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Enzymatic asymmetrisation of prochiral α,α-disubstituted-malonates and -1,3-propanediols: formal asymmetric syntheses of (−)-aphanorphine and (+)-eptazocine[1]

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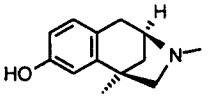
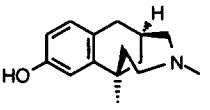
Abstract: Formal asymmetric syntheses of (−)-aphanorphine and (+)-eptazocine are reported via the two key intermediates **3a** and **3b** obtained in 94–97% ee, from the readily available chirons (R)-**5** and (R)-**9**. Which resulting from enzyme-catalysed asymmetrisation of prochiral α,α-disubstituted-1,3-propanediols and -malonates respectively. © 1997 Elsevier Science Ltd. All rights reserved.

Stereogenic quaternary carbon centres are found in many naturally occuring compounds and benzylic centres in particular in various analgesics such as (−)-aphanorphine **1** and (−)-eptazocine **2**.[2] Convenient methods for their enantioselective construction have been investigated.[3,4] In previous papers, we have described the asymmetric construction of quaternary carbons from chiral malonates [5] and their subsequent transformation into both enantiomers of (−)-aphanorphine **1** and (+)-eptazocine **2**.[6]

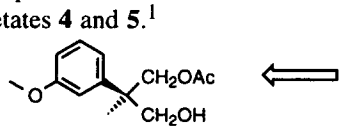


(-)-**1**- aphanorphine

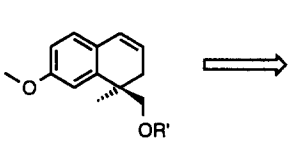


2-(+)- eptazocine

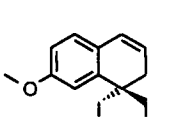
Pharmacological active alkaloids such as eptazocine and aphanorphine have been prepared from the dihydronaphthalene **3**, an efficient common precursor, which could be readily accessed from chiral monoacetates **4** and **5**.[1]



(*R*)-(+)-**4**



(*R*)-(-)-**3a** : R' = H
(*R*)-(-)-**3b** : R' = Bn



(*R*)-(+)-**5**

Herein we wish to describe two routes to (−)-aphanorphine **1** and (+)-eptazocine **2**.

The chiral monoacetate (*R*)-**4** was readily prepared by transesterification of diol **6** in presence of isopropenyl acetate with lipase *Pseudomonas cepacia* immobilised on Hyflo Super Cell (PSL/HSC, for details see ref. [1]) with 85.5% yield and 71% ee. The transformation was accomplished by protection (TBDMSCl, DMAP, CH_2Cl_2, 74%) and subsequent hydrolysis (K_2CO_3, MeOH, rt, 3 h, 90%) into **7a** (70% ee).

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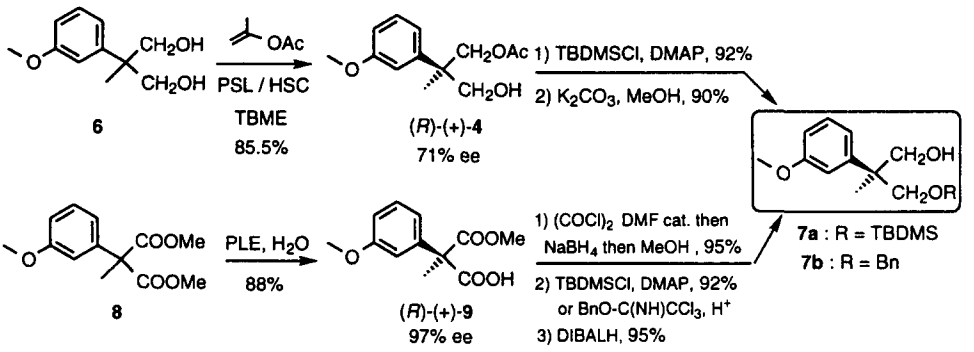
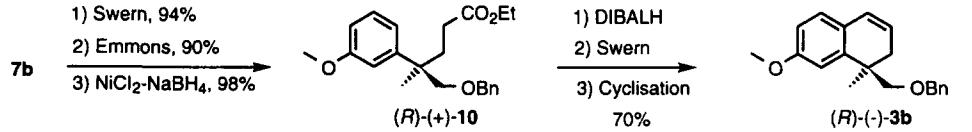
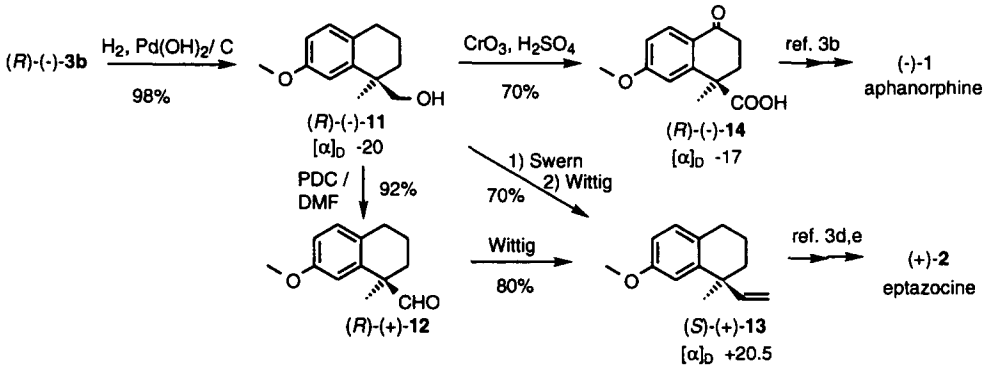


A second and more efficient approach was also investigated. As we described earlier the enantioselective enzymatic hydrolysis of prochiral malonates **8** (PLE, H_2O, 88%) gave the half-ester (*R*)-**9** with 94% ee (97% ee after crystallisation).[6] Subsequent chemoselective reduction of the acid, protection of the resulting alcohol and reduction of the ester function afforded the alcohol **7b** with 83% overall yield.[6]

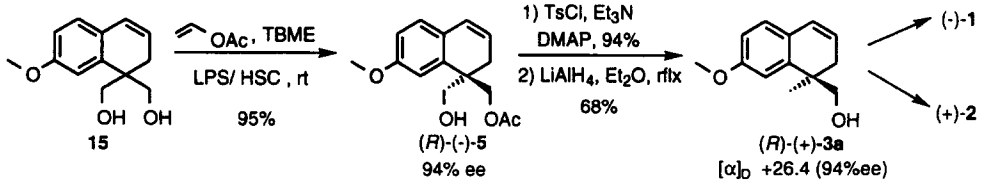


Thus, for our strategy, the protected alcohol **7b** was subjected to Swern oxidation (94%) and subsequent Emmons reaction under Masamune's conditions [$(EtO)_2P(O)CH_2CO_2Et$, DBU, LiCl, 90%).[8] The resulting conjugated ester was reduced without affecting the ester group by the use of nickel boride generated in situ ($NaBH_4.NiCl_2.6H_2O$)[9] to afford the ester (*R*)-(+)-**10** with 98% yield.[10] Reduction (DIBALH) of (*R*)-(+)-**10**, then Swern oxidation[7] followed by a one pot acidic Friedel-Craft cyclisation and dehydration (cat. 6N HCl, CH_2Cl_2, on silica gel) furnished the dihydronaphthalene **3b**[11] in 70% overall yield from **10** [$[\alpha]_D^{20}$ −7.1 (c=1, $CHCl_3$)].



With dihydronaphthalene (−)-**3b** in hand, hydrogenolysis (H_2, $Pd(OH)_2/C$, 3 h, 98%) gave complete reduction to the alcohol (*R*)-**11**.[12] Oxidation to the aldehyde (+)-**12** was accomplished with high yield (PDC/DMF, 92%). A Wittig reaction (Ph_3PCH_3Br, nBuLi, THF, 80%) converted (+)-**12** into the olefin (*S*)-(+)-**13**, ($[\alpha]_D^{20}$ +20.5 (c=1, $CHCl_3$), 97% ee): lit.[3e] $[\alpha]_D^{20}$ −21.1 (c=3.8, $CHCl_3$), for its antipode (*R*). The enantiomeric excess was determined by GC using a chiral column (Cydex B, 82°C, 0.7 bar). Spectroscopic data for olefin **13** were found to be in agreement with those reported.[3e] The (*R*)-(−)-**13**, prepared from another synthetic route, has already been shown to be an intermediate in the synthesis of (−)-eptazocine **2**.[3d,e] Moreover oxidation of alcohol **11** (CrO_3, H_2SO_4)[13] gave the keto acid **14**[14] with 70% yield, ($[\alpha]_D^{20}$ −17 (c=0.7, $CHCl_3$), ee 97%). The transformation constitutes a formal

synthesis of (−)-aphanorphine as reported.[3b] On the other hand the alcohol (*R*)-**3a**, key intermediate in the synthesis of (−)-aphanorphine,[3b] could also be obtained from the prochiral diol **15**.



As we previously reported,[1] this prochiral diol **15**[15] gave in high ee (94%) the monoacetate (*R*)-**5**, and its transformation into (*R*)-**3a** was accomplished in two steps: protection of the alcohol **5** (TsCl, NEt_3, DMAP cat., CH_2Cl_2, 94%) followed by complete reduction ($LiAlH_4$, THF, reflux, 1h, 70%)[16] into the expected (*R*)-**3**. $[\alpha]_D^{20}$ +26.4 (c=1, $CHCl_3$),[17] 94% ee determined by GC (Cydex B, 140°, 1 bar); lit.[3e] $[\alpha]_D^{20}$ −27.4 (c=2.1, $CHCl_3$) for its antipode (*S*).

In summary, a method for the synthesis of chiral benzylic quaternary centres has been developed in which the chirons were readily available by enzyme-catalysed asymmetrisation (ee 94–97%). The synthesis of chiral nonracemic alcohols (*R*)-**3a** and (*R*)-**11**, key intermediates in the syntheses of (−)-aphanorphine and (+)-eptazocine, has demonstrated the utility of this methodology. Further synthetic applications of this approach to other alkaloids e.g. pentazocine and normetazocine are currently under investigation.

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10. ***Data of (+)-10***: $[\alpha]_D^{20}$ +4.6 (c=1, $CHCl_3$); *IR (neat)* 1725, 1610, 1600, 1585 cm^{-1}; *^1H NMR ($CDCl_3$)* δ 7.42–7.13 (m, 6H), 6.98–6.84 (m, 2H), 6.84–6.71 (m, 1H), 4.49 (s, 2H), 4.06 (q, J=7.4 Hz, 2H), 3.80 (s, 3H), 3.50 (s, 2H), 2.25–1.92 (m, 4H), 1.37 (s, 3H), 1.22 (t, J=7.4 Hz, 3H); *^{13}C NMR ($CDCl_3$)* δ 173.9 (s), [12 arom.C, 159.5 (s), 146.6 (s), 138.5 (s), 129.1 (d), 128.2 (2d), 127.4 (3d), 118.9 (d), 113.1 (d), 110.8 (d)], 78.8 (t), 73.2 (t), 60.2 (t), 55.1 (q), 42.0 (s), 33.7 (t), 29.6 (t), 22.6 (q), 14.2 (q). *Anal. calcd for $C_{22}H_{28}O_4$*: C, 74.12; H, 7.92. Found: C, 73.92; H, 7.72.

11. ***Data of (−)-3b***: $[\alpha]_D^{20}$ −7.1 (c=1, $CHCl_3$); *^1H NMR ($CDCl_3$)* δ 7.45–7.20 (m, 5H), 7.00 (d, J=8.2 Hz, 1H), 6.92 (d, J=2.4 Hz, 1H), 6.73 (dd, J=8.2, 2.4 Hz, 1H), 6.40 (br.d, J=9.3 Hz, 1H), 5.88–5.73 (m, 1H), 4.50 (s, 2H), 3.81 (s, 3H), 3.40 (AB syst.$\Delta\nu_{AB}$=64.7 Hz, J_{AB}=9.3 Hz, 2H), 2.58 (A part of ABXY syst., J_{AB}=17.4 Hz, J_{AX}=5. 3 Hz, J_{AY}=1Hz, 1H), 2.15 (B part of ABXY, J_{AB}=17.4 Hz, J_{BX}=3.5 Hz, J_{BY}=2.5 Hz, 1H), 1.37 (s, 3H); *^{13}C NMR ($CDCl_3$)* δ [12 arom.C, 158.9 (s), 142.0 (s), 138.7 (s), 128.2 (2d), 127.5 (d), 127.35 (2d), 127.3 (d), 126.9 (s), 112.1 (d), 110.6 (d)], 126.8 (d, C=C), 124.2 (d, C=C), 75.7 (t), 73.2 (t), 55.2 (q), 38.2 (s), 32.9 (t), 23.6 (q). *Anal. calcd for $C_{20}H_{22}O_2$:* C, 81.59; H, 7.54. Found: C, 81.47; H, 7.49.
12. ***Data of (R)-11***: $[\alpha]_D^{20}$ −20 (c=1, $CHCl_3$); *IR (neat)* 3400, 1615, 1575, 1500, 1240, 1040 cm^{-1}; *^1H NMR ($CDCl_3$)* δ 7.05 (d, J=8.5 Hz, 1H), 6.85 (d, J=2.8 Hz, 1H), 6.72 (dd, J=8.5, 2.8 Hz, 1H), 3.80 (s, 3H), 3.68 (AB syst. $\Delta\nu_{AB}$=97.5 Hz, J_{AB}=10.5 Hz, 2H), 2.71 (t, J=6.5 Hz, 2H), 2.12–1.91 (m, 1H), 1.91–1.65 (m, 2H), 1.65–1.45 (m, 1H), 1.45–1.28 (br.s, OH), 1.25 (s, 3H); *^{13}C NMR ($CDCl_3$)* δ [6 arom.C, 157.8 (s), 142.2 (s), 130.4 (s), 130.2 (d), 112.1 (d), 111.4 (d)], 71.7 (t), 55.2 (q), 39.5 (s), 33.4 (t), 29.7 (t), 26.6 (t), 19.6 (q). *Anal. calcd for $C_{13}H_{18}O_2$:* C, 75.68; H, 8.80. Found: C, 75.67; H, 8.83.
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14. ***Data of 14***: $[\alpha]_D^{20}$ −17 (c=0.7, $CHCl_3$); *IR ($CHCl_3$)* 3500, 3300, 1745, 1710, 1680, 1605, 1290 cm^{-1}; *^1H NMR ($CDCl_3$)* δ 10.50 (br.s, H), 8.10–8.00 (m, 1H), 6.95–6.80 (m, 2H), 3.88 (s, 3H), 3.00–2.40 (m, 3H), 2.24–1.95 (m, 1H), 1.70 (s, 3H); *^{13}C NMR ($CDCl_3$)* δ 196.8 (s), 180.8 (s), [6 arom.C, 163.9 (s), 146.8 (s), 130.1 (d), 125.3 (s), 113.1 (d), 112.7 (d)], 55.5 (q), 45.9 (s), 34.9 (t), 33.7 (t), 25.7 (q).
15. Very recently, the corresponding malonate was used to prepare the chiral acid ester according to ref. 5(c),6 by enzymatic hydrolysis with PLE, see: Hallinan, K.O.; Honda, T. *Tetrahedron* **1995**, *51*, 12211.
16. Better yield was obtained with $LiAlH_4$ in THF at reflux rather than in ether (see ref. 1). Other conditions (DIBALH, $LiBEt_3H$, or $NaBH_4$–DMSO) did not improve the yield.
17. Unfortunately an error in the specific rotation of the alcohol (*R*)-(+)-**3** was reported by us (ref. 6), the value should be +28 and not +18.3 (c=1, $CHCl_3$).

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