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A chemoenzymatic synthesis of (2*R*)-8-substituted-2-aminotetralins

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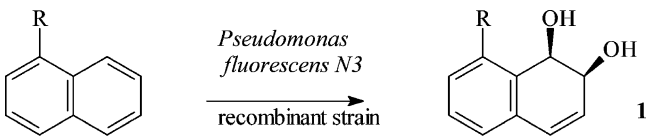
Abstract—(2*R*)-2-Amino-8-methoxy-1,2,3,4-tetrahydronaphthalene, a useful precursor of the 5-hydroxytryptamine receptor agonist 8-OH-DPAT ((2*R*)-2-(dipropylamino)-8-hydroxytetrahydronaphthalene), has been synthesized from 1-methoxynaphthalene through a chemoenzymatic protocol. The same protocol has been subsequently applied to the synthesis of other (2*R*)-2-amino-1,2,3,4-tetrahydronaphthalenes. © 2002 Published by Elsevier Science Ltd.

1. Introduction

In previous papers we reported the bioconversion of substituted naphthalenes to the corresponding (1*R*,2*S*)-1,2-dihydroxy-1,2-dihydronaphthalenes (*cis*-dihydrodiols) using recombinant strains from *Pseudomonas fluorescens N3*[1] (Fig. 1).

(1*R*,2*S*)-1,2-Dihydroxy-1,2-dihydronaphthalenes **1** represent a pool of enantiopure compounds which may be used as chiral synthons and chiral auxiliaries. To this end (1*R*,2*S*)-1,2-dihydroxy-1,2-dihydronaphthalene (from the bioconversion of naphthalene) has already been converted to a series of chiral 1,2-diols, 1,2-amino alcohols and 1,2-diamines:[2] (2*R*,3*R*)-2,3-dihydroxy-1,2,3,4-tetrahydronaphthalene[3] has proven to be a useful chiral auxiliary for the production of enantiopure alcohols and acids (via stereoselective 1,4-conjugate additions of alkyl cuprates to α,β-unsaturated esters) and for enantiopure α-dialkylated β-ketoesters (via stereoselective alkylations of β-ketoesters).[4]



a) R = H; b) R = C_2H_5; c) R = OCH_3;
d) R = $COOCH_3$; e) R = Cl; f) R = NO_2

Figure 1.

Herein we report a chemoenzymatic synthesis of (2*R*)-2-amino-8-methoxy-1,2,3,4-tetrahydronaphthalene **6d**, a useful precursor of (2*R*)-2-(dipropylamino)-8-hydroxytetrahydronaphthalene (8-OH-DPAT)[5] which is a potent and centrally active 5-hydroxytriptamine (serotonin, 5-HT) receptor agonist with selectivity for 5-HT_{1A} receptors. Since the first report on its pharmacological profile, 8-OH-DPAT has been frequently used in the elucidation of serotonergic mechanisms. Furthermore, molecules interacting with the 5-HT_{1A}-subtype of serotonin (5-HT)-receptors are of potential clinical interest for the treatment of depression and anxiety.

2. Results and discussion

(2*R*)-2-Amino-8-methoxy-1,2,3,4-tetrahydronaphthalene **6d** was synthesized from (1*R*,2*S*)-8-methoxy-1,2-dihydroxy-1,2-dihydronaphthalene **1d** (obtained by biotransformation of 8-methoxy naphthalene) according to the protocol reported in the Scheme 1.

The protocol was firstly optimized on the more convenient (1*R*,2*S*)-1,2-dihydroxy-1,2-dihydronaphthalene **1a**, obtained with higher yields from the bioconversion of naphthalene, and now also a commercially available compound.[6] The optimized protocol was then applied to the preparation of **6d** and (2*R*)-2-amino-1,2,3,4-tet-

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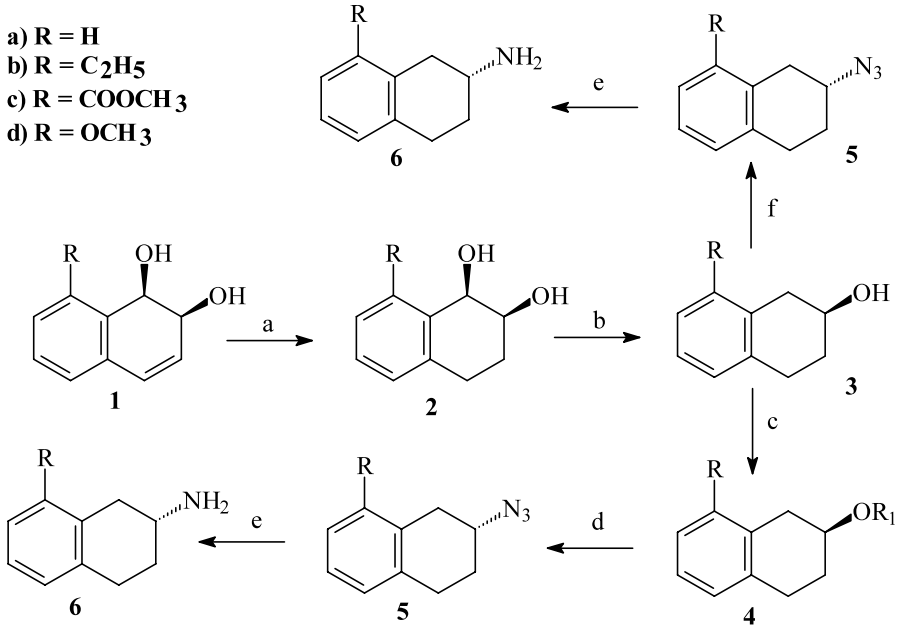

Scheme 1.

rahydronaphthalenes **6b–c**, which are also precursors of bioactive compounds, albeit less active ones than 8-OH-DPAT.

The synthetic protocol reported in Scheme 1 presents two key steps, which required detailed investigation to optimize the experimental conditions.

The first step, involving deoxygenation at the 1-position (benzylic) has been investigated using several experimental conditions, mainly: (a) hydrogenation over palladium on charcoal in the presence of an acid (acetic or trifluoracetic acid) in a polar solvent, either protic (such as methanol) or non-protic (such as ethyl acetate); (b) hydride reduction (sodium borohydride, lithium aluminium hydride or sodium cyanoborohydride) in the presence of a Lewis acid (zinc chloride, zinc iodide, borotrifluoride or aluminium trichloride) in a polar solvent.

The best results were obtained by hydrogenation with palladium on charcoal in the presence of acetic acid (93% yields). Reduction with hydrides in the presence of a Lewis acid afforded only a few percent yield of the expected product with substantial recovery of the starting diol. Under the experimental conditions used for deoxygenation of the 2-position, the 3,4-double bond is also reduced. However, it is not convenient to use a single step to perform both the reduction of the double bond and the deoxygenation of the benzylic position. The *cis*-dihydrodiols **1** are in fact very sensitive to acids, which catalyze the elimination of water to afford the corresponding naphthols which, in turn, autocatalyze the elimination reaction.

For the second key step, the conversion of the hydroxy group at the 2-position to an azido group, two approaches have been tested: (a) a direct approach using biphenyl phosphoryl azide in the presence of triphenylphosphine and diethyl azodicarboxylate[7] and (b) an indirect two-step approach via an intermediate tosylate/mesylate which was subsequently treated with sodium azide.

The latter method has the advantage of higher yields [79% total yields for the two steps, almost twice the 43% obtained in procedure (a)] and does not require chromatographic separations, whereas in contrast purification of the crude material from approach (a) is somewhat troublesome.

The azide **5a** was converted to the 2-amino-tetralin **6a** by hydrogenation on palladium on charcoal in ethyl acetate (83% yield from **5a** and 60.9% total yields from **1a**). The absolute configuration and the enantiomeric purity of **6a** were determined by measurement of the specific rotation and by ^{1}H NMR analysis of the corresponding Mosher's amide [(+)-α-methoxy-α-trifluoromethylphenylacetamide].[8,9]

Once optimized on (1*R*,2*S*)-1,2-dihydroxy-1,2-dihydronaphthalene, the synthetic protocol was then transferred to the synthesis of 2-amino-tetralins **6b–d**, with comparable results in terms of course of the reactions, albeit with lower yields (43 to 47% total yields from **1b–d**).

As reported above for **6a**, the absolute configuration and the enantiomeric purity of (1*R*,2*S*)-1,2-dihydroxy-

1,2-dihydronaphthalene **6b–d** were determined by measurement of their specific rotations and by ^{1}H NMR analysis of the corresponding Mosher' s amide.[8,9]

In summary, we have developed a simple and convenient chemoenzymatic method to synthesize a number of (2*R*)-2-aminotetralins. Added to the implicit advantage of using a biotransformation step for the production of the enantiopure precursors **1a–d**, some other advantages of this strategy are: the availability of the starting naphthalenes used for the biotransformations; the use of simple chemical steps to elaborate the bioproducts using common, low cost reagents and without the need for anhydrous conditions or freshly distilled solvents; reasonable to good total yields and high stereoselection.

3. Experimental

Reagent grade tetrahydrofuran was dried at reflux over $LiAlH_4$ and distilled. Reagent grade dimethylformamide was distilled at reduced pressure under nitrogen and stored over 4 Å molecular sieves. Anhydrous pyridine from Aldrich was used. Naphthalene, 1-ethyl naphthalene, 1-methoxy naphthalene were purchased from Aldrich and directly used. 1-Carbomethoxynaphthalene was synthesized from 1-naphthoic acid (Aldrich) by treatment with methyl iodide in sodium hydroxide–dimethyl sulfoxide solution as already described in the literature.[1] Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded at 200 and 300 MHz on Brucker spectrometers. MS spectra were recorded with a VG7070 E9 spectrometer. Melting points were obtained by using a Buchi 535 apparatus. The $[\alpha]_D$ were obtained with a Perkin–Elmer 241 polarimeter and the elemental analyses for the new compounds were determined on a Perkin–Elmer 240 Analyser. Flash-column chromatographies were performed on silica gel Merck Kieselgel 60 (230–400 mesh ASTM). Thin-layer chromatographies were performed on silica gel plates (60 F254, Merck): spots were detected visually by ultraviolet irradiation (254 nm) or by spraying with methanol:H_2SO_4 9:1, followed by heating at 100°C.

3.1. Biotransformations

3.1.1. Typical procedure.[1] *E. coli* JM109 transformed with the recombinant plasmid (pVL1778)[1] was grown (initial OD equal to 0.1) at 37°C in a 3000 mL flask containing 600 mL of M9 medium with glucose 0.2% (wt/vol), thiamine 1 μg/mL, ampicillin 100 μg/mL, and the inducer salicylic acid 1 mM. When the culture reached the A_{540} of 1.0, the cells were collected, washed twice and resuspended in the same medium, supplied with 1 g/L of the aromatic hydrocarbon and put on a rotatory shaker; the reaction was followed at different incubation times (1–24 h) at 30°C. The cells were then removed by centrifugation for 10 min. The solution was extracted with ethyl acetate (3×300 mL), the organic phases were collected, dried (Na_2SO_4), and evaporated under vacuum. If needed, the product was purified on a silica gel flash column using a 1:1 mixture of hexane–ethyl acetate as eluent.

The bioconversion rates and therefore the bioproduct amounts at a given time depend on the aromatic hydrocarbon used: the latter, easily separable from the bioproduct, can be continuously recycled if not completed biotransformed.

3.2. Syntheses

3.2.1. (1*R*,2*S*)-1,2-Dihydroxy-1,2,3,4-tetrahydronaphthalenes 2a–d, typical procedure. (1*R*,2*S*)-1,2-Dihydroxy-8-methoxy-1,2-dihydronaphthalene **1d** (0.121 g, 0.63 mmol) in ethyl acetate (15 mL) was hydrogenated in the presence of 10% palladium on charcoal (0.039 g) for about 30 min. The suspension was filtered through a Celite pad and the solvent removed under reduced pressure to afford (1*R*,2*S*)-1,2-dihydroxy-8-methoxy-1,2,3,4-tetrahydronaphthalene **2d** (0.123 g) in quantitative yield.

3.2.1.1. (1*R*,2*S*)-1,2-Dihydroxy-8-methoxy-1,2,3,4-tetrahydronaphthalene 2d. Colourless crystals; mp = 129–130°C (*n*-hexane–ethyl acetate); $[\alpha]_D = -26.9$ ($c = 1.1$ $CHCl_3$) ^{1}H NMR ($CDCl_3$): δ 1.85 (1H, m, H-3), 2.0 (1H, m, H-3′) 2.72 (1H, ddd, $J = 16.5$, 9.0, 5.3 Hz, H-4), 2.97 (1H, dd, $J = 16.5$, 5.3 Hz, H-4′), 3.89 (3H, s), 3.95 (1H, dd, $J = 9.8$, 3.7 Hz, H-2), 5.0 (1H, d, $J = 3.7$ Hz, H-1), 6.7 (1H, d, $J = 7.1$ Hz, H-5 or H-7), 6.8 (1H, d, $J = 7.1$ Hz, H-7 or H-5), 7.2 (1H, dd, $J = 7.1$, 7.1 Hz, H-6); ^{13}C NMR ($CDCl_3$): 26.3 (t), 27.6 (t), 55.4 (q), 64.9 (d), 66.9 (d), 107.7 (d), 121.2 (d), 125.2 (s), 128.6 (d), 138.1 (s), 158.3 (s); EI MS, m/z: 194 (M^+), 176 ($M^+ - H_2O$). Calcd for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found: C, 68.23; H, 6.71%.

3.2.1.2. (1*R*,2*S*)-Dihydroxy-1,2,3,4-tetrahydronaphthalene 2a. (Quantitative yield) colorless crystals; mp = 140–142°C (*n*-hexane–ethyl acetate); $[\alpha]_D = -43.0$ ($c =$ 3.28 mg/mL, MeOH) (lit.:[10] $[\alpha]_D = -38.0$ ($c = 8.7$ mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.86 (1H, dddd, $J = 13.5$, 6.0, 6.0 3.6 Hz, H-3), 1.99 (1H, dddd, $J = 13.5$, 9.7, 9.0, 6.0 Hz, H-3′), 2.73 (1H, ddd, $J = 17.1$, 9.0, 6.0 Hz, H-4), 2.93 (1H, ddd, $J = 17.1$, 6.0, 6.0 Hz, H-4′), 3.93 (1H, ddd, $J = 9.7$, 3.6, 3.6 Hz, H-2), 4.62 (1H, d, $J = 3.6$ Hz, H-1), 6.99 (1H, d, $J = 4.7$ Hz, H-5 or H-7), 7.19 (2H, dd, $J = 4.7$, 4.7 Hz), 7.38 (1H, d, $J = 4.7$ Hz); ^{13}C-NMR ($CDCl_3$), 26.11 (t), 26.80 (t), 69.45 (d), 69.90 (d), 126.25 (d), 127.95 (d), 129.45 (d), 129.78 (d), 136.14 (s), 136.38 (s); MS (EI), m/z: 164 (M^+), 146 ($M^+ - H_2O$).

3.2.1.3. (1*R*,2*S*)-1,2-Dihydroxy-8-ethyl-1,2,3,4-tetrahydronaphthalene 2b. (Quantitative yield) colorless crystals mp = 164°C (*n*-hexane–ethyl acetate); $[\alpha]_D = -44.35$ ($c = 0.354$ mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.27 (3H, t, $J = 7.8$ Hz, $\underline{CH_2}$–CH_3), 1.86 (1H, dddd, $J = 12.0$, 11.2, 6.0, 3.0 Hz, H-3), 1.95 (1H, dddd, $J = 12.0$, 12.0, 7.6, 4.2 Hz, H-3′), 2.7–2.95 (2H, m, H-4, H-4′), 2.9 (2H, q, $J = 7.8$ Hz, CH_2–$\underline{CH_3}$), 3.83 (1H, ddd, $J = 11.2$, 4.2, 4.2 Hz, H-2), 4.85 (d, 1H, $J = 4.2$ Hz, H-1), 6.67 (1H, dd, $J = 7.8$, 7.8 Hz, H-6), 7.1 (1H, d, $J = 7.8$ Hz, H-5 or

H-7), 7.2 (1H, d, $J=7.8$ Hz, H-7 or H-5); ^{13}C NMR ($CDCl_3$):15.65 (q), 24.51 (t), 25.36 (t), 28.89 (t), 66.37 (d), 70.49 (d), 126.48 (2C, d), 128.39 (d), 134.0 (s), 136.24 (s), 144.88 (s); EI MS, m/z: 192 (M^+), 174 (M^+-H_2O), 159 ($M^+-H_2O-CH_3$). Calcd for $C_{12}H_{16}O_2$: C, 75; H, 8.3. Found: C, 74.5; H, 7.98%.

3.2.1.4. (1*R*,2*S*)-1,2-Dihydroxy-8-carbomethoxy-1,2,3,4-tetrahydronaphthalene 2c. (Quantitative yield) colorless crystals, mp = 150°C (*n*-hexane–ethyl acetate); $[\alpha]_D=-169$ ($c=2.68$ mg/mL, $CHCl_3$) ^{1}H NMR ($CDCl_3$): δ 1.78–2.21 (2H, m, H-3, H-3′), 2.68-3.02 (2H, m, H-4, H-4′), 3.78 (1H, ddd, $J=13.7$, 4.8, 4.8 Hz, H-2), 3.85 (3H, s), 4.96 (1H, d, $J=4.8$ Hz, H-1), 7.15–7.39 (2H, m, H-5, H-7), 7.68 (1H, dd, $J=7.1$, 7.1 Hz, H-6); ^{13}C NMR ($CDCl_3$): 25.42 (t), 28.95 (t), 52.51 (q), 66.09 (d), 69.44 (d), 127.48 (d), 128.63 (d), 130.75 (s), 133.43 (d), 137.32 (s), 138.14 (s), 169.16 (s). MS, (EI) m/z: 204 (M^+-H_2O). Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.3. Found: C, 64.55; H, 6.15%

3.2.2. (2*S*)-2-Hydroxy-1,2,3,4-tetrahydronaphthalenes 3a–d, typical procedure. (1*R*,2*S*)-1,2-Dihydroxy-8-methoxy-1,2,3,4-tetrahydronaphthalene **2d** (0.114 g, 0.59 mmol) dissolved in ethyl acetate (15 mL) was hydrogenated over palladium on charcoal in the presence of acetic acid (two drops). The suspension was filtered on a Celite pad and the solvent removed under reduced pressure. The crude material (0.1 g) was chromatographed on silica gel (*n*-hexane:ethyl acetate 8:2) to give of (2*S*)-2-hydroxy-8-methoxy-1,2,3,4-tetrahydronaphthalene **3d** (0.075 g, 0.42 mmol, 71%) and 8-methoxy-2-oxo-1,3,4-trihydronaphthalene (0.012 g, 0.07 mmol, 12%).

3.2.2.1. (2*S*)-2-Hydroxy-8-methoxy-1,2,3,4-tetrahydronaphthalene 3d. Colorless crystals, mp = 104°C (*n*-hexane–ethyl acetate); $[\alpha]_D=-50.5$ ($c=8.7$ mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.78 (1H, dddd, $J=12.5$, 7.8, 7.5, 5.0 Hz, H-3), 2.0 (1H, dddd, $J=12.5$, 8.8, 5.3, 2.8 Hz, H-3′), 2.55 (1H, dd, $J'=17.5$, 7.5 Hz, H-1), 2.8 (1H, ddd, $J=16.3$, 8.8, 7.5 Hz, H-4), 2.94 (1H, ddd, $J=16.3$, 5.3, 5.0 Hz, H-4′), 3.07 (1H, dd, $J=17.5$, 5.0 Hz, H-1′), 3.8 (3H, s), 4.13 (1H, dddd, $J=7.8$, 7.5, 5.0, 2.8 Hz, H-2), 6.65 (1H, d, $J=7.6$ Hz, H-5 or H-7), 6.72 (1H, d, $J=7.6$ Hz, H-7 or H-5), 7.1 (1H, dd, $J=7.6$, 7.6 Hz, H-6); ^{13}C NMR ($CDCl_3$): 27.1 (t), 30.9.(t), 32.4 (t), 55.3 (q), 67.1 (d), 107.1, (d), 120.8 (d), 123.3 (s), 126.3 (d), 137.1 (s), 157.5 (s); EI MS, m/z: 178 (M^+), 163 (M^+-Me), 160 (M^+-H_2O), 147 (M^+-OMe), 145 (M^+-H_2O-Me), 129 (M^+-H_2O-OMe). Calcd for $C_{11}H_{14}O_2$: C, 74.16; H, 7.86. Found: C, 71.73; H, 7.17%.

3.2.2.2. (2*S*)-2-Hydroxy-1,2,3,4-tetrahydronaphthalene 3a. (93%), Colorless oil; $[\alpha]_D=-61.9$ ($c=10.7$ mg/mL, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.80 (1H, dddd, $J=12.0$, 6.0, 6.0, 1.5 Hz, H-3), 2.05 (1H, dddd, $J=12.0$, 6.0, 7.5, 7.5 Hz, H-3′), 2.78 (1H, dd, $J'=16.5$, 7.5 Hz, H-1), 2.82 (1H, ddd, $J'=16.5$, 7.5, 6.0 Hz, H-4), 2.97 (1H, ddd, $J=16.5$, 6.0, 6.0 Hz, H-4′), 3.10 (1H, dd, $J=16.5$, 4.5 Hz, H-1′), 4.15 (1H, dddd, $J=7.5$, 7.5, 4.5, 1.5 Hz, H-2), 7.1–7.25 (4H, m, aromatic hydrogens); ^{13}C NMR ($CDCl_3$): 27.8 (t), 32.1 (t), 38.9 (t), 67.7 (d), 124.6 (d), 126.6 (d), 129.3 (d), 130.2 (d), 135.1 (s), 136.4 (s); EI MS, m/z: 148 (M^+), 130 (M^+-H_2O). Calcd for $C_{10}H_{12}O$: C, 81.08; H, 8.11. Found: C, 80.98; H, 8.09%.

3.2.2.3. (2*S*)-8-Ethyl-2-hydroxy-1,2,3,4-tetrahydronaphthalene 3b. (98%), Colorless oil; $[\alpha]_D=-46.3$ ($c=5.38$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.29 (3H, t, $J=7.4$ Hz, CH_2–$\underline{CH_3}$), 1.84 (1H, dddd, $J=15.0$, 15.0, 10.0, 7.0 Hz, H-3), 2.12 (1H, m, H-3′), 2.55-3.08 (3 H, m, H-1, H-4, H-4′), 2.66 (2H, q, $J=7.4$ Hz, $\underline{CH_2}$–CH_3), 3.16 (1H, dd, $J=16.4$, $J=5.0$ Hz, H-1′), 4.20 (1H, m, H-2), 6.99–7.22 (3H, m, aromatic hydrogens); ^{13}C NMR ($CDCl_3$): 14.16 (q), 25.55 (d), 27.71 (t), 31.27 (t), 35.12 (t), 67.64 (d), 125.40 (d), 125.74 (d), 126.24 (d), 132.15 (s), 135.56 (s), 142.43 (s); EI MS, m/z: 176 (M^+), 158 (M^+-H_2O), 143 (M^+-H_2O-Me). Calcd for $C_{12}H_{16}O$: C, 81.82; H, 9.15. Found: C, 80.54; H, 8.92%.

3.2.2.4. (2*S*)-8-Carbomethoxy-2-hydroxy-1,2,3,4-tetrahydronaphthalene 3c. (70%), Colorless oil, $[\alpha]_D=-3.2$ ($c=5.67$ mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.73 (1H, m, H-3), 2.03 (1H, m, H-3′), 2.73–3.19 (2H, m, H-4, H-4′), 3.04 (1H, dd, $J=16.0$, 6.4 Hz, H-1), 3.44 (1H, dd, $J=16.0$, 4.8 Hz, H-1′), 3.86 (3H, s), 4.15 (1H, m, H-2), 7.11–7.17 (2H, m), 7.70 (1H, d, $J=8.0$ Hz); ^{13}C NMR ($CDCl_3$): 27.19 (t), 30.20 (t), 36.73 (t), 51.81 (q), 66.68 (d), 125.39 (d), 128.24 (d), 130.50 (s), 132.55 (d), 135.60 (s), 136.97 (s), 168.40 (s); EI MS, m/z: 206 (M^+), 188 (M^+-H_2O). Calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 69.56; H, 6.90%.

3.2.3. (2*S*)-2-*p*-Toluenesulphonyloxy-1,2,3,4-tetrahydronaphthalenes 4a–d, typical procedure. To a solution of alcohol **3d** (0.065 g, 0.36 mmol) in dry pyridine (0.7 mL) at 0°C was added *p*-toluensulphonyl chloride (0.102 g, 0.43 mmol). The reaction was monitored by thin layer chromatography (silica gel, eluting with *n*-hexane:ethyl acetate 7:3), then poured into ice water and extracted with ethyl acetate (3×7 mL). The combined organic extracts were washed with 0.3N HCl to acid pH, then with a saturated NaCl solution to neutral pH. The organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude material (0.116 g) was chromatographed (silica gel, eluting with *n*-hexane:ethyl acetate 9:1) and afforded tosylate **4d** (0.089 g, 0.27 mmol, 75%) and unreacted alcohol **3d** (0.006 g, 0.034 mmol, 10%).

3.2.3.1. (2*S*)-8-Methoxy-2-toluenesulphonyloxy-1,2,3,4-tetrahydronaphthalene 4d. Colorless oil; $[\alpha]_D=-33.5$ ($c=11.9$ mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.95–2.05 (2H, m, H-3, H-3′), 2.5 (3H, s), 2.79 (1H, ddd, $J=17.0$, 6.0, 6.0 Hz, H-4), 2.81 (1H, dd, $J=17.0$, 5.5 Hz, H-1′), 2.95 (1H, ddd, $J=17.0$, 6.0, 6.0 Hz, H-4′), 2.96 (1H, dd, $J=17.0$, 5.5 Hz, H-1′), 3.76 (3H, s), 4.85 (1H, dddd, $J=5.5$, 5.5, 5.4, 5.4 Hz, H-2), 6.62 (1H, d, $J=7.9$ Hz, H-5 or H-7), 6.68 (1H, d, $J=7.9$ Hz, H-7 or H-5), 7.1 (1H, dd, $J=7.9$ $J=7.9$ Hz, H-6), 7.35 (2H, d, $J=7.9$ Hz, H-3′ or H-5′), 7.82 (2H, d, $J=7.9$ Hz, H-2′ or H-6′); ^{13}C NMR ($CDCl_3$): 21.6 (q), 25.96 (t), 28.2 (t), 29.4 (t), 55.1 (q), 78.5 (d), 107.1 (d), 120.6 (d), 121.4 (s), 126.6 (d), 127.6 (2C, d), 129.7 (2C, d), 134.5 (s), 136.1 (s), 144.4 (s), 157.2 (s); EI MS, m/z: 332 (M^+),

160 (M^+–PTSH). Calcd for $C_{18}H_{20}O_4S$: C, 65.06; H, 6.02. Found: C, 65.35; H, 6.1%.

3.2.3.2. (2*S*)-2-*p*-Toluenesulphonyloxy-1,2,3,4-tetrahydronaphthalene 4a. (83%): Colorless crystals; mp = 86°C (*n*-hexane–ethyl acetate); $[\alpha]_D = -42.9$ ($c = 16.4$ mg/mL, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.95-2.05 (2H, m, H-3, H-3′), 2.47 (3H, s), 2.68–3.14 (3H, H-1, H-4, H-4′), 3.20 (1H, dd, $J = 17.0$, 5.0 Hz, H-1′), 4.94 (1H, dddd, $J = 12.9$, 6.4, 7.1, 7.1 Hz, H-2), 6.95–7.20 (4H, aromatic hydrogens), 7.35 (2H, d, $J = 7.9$ Hz, H-2″, H-6″ or H-3″, H-5″), 7.83 (2H, d, $J = 7.9$ Hz, H-3″, H-5″ or H-6″, H-2″); ^{13}C NMR ($CDCl_3$): 21.6 (q), 26.15 (t), 28.66 (t), 35.23 (t), 78.33 (d), 126.10 (d), 126.34 (d), 127.66 (2C, d), 128.55 (d), 129.17 (d), 129.85 (2C, d), 132.46 (s), 134.59 (s), 134.94 (s), 144.59 (s); EI MS, m/z: 172 ($PTSH^+$), 130 (M^+–PTSH). Calcd for $C_{17}H_{18}O_3S$: C, 67.50; H, 6.00. Found: C, 67.09; H, 5.86%.

3.2.3.3. (2*S*)-8-Ethyl-2-toluenesulphonyloxy-1,2,3,4-tetrahydronaphthalene 4b. (76%) colorless syrup; $[\alpha]_D = -43.2$ ($c = 8.19$ mg/mL, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.16 (3H, t, $J = 7.5$ Hz, $\underline{CH_3}$–CH_2), 1.97–2.10 (2H, H-3, H-3′), 2.48 (3H, s), 2.49 (2H, q, $J = 7.5$ Hz, CH_3-$\underline{CH_2}$), 2.72–3.07 (4H, H–1, H-1′, H-4, H-4′), 5.00 (1H, m, H-2), 6.92–7.10 (3H, aromatic hydrogens), 7.38 (2H, d, $J = 8.0$ Hz, H-2″, H-6″ or H-3″, H-5″), 7.86 (2H, d, $J = 8.0$ Hz, H-3″, H-5″ or H-6″, H-2″); ^{13}C NMR ($CDCl_3$): 13.95 (q), 21.45 (q), 25.37 (t), 26.63 (t), 28.25 (t), 32.02 (t), 78.86 (d), 125.62 (d), 126.14 (2C, d), 127.54 (2C, d), 129.69 (2C, d), 130.26 (s), 134.41 (s), 134.73 (s), 142.20 (s), 144.50 (s); EI MS, m/z: 158 (M^+–PTSH). Calcd for $C_{19}H_{22}O_3S$: C, 69.1; H, 6.70. Found: C, 69.23; H, 6.83%.

3.2.3.4. (2*S*)-8-Carbomethoxy-2-toluenesulphonyloxy-1,2,3,4-tetrahydronaphthalene 4c. (90%), Colorless syrup; $[\alpha]_D = -4.4$ ($c = 14.4$ mg/mL, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.99 (1H, m, H-3), 2.08 (1H, m, H-3′), 2.42 (3H, s), 2.78 (1H, ddd, $J = 17.1$, 6.4, 6.4 Hz, H-4), 3.02 (1H, ddd, $J = 17.1$, 6.4, 6.4 Hz, H-4′), 3.21 (1H, dd, $J = 17.1$, 6.4 Hz, H-1), 3.31 (1H, dd, $J = 17.1$, 4.8 Hz, H-1′), 3.80 (3H, s), 4.97 (1H, m, H-2), 7.14 (1H, dd, $J = 7.9$, 7.9 Hz, H-6), 7.18 (1H, d, $J = 7.9$ Hz, H-5 or H-7), 7.30 (2H, d, $J = 7.9$ Hz, H-2″, H-6″ or H-3″, H-5″), 7.69 (1H, d, $J = 7.9$ Hz, H-7 or H-5), 7.77 (2H, d, $J = 7.9$ Hz, H-3″, H-5″ or H-6″, H-2″); ^{13}C NMR ($CDCl_3$): 21.54 (q), 26.10 (t), 27.61 (t), 33.64 (t), 51.76 (q), 78.04 (d), 125.81 (d), 127.61 (2C, d), 128.71 (d), 129.75 (2C, d), 130.09 (s), 132.72 (d), 133.91 (s), 134.65 (s), 136.27 (s), 144.48 (s), 167.64 (s). EI MS, m/z: 360 (M^+), 329 (M^+–OCH_3), 188 (M^+–PTSH), 156 (M^+–PTSH–H_3OH). Calcd for $C_{19}H_{20}O_5S$: C, 63.33; H, 5.56. Found: C, 63.81; H, 5.83%.

3.2.4. (2*R*)-2-Azido-1,2,3,4-tetrahydronaphthalenes 5a–d.
(a) From tosylates 4a–d, typical procedure. To a solution of tosylate **4d** (0.073 g, 0.22 mmol) in dimethylformamide (0.7 mL) was added sodium azide (Fluka) (0.23 g, 0.35 mmol). The reaction flask was immersed into a pre-heated (110°C) oil bath. The reaction was monitored by thin-layer chromatography (silica gel, eluting with *n*-hexane:ethyl acetate 7:3). After 1 h at 110°C, the solution was cooled, diluted with water (4 mL) and extracted with *n*-pentane (3×5 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to afford azide **5d** (0.040 g, 0.2 mmol, 91%).

(b) From alcohols 3a–d, typical procedure. (1*R*,2*S*)-1,2-Dihydroxy-1,2,3,4-tetrahydronaphthalene **3a** (0.145 g, 0.98 mmol) was added at 0°C to a solution of triphenylphosphine (0.257 g, 0.98 mmol) and diethylazodicarboxylate (0.171 g, 0.98 mmol) in dry tetrahydrofuran (3 mL). After stirring the mixture for 10 min. diphenylphosphoryl azide (0.270 g, 0.98 mmol) was added dropwise. The reaction was monitored by thin-layer chromatography (silica gel, eluting with *n*-hexane:ethyl acetate 1:1). After stirring the mixture for 43 h, the solvent was removed under reduced pressure. The crude material (1.043 g) was purified by column chromatography (silica gel, eluting with *n*-hexane:ethyl acetate 8/2, 1/1) to afford azide **5a** (0.073 g, 0.42 mmol, 43%), accompanied by an unidentified compound (0.021 g).

3.2.4.1. (2*R*)-2-Azido-8-methoxy-1,2,3,4-tetrahydronaphthalene 5d. (Procedure a): colorless oil; $[\alpha]_D = +34.8$ ($c = 5.4$ mg/mL, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.86 (1H, dddd, $J = 13.0$, 9.0, 6.0, 6.0 Hz, H-3), 2.09 (1H, dddd, $J = 13.0$, 6.0, 6.0, 3.0 Hz, H-3′), 2.66 (1H, dd, $J = 17.0$, 8.0 Hz, H-1), 2.83 (1H, ddd, $J = 17.0$, 9.0, 6.0 Hz, H-4), 2.96 (1H, ddd, $J = 17.0$, 6.0, 6.0 Hz, H-4′), 3.09 (1H, dd, $J = 17.0$, 6.0 Hz, H-1′), 3.80 (3H, s), 3.85 (1H, dddd, $J = 8.0$, 6.0, 6.0, 3.0 Hz, H-2), 6.6 (1H, d, $J = 7.8$ Hz, H-5 or H-7), 6.7 (1H, d, $J = 7.8$ Hz, H-7 or H-5), 7.15 (1H, dd, $J = 7.8$, 7.8 Hz, H-6); ^{13}C NMR ($CDCl_3$): 27.2 (t), 27.7 (t), 28.7 (t), 55.5 (d), 57.2 (q), 107.2 (d), 120.8 (d), 122.4 (s), 126.6 (d), 136.5 (s), 157.4 (s); EI MS, m/z: 203 (M^+), 175 (M^+–N_2), 161 (M^+–N_3), 160 (M^+–CH_3–N_2).

3.2.4.2. (2*R*)-2-Azido-1,2,3,4-tetrahydronaphthalene 5a. (97%) (Procedure a): colorless oil; $[\alpha]_D = +59.3$ ($c = 6$ mg/mL, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.9 (1H dddd, $J = 17.0$, 5.0, 5.0, 1.7 Hz, H-3), 2.10 (1H, dddd, $J = 17.0$, 7.5, 5.5, 5.5 Hz, H-3′), 2.82 (1H, dd, $J = 16.5$, 8.6 Hz, H-1), 2.85 (1H, ddd, $J = 16.5$, 5.5, 5.0 Hz, H-4), 2.88 (1H, ddd, $J = 16.5$, 5.5, 5.0 Hz, H-4′), 3.08 (1H, dd, $J = 16.5$, 5.0 Hz, H-1′), 3.88 (1H, dddd, $J = 8.6$, 7.5, 5.0, 1.7 Hz, H-2), 7.05-7.15 (4H, aromatic hydrogens); ^{13}C NMR ($CDCl_3$): 27.04 (t), 28.08 (t), 29.68 (t), 57.07 (d), 126.05 (d), 126.32 (d), 128.70 (d), 129.23 (d), 133.67 (s), 135.17 (s); MS (FAB), m/z: 185 (M^++Ca–N_2).

3.2.4.3. (2*R*)-2-Azido-8-ethyl-1,2,3,4-tetrahydronaphthalene 5b. (76%) (Procedure a): colorless thick oil; $[\alpha]_D = +34.1$ ($c = 20$ mg/mL, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.27 (3H, t, $J = 7.5$ Hz, $\underline{CH_3}CH_2$), 1.88 (1H, dddd, $J = 15.5$, 9.9, 9.9, 5.8 Hz, H-3), 2.17 (1H, H-3′) 2.64 (2H, q, $J = 7.5$ Hz, $CH_3\underline{CH_2}$), 2.74 (1H, dd, $J = 17.1$, 8.6 Hz, H-1), 2.84–3.06 (2H, H-4, H-4′), 3.12 (1H, dd $J = 17.1$, 6.2 Hz, H-1′), 3.91 (1H, m, H-2), 7.01 (1H, d, $J = 7.1$ Hz, H-5 or H-7), 7.08 (1H, d, $J = 7.1$ Hz, H-7 or H-5), 7.16 (1H, dd, $J = 7.1$, 7.1 Hz,

H-6); ^{13}C NMR ($CDCl_3$): 14.30 (q), 25.68 (t), 27.84 (2C, t), 31.63 (t), 57.71 (d), 125.81 (d), 126.23 (d), 124.54 (d), 131.30 (s), 135.23 (s), 142.50 (s); EI MS, m/z: 201 (M^+), 158 (M^+-N_2–Me), 144 (M^+-N_3–Me).

3.2.4.4. (2*R*)-2-Azido-8-carbomethoxy-1,2,3,4-tetrahydronaphthalene 5c. (90%) (Procedure a): colorless thick oil; $[\alpha]_D=+8.8$ ($c=26.1$ mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.7 (1H, m, H-3), 2.06 (1H, m, H-3′), 3.2–3.75 (4H, H-1, H-1′ H-4, H-4′), 3.45 (1H, dd, $J=18.0$, 5.0 Hz, H-1′), 3.9 (3H, s), 7.15 (1H, d, $J=6.5$ Hz, H-5 or H-7), 7.20 (1H, d, $J=6.5$ Hz, H-7 or H-5), 7.78 (1H, dd, $J=6.5$, 6.5 Hz, H-6); ^{13}C NMR ($CDCl_3$): 27.04 (t), 27.22 (t), 33.04 (t), 51.81 (d), 56.96 (q), 125.69 (d), 128.58 (d), 132.74 (d), 130.10 (s), 134.83 (s), 136.41 (s), 167.81 (s); EI MS, m/z: 203 (M^+-N_2), 200 (M^+–OMe), 188 (M^+-N_2–Me).

3.2.5. (2*R*)-2-Amino-1,2,3,4-tetrahydronaphthalenes 6a–d, typical procedure. A suspension of **5d** (0.038 g, 0.19 mmol) and 10% palladium (0.013 g) on charcoal in ethyl acetate (3 mL) were stirred under a hydrogen atmosphere. The reaction was monitored by thin-layer chromatography (silica gel, eluting with chloroform:methanol:*iso*-propylamine 9:0.5:0.5). After 2 h, the suspension was filtered on a Celite pad. The solvent was removed under reduced pressure and gave amine **6d** (0.030 g, 0.17 mmol, 89%).

3.2.5.1. (2*R*)-2-Amino-8-methoxy-1,2,3,4-tetrahydronaphthalene 6d. Colorless crystals; mp = 103–104°C (ethyl acetate–di-*iso*-propyl ether); $[\alpha]_D=+79.7$ ($c=5.8$ mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.55 (1H, dddd, $J=12.3$, 8.5, 5.5, 1.5 Hz, H-3), 1.95 (1H, dddd, $J=12.3$, 4.3, 4.3, 1.5 Hz, H-3′), 2.26 (1H, dd, $J=16.7$, 8.9 Hz, H-1), 2.8-2.85 (2H, H-4, H-4′), 3.05 (1H, dd, $J=16.7$, 5.1 Hz, H-1′), 3.10 (1H, dddd, $J=8.9$, 8.5, 5.1, 1.5 Hz, H-2), 3.8 (3H, s), 6.65 (1H, d, $J=7.5$ Hz, H-5 or H-7), 6.70 (1H, d, $J=7.5$ Hz, H-7 or H-5), 7.1 (1H, dd, $J=7.5$, 7.5 Hz, H-6); ^{13}C NMR ($CDCl_3$): 28.9 (t), 32.2 (t), 33.2 (t), 47.2 (d), 55.2 (q), 107.0 (d), 120.9 (d), 124.2 (s), 125.6 (d), 137.2 (s), 157.4 (s); EI MS, m/z: 177 (M^+), 160 (M^+-NH_3), 145 ($M^+-NH_3-CH_3$). Calcd for $C_{11}H_{15}NO$: C, 74.58; H, 8.47. Found: C, 74.20; H, 8.20%.

3.2.5.2. (2*R*)-2-Amino-1,2,3,4-tetrahydronaphthalene 6a. (83%); Colorless crystals; mp = 97–99°C (ethyl acetate–di-*iso*-propyl ether) $[\alpha]_D=+85.4$ ($c=5.0$ mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.63 (1H, dddd, $J=14.0$, 10.0, 9.5, 6.7 Hz, H-3), 1.99 (1H, m, H-3′), 2.58 (1H, ddd, $J=17.0$, 9.5 Hz, H-1), 2.85 (1H, m, H-4), 2.91 (1H, m, H-4′), 3.02 (1H, ddd, $J=17.0$, 4.0 Hz, H-1′), 3.21 (1H, dddd, $J=9.5$, 9.5, 4.0, 3.0 Hz, H-2), 7.02–7.20 (4H, aromatic hydrogens); ^{13}C NMR ($CDCl_3$): 28.06 (t), 38.82 (t), 39.37 (t), 47.08 (d), 2×125.77 (d), 128.67 (d), 129.31 (d), 135.26 (s), 135.85 (s); EI MS, m/z: 147 (M^+), 130 (M^+-NH_3). Calcd for $C_{10}H_{13}N$: C, 81.63; H, 8.84. Found: C, 81.93; H, 8.70%.

3.2.5.3. (2R)-2-Amino-8-ethyl-1,2,3,4-tetrahydronaphthalene 6b. (83%); Colorless crystals, mp = 111–112°C (ethyl acetate–di-isopropyl ether); $[\alpha]_D=+73.0$ ($c=8.05$ mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.19 (3H, t, $J=8.0$ Hz, $\underline{CH_3}CH_2$), 1.58 (1H, dddd, $J=13.0$, 10.0, 4.0, 4.0 Hz, H-3), 1.99 (1H, dddd, $J=13.0$, 8.0, 8.0, 2.5 Hz, H-3′), 2.4 (1H, dd, $J=16.0$, 5.0 Hz, H-1), 2.59 (2H, q, $J=8.0$ Hz, $CH_3\underline{CH_2}$), 2.89 (2H, m, H-4, H-4′), 3.04 (1H, dd, $J=16.0$, 5.0 Hz, H-1′), 3.19 (1H, dddd, $J=10.0$, 8.0, 5.0, 2.5 Hz, H-2), 6.95 (1H, d, $J=7.5$ Hz, H-5 or H-7), 7.02 (1H, d, $J=7.5$ Hz, H-7 or H-5), 7.08 (1H, dd, $J=7.5$, 7.5 Hz, H-6); ^{13}C NMR ($CDCl_3$): 14.28 (q), 25.65 (t), 28.88 (t), 32.52 (t), 35.93 (t), 47.84 (d), 125.46 (d), 125.75 (d), 126.59 (d), 132.98 (s), 135.81 (s), 142.4 (s); EI MS, m/z: 175 (M^+), 158 (M^+-NH_3) 143 (M^+-NH_3–Me). Calcd for $C_{12}H_{17}N$: C, 82.29; H, 9.7. Found: C, 82.09; H, 9.6%.

3.2.5.4. (2*R*)-2-Amino-8-carbomethoxy-1,2,3,4-tetrahydronaphthalene 6c. (80%); Colorless crystals, mp = 102–104°C (ethyl acetate–di-isopropyl ether); $[\alpha]_D=+119.25$ ($c=5.2$ mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.60 (1H, m, H-3), 2.00 (1H, m, H-3′), 2.77 (1H, dd, $J=17.0$, 9.0 Hz, H-1), 2.90–2.95 (2H, m, H-4, H-4′), 3.15 (1H, m, H-2), 3.40 (1H, dd, $J=17.0$, 5.0Hz, H-1′), 3.85 (3H, s), 7.15 (1H, dd, $J=7.9$ Hz, H-6), 7.25 (1H, d, $J=7.9$ Hz, H-5 or H-7), 7.68 (1H, d, $J=7.9$ Hz, H-7 or H-5). ^{13}C NMR ($CDCl_3$) 28.80 (t); 31.54 (t); 37.86 (t); 47.20 (d); 51.76 (q); 125.27 (d); 128.06 (d); 130.25 (s); 132.58 (d); 136.49 (s); 137.08 (s); 168.26 (s). EI MS, m/z: 205 (M^+), 188 (M^+-NH_3); 174 (M^+–OMe), 156 (M^+-NH_3–MeOH). Calcd for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.32. Found: C, 70.51; H, 7.12%

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