-cymene)-(*S*,*S*)TsDPEN]. The reactions of the three six-membered ketones proceeded cleanly to yield the corresponding alcohols **8** in high yield and e.e. (Scheme 2). Conversions, measured by NMR of crude mixtures, were almost quantitative, whilst isolated yields were also high. All of the reduction products appeared (by 300 MHz NMR) to be single diastereoisomers, suggesting that the reduction was highly stereoselective. More gratifyingly, the enantiomeric excesses of the products were uniformly high, confirming that one enantiomer of ketone had been predominantly reduced over the other. In contrast, reduction of the five-membered ketone substrate gave the product in low yield and e.e., suggesting that the method is particularly appropriate for six-membered rings.



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It should be noted that 1-phenyl-2-indanone appears to be unstable, and even when stored at 4°C for more than 1 week, decomposition products appear to inhibit the reaction, thus the reduction needs to be carried out directly after isolation of the pure ketone.

The 1-phenyl-2-tetranol was converted to its tosylate **9** using *p*-toluenesulphonyl chloride in pyridine. An X-ray crystal structural analysis of this confirmed that the material has *cis* stereochemistry, with 1*R*,2*S* absolute configuration (Fig. 1). This enantiomer is the one predicted on the basis of the known selectivity of reductions using (*S*,*S*)-TsDPEN/Ru(II) complexes.

Attempts were made to displace the tosylate with phenyl magnesium bromide, phenyl magnesium bromide/$CeCl_3$, benzylamine and potassium diphenylphosphide. In all cases this only gave the elimination product, probably via an E2 mechanism.

3. Conclusion

In conclusion, we have demonstrated this DKR–transfer hydrogenation to be an effective method for the preparation of enantiomerically pure *cis* 1-aryl-2-tetranols, paving the way for a synthetic approach to benzazepines. Work in this area within our group is ongoing and further results will be reported shortly.

4. Experimental

4.1. General procedure for synthesis of 1-aryl substituted cyclic alkenes

Magnesium shavings (2.13 g, 8.75×10^{-2} mol) were stirred in THF (100 mL) and I_2 (trace) was added. Bromobenzene (8.6 mL, 8.21×10^{-2} mol) was added dropwise to the mixture; the reaction was exothermic, and the mixture was stirred for 20 min. 1-Tetralone (7.3 mL, 5.47×10^{-2} mol) was then added, (exothermic), the reaction was stirred for 17 h. Water (30 mL) was slowly added, (exothermic), the product was extracted with DCM (2×100 mL), dried over magnesium sulphate and the solvent removed to yield the tertiary alcohol as a red-brown oil (11.85 g, 5.47×10^{-2} mol). This alcohol was dissolved in toluene (100 mL) and *p*-toluenesulphonic acid (1.04 g, 5.47×10^{-3} mol) was added. The reaction was heated under reflux for 1 h after which time it was cooled to ambient temperature and washed with water (2×20 mL), dried over magnesium sulphate and the solvent removed to give a brown oil. This was then purified by column chromatography on silica, using ethyl acetate/hexane (3%) to yield the product.

4.1.1. 3,4-Dihydro-1-phenylnaphthalene 6 (*n*=1, X=H). White solid (8.12 g, 72%, two steps); mp 38–39°C; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 2.4 (2H, m, CH_2CH_2CH), 2.8 (2H, t, J=7.6 Hz, CH_2CH_2CH), 6.0 (1H, t, J=4.7 Hz, C*H*), 7.0 (1H, d, J=7.2 Hz, Ar*H*),

7.0–7.2 (3H, m, Ar*H*), 7.3–7.4 (4H, m, Ar*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$, Me_4Si): δ 23.9 (t), 28.7 (t), 125.8 (d), 126.3 (d), 126.6 (d), 127.4 (d), 128.0 (d), 128.6 (d), 129.2 (d), 135.5 (s), 137.2 (s), 140.3 (s), 141.2 (s). Matches authentic material purchased from Lancaster.

4.1.2. 3,4-Dihydro-1-(*p*-chlorophenyl)naphthalene 6 (*n*=1, X=Cl). Yellow solid (62%, two steps); mp 90–92°C; ν_{max} (neat): 2921, 2882, 2828, 2359, 1484, 1085, 811, 766, 736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 2.4 (2H, m, CH_2CH$_2$CH), 2.9 (2H, m, CH$_2$CH_2CH), 6.1 (1H, t, J=4.7 Hz, C*H*), 6.9–7.0 (8H, m, Ar*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$, Me_4Si): δ 23.9 (t), 28.6 (t), 125.6 (d), 126.7 (d), 127.2 (d), 127.6 (d), 128.1 (d), 128.3 (d), 128.8 (d), 130.5 (d), 133.3 (s), 135.1 (s), 137.2 (s), 139.3 (s); MS (EI): m/z 240 (100%, M$^+$), 205 (75%, M$^+$–Cl). Anal. found: C, 79.45; H, 5.43. $C_{16}H_{13}Cl$ requires: C, 79.83; H, 5.44%.

4.1.3. 3,4-Dihydro-1-(*p*-methoxyphenyl)naphthalene 6 (*n*=1, X=OMe). White solid (77%, two steps); mp 39–40°C; ν_{max} (neat): 2921, 1604, 1507, 1439, 1243, 1173, 815, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 2.4 (2H, m, CH_2CH$_2$CH), 2.8 (2H, m, CH$_2$CH_2CH), 3.8 (3H, s, OCH_3), 6.0 (1H, t, J=4.7 Hz, C*H*), 6.9–7.3 (8H, m, Ar*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$, Me_4Si): δ 23.9 (t), 29.8 (t), 55.7 (q), 114.0 (d), 125.8 (d), 126.6 (d), 127.3 (d), 128.0 (d), 130.2 (d), 133.6 (s), 135.7 (s), 137.3 (s), 139.7 (s), 159.2 (s); MS (EI): m/z 236.119645 ($C_{17}H_{16}O$ requires 236.120115), 236 (100%, M$^+$), 221 (45%), 205 (35%), 178 (27%), 165 (23%), 128 (23%), 121 (28%).

4.1.4. 1-Phenylindene 6 (*n*=0, X=H). Yellow oil (74% yield, two steps); ν_{max} (neat): 3024, 2880, 2359, 2339, 1723, 1658, 1488, 1444, 1388, 1267, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): δ 3.5 (2H, d, J=2.0 Hz, CH_2), 6.6 (1H, t, J=2.0 Hz, C*H*), 7.3–7.6 (9H, m, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$, Me_4Si): δ 38.6 (t), 120.8 (d), 124.6 (d), 125.3 (d), 126.6 (d), 128.0 (d), 128.2 (d), 129.0 (d), 131.4 (d), 136.6 (s), 144.3 (s), 145.2 (s), 145.6 (s); MS (EI): m/z 192.0936 ($C_{15}H_{12}$ requires 192.0939), 192 (100%, M$^+$), 179 (41%), 165 (43%).

4.2. General procedure for the synthesis of ketones

m-CPBA (6.8 g, 3.94×10^{-2} mol) and sodium bicarbonate (3.64 g, 4.33×10^{-2} mol) were dissolved in DCM/water (1:1, 200 mL) and stirred for 20 min. 2,4-Dihydro-1-phenylnaphthalene (8.12 g, 3.94×10^{-2} mol) in DCM/water (1:1, 120 mL) was added and the reaction was stirred for 1 h. The organic layer was separated, and the aqueous layer extracted with DCM (30 mL). The combined organic layers were dried over magnesium sulphate, and evaporated to yield the epoxide as a brown oil (10.1 g). This was processed directly to 1-phenyl-2-tetralone without full characterisation; zinc iodide (1.21 g, 3.78×10^{-3} mol), was heated to 120°C under vacuum for 1 h, cooled to ambient temperature, then the epoxide (2.80 g, 1.26×10^{-2} mol) dissolved in toluene (150 mL) was added. The reaction was heated to reflux for 1 h. The reaction was cooled to ambient temperature then washed with water (2×50 mL), dried over magnesium sulphate, and evaporated to yield a brown oil. Purification by column chromatography on silica using ethyl acetate (1%) in hexane yielded the product.

4.2.1. 1-Phenyl-2-tetralone 7 (*n*=1, X=H). Pale yellow oil (1.42 g, 50%, two steps); ν_{max} (neat): 30.24, 1709, 1661, 1596, 1491, 1447, 1267, 1145, 741, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 2.6 (1H, m, CH$_2$CH*H*CO), 2.7 (1H, m, CH$_2$C*H*HCO), 3.1 (2H, m, CH_2CH$_2$CHO), 4.8 (1H, s, COC*H*Ph), 7.0–7.4 (9H, m, Ar*H*); ^{13}C NMR (300 MHz, $CDCl_3$, Me_4Si): δ 28.6 (t), 37.4 (t), 60.2 (d), 129.2 (d), 129.1 (d), 128.9 (d), 128.6 (d), 127.9 (d), 127.6 (d), 127.5 (d); MS (EI): m/z 222.103699 ($C_{16}H_{14}O$ requires 222.104465), 222 (100%, M$^+$), 194 (70%), 179 (45%), 165 (30%).

4.2.2. 1-(*p*-Chlorophenyl)-2-tetralone 7 (*n*=1, X=Cl). Yellow solid which turned green in the fridge overnight (39%, two steps); ν_{max} (neat): 2944, 2360, 1708, 1653, 1487, 1455, 1397, 1085, 1014, 811, 741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 2.5–2.7 (2H, m, CH_2CH$_2$CO), 3.0–3.1 (2H, m, CH$_2$CH_2CO), 4.7 (1H, s, C*H*Ph), 6.9–7.3 (8H, m, Ar*H*); ^{13}C NMR (300 MHz, $CDCl_3$, Me_4Si): δ 28.9 (t), 35.9 (t), 59.5 (d), 128.1 (d), 128.9 (d), 129.3 (d), 130.1 (d), 130.7 (d), 133.1 (s), 134.5 (s), 136.9 (s), 209.3 (s); MS (EI): m/z 256.057281 ($C_{16}H_{13}ClO$ requires 256.065493), 256 (95%, M$^+$), 228 (100%), 193 (85%), 179 (92%).

4.2.3. 1-(*p*-Methoxyphenyl)-2-tetralone 7 (*n*=1, X=OMe). Yellow oil (23%, two steps); ν_{max} (neat): 2953, 1704, 1609, 1509, 1440, 1302, 1246, 1775, 1147, 1106, 1027, 813, 786 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 2.5–2.6 (1H, m, CH*H*CH$_2$CO), 2.7–2.8 (1H, m, C*H*HCH$_2$CO), 2.9–3.1 (2H, m, CH$_2$CH_2CO), 3.7 (3H, s, CH_3), 4.7 (1H, s, C*H*Ph), 6.9–7.3 (8H, m, Ar*H*); ^{13}C NMR (300 MHz, $CDCl_3$, Me_4Si): δ 28.6 (t), 37.3 (t), 55.7 (q), 59.4 (d), 114.5 (d), 127.6 (d), 127.7 (d), 128.3 (d), 130.1 (d), 137.1 (s), 137.2 (s), 137.3 (s), 159.2 (s), 210.0 (s); MS (EI): m/z 252.113672 ($C_{17}H_{16}O_2$ requires 252.115030), 252 (100%, M$^+$), 223 (54%), 209 (27%), 193 (55%), 178 (24%), 165 (22%), 155 (32%), 138 (32%), 115 (24%).

4.2.4. 1-Phenylindan-2-one 7 (*n*=0, X=H). Purified three times by chromatography on silica 1% EtOAc/hexane to yield a yellow oil (4%); ν_{max} (neat): 3024, 2363, 1750, 1598, 1493, 1450, 1136, 1068, 737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 3.7 (2H, s, CH_2), 4.7 (1H, s, C*H*), 7.1–7.4 (9H, m, Ar*H*); ^{13}C NMR (300 MHz, $CDCl_3$, Me_4Si): δ 43.4 (t), 60.2 (d), 125.3 (d), 126.4 (d), 127.7 (d), 128.3 (d), 128.4 (d), 128.9 (d), 129.2 (d), 138.1 (s), 138.5 (s), 141.7 (s); MS (EI): m/z 208.0870 ($C_{15}H_{12}O$ requires 208.0888), 207 (71%), 180 (100%, M$^+$), 165 (28%).

4.3. General procedure for DKR-asymmetric reduction

Ruthenium *p*-cymene dimer (0.0103 g, 1.69×10^{-5} mol, 0.25%) and (*S*,*S*)-TsDPEN (0.0123 g, 3.38×10^{-5} mol, 0.50%) were stirred in formic acid/triethylamine (5:2, 3.4 mL) at 28°C, for 20 min. 1-Phenyl-2-tetralone (1.5

g, 6.76×10^{-3} mol), was added and the reaction stirred at 28°C for 92 h; the reaction was followed by TLC on silica. The reaction mixture was filtered through a plug of silica and the product eluted with ethyl acetate (2×100 mL). The solution was evaporated to yield a brown oil (2.34 g) and purified by column chromatography on silica using ethyl acetate/hexane (5%) to yield the alcohol.

4.3.1. (1*R*,2*S*)-1-Phenyl-2-hydroxy-1,2,3,4-tetrahydronaphthalene 8 (*n*=1, X=H). Viscous colourless oil (1.40 g, 91%); $[\alpha]_D^{20}=-91.75$ (*c* 2.060, $CHCl_3$); ν_{max} (neat): 3239, 3024, 2931, 2880, 1735, 1601, 1488, 1242, 1051, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 1.9 (2H, m, C*H*$_2$CH$_2$CHOH), 2.9 (1H, dt, *J*=6.7 Hz, 17.2, CH*H*CHOH), 3.1 (1H, dt, *J*=6.0, 17.2 Hz, CHHCHOH), 4.2 (1H, m, C*H*OH), 4.4 (1H, d, *J*=4.9 Hz, PhC*H*CHOH), 6.9 (1H, d, *J*=7.9 Hz, Ar*H*), 7.0–7.4 (8H, m, Ar*H*); ^{13}C NMR (300 MHz, $CDCl_3$, Me_4Si): δ 27.3 (t), 28.1 (t), 51.7 (d), 69.8 (d), 126.5 (d), 126.9 (d), 127.3 (d), 128.8 (d), 129.1 (d), 131.1 (d), 131.2 (d), 136.6 (s), 138.3 (s), 143.6 (s); MS (EI): *m*/*z* 224 (13%, M^+), 206 (100%), 179 (84%), 165 (30%), 152 (8%), 128 (8%), 115 (9%), 91 (10%); chiral HPLC (5% IPA/hexane, 0.5 mL/min): R_t 20.2, 24.5 min, 94% e.e. Compared with authentic racemic material. Anal. found: C, 85.49; H, 7.02. $C_{16}H_{16}O$ requires: C, 85.67; H, 7.19%.

4.3.2. (1*R*,2*S*)-1-(*p*-Chlorophenyl)-2-hydroxy-1,2,3,4-tetrahydronaphthalene 8 (*n*=1, X=Cl). Viscous colourless oil (91%); $[\alpha]_D^{20}=-124.7$ (*c* 1.650, EtOH); ν_{max} (neat): 3377, 2931, 2359, 1907, 1487, 1406, 1087, 1054, 1013, 963, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 1.9 (2H, m, C*H*$_2$CH$_2$CHOH), 2.9 (1H, m, CH$_2$C*H*HCHOH), 3.1 (1H, m, CH$_2$CH*H*CHOH), 4.1–4.2 (1H, m, C*H*OH), 4.3 (1H, d, *J*=4.8 Hz, C*H*CHOH), 6.9–7.3 (8H, m, Ar*H*); ^{13}C NMR (300 MHz, $CDCl_3$, Me_4Si): δ 27.2 (t), 28.2 (t), 51.0 (d), 69.7 (d), 126.6 (d), 127.1 (d), 128.8 (d), 129.1 (d), 131.0 (d), 132.3 (d), 133.2 (s), 136.8 (s), 137.2 (s), 140.3 (s); MS (EI): *m*/*z* 258.079932 ($C_{16}H_{15}OCl$ requires 258.081143), 258 (5%, M^+), 239 (7%), 179 (19%), 117 (15%), 87 (79%), 85 (98%), 83 (100%); 95% e.e. determined with 8% europium tris[3-(heprafluropropylhydroxymethylene)-(+)-camphorate]. Compared with authentic racemic material.

4.3.3. (1*R*,2*S*)-1-(*p*-Methoxyphenyl)-2-hydroxy-1,2,3,4-tetrahydronaphthalene 8 (*n*=1, X=OMe). Viscous colourless oil (88%); $[\alpha]_D^{20}=-96.1$ (C=3.905 EtOH); ν_{max} (neat): 3419, 2932, 2833, 1607, 1507, 1457, 1240, 1176, 1034, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 1.8 (1H, br s, O*H*), 1.9 (2H, m, C*H*$_2$CH$_2$CHOH), 2.8–2.9 (1H, m, CH$_2$CH*H*CHOH), 3.0–3.1 (1H, m, CH$_2$C*H*HCHOH), 3.7 (3H, s, OC*H*$_3$), 4.1 (1H, m, C*H*OH), 4.3 (1H, d, *J*=4.8 Hz, C*H*CHOH), 6.8–7.2 (8H, m, Ar*H*); ^{13}C NMR (300 MHz, $CDCl_3$, Me_4Si): δ 27.4 (t), 28.1 (t), 50.8 (d), 55.7 (d), 69.9 (q), 114.2 (d), 126.4 (d), 126.8 (d), 129.0 (d), 131.1 (d), 132.0 (d), 133.7 (s), 136.9 (s), 138.1 (s), 159.0 (s); MS (EI): *m*/*z* 254.129942 ($C_{17}H_{18}O_2$ requires 254.130680), 254 (64%), 209 (83%), 179 (100%), 165 (85%), 115 (56%), 77 (42%); chiral HPLC (5% IPA/hexane, 1.0 mL/min): R_t 10.9, 12.5 min, 99% e.e. Compared with authentic racemic material.

4.3.4. (1*R*,2*S*)-1-Phenylindan-2-ol 8 (*n*=0, X=H). Colourless oil (21% yield); $[\alpha]_D^{20}=-49.7$ (*c* 0.910, $CHCl_3$); ν_{max} (neat): 3534, 3412, 3022, 2907, 2361, 2246, 1949, 1601, 1492, 1451, 1316, 1191, 1075, 1042, 980, 723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 2.8 (1H, dd, *J*=2.8, 13.4 Hz, C*H*H), 3.1 (1H, dd, *J*=5.5, 10.7 Hz, CH*H*), 4.3 (1H, d, *J*=5.5 Hz, C*H*Ph), 4.5 (1H, m, CHC*H*CH$_2$), 7.0–7.4 (9H, m, Ar*H*); ^{13}C NMR (300 MHz, $CDCl_3$, Me_4Si): δ 40.4 (t), 57.0 (d), 75.4 (d), 124.9 (d), 125.3 (d), 127.0 (d), 127.2 (d), 128.5 (d), 129.8 (d), 137.6 (d), 141.9 (d), 142.9 (d); MS (EI): *m*/*z* 210.1045 ($C_{15}H_{14}O$ requires 210.1045), 210 (73%, M^+), 192 (100%), 178 (53%), 165 (59%), 91 (37%); 28% e.e. determined by conversion to Mosher's ester. Compared with authentic racemic material.

4.3.5. (1*R*,2*S*)-1-Phenyl-2-hydroxy-1,2,3,4-tetrahydronaphthalene *p*-toluenesulphonyl ester, 9. 1-Phenyl-2-tetranol (0.25 g, 1.123×10^{-3} mol) and *p*-toluenesulphonyl chloride (0.24 g, 1.225×10^{-3} mol) was dissolved in pyridine (5.4 mL) and stirred for 16 h. Hydrochloric acid (1.5 mL, 5 M), and water (10 mL) was added and a white precipitate formed. The product was extracted with DCM (2×20 mL), evaporated to yield a brown oil (0.4085 g) and purified by column chromatography on silica using ethyl acetate/hexane (15%) to yield a colourless crystalline solid (0.3332 g, 78%); mp 118–120°C; $[\alpha]_D^{20}=-80.4$ (*c* 1.035, $CHCl_3$); ν_{max} (neat): 2941, 1330, 1168, 937, 897 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 1.9 (1H, m, CH*H*CH$_2$CHOH), 2.3 (1H, m, C*H*HCH$_2$CHOH), 2.4 (3H, s, C*H*$_3$), 2.8–2.9 (1H, dt, *J*=17.1, 7.0 Hz, C*H*HCHOTs), 3.1–3.2 (1H, dt, *J*=17.3, 6.6 Hz, CH*H*CHOH), 4.4 (1H, d, *J*=4.9 Hz, C*H*Ph), 5.0 (1H, m, C*H*OTs), 6.8–7.2 (11H, m, Ar*H*), 7.6 (2H, d, *J*=8.5 Hz, Ar*H*); ^{13}C NMR (300 MHz, $CDCl_3$, Me_4Si): δ 22.0 (q), 26.2 (d), 26.7 (d), 49.9 (d), 80.9 (d), 126.6 (d), 126.8 (d), 127.2 (d), 127.2 (d), 128.0 (d), 128.9 (d), 130.0 (d), 130.7 (d), 131.2 (d), 134.2 (s), 136.0 (s), 136.4 (s), 140.6 (s), 144.7 (s); MS (EI): *m*/*z* 378 (20%, M^+), 270 (59%), 207 (87%), 179 (72%), 165 (68%), 91 (100%). Anal. found: C, 72.83; H, 5.81. $C_{23}H_{22}O_3S$ requires: C, 72.99; H, 5.86%.

Acknowledgements

We thank the EPSRC and GlaxoSmithKline for support of a CASE studentships (to P.P.). Professor D. Games and Dr. B. Stein of the EPSRC National Mass Spectroscopic Service (Swansea) are thanked for HRMS analysis of certain compounds. We also acknowledge the generous loan of ruthenium and rhodium salts by Johnson-Mathey Limited, a personal communication from J. Clader and G. Wu (Schering-Plough) and the use of the EPSRC's Chemical Database Service at Daresbury.[11]

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