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An efficient asymmetric synthesis of key intermediates in the synthesis of aphanorphine and eptazocine

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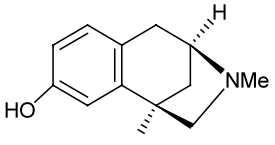
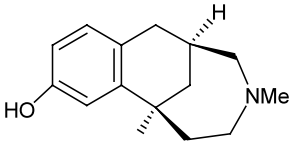
Abstract—Efficient, formal syntheses of aphanorphine and eptazocine are reported that involve epoxide cyclizations. The necessary chiral epoxides were prepared following treatment of diols prepared by Sharpless asymmetric osmylations of an alkene. The cyclizations formed a ring compound with the same enantiomeric purity as the starting epoxide.

1. Introduction

The narcotic aphanorphine[1–7] **1** and the analgesic eptazocine[7–12] **2** have received significant recent attention. The interest in these morphine analogs arises from their significant bioactivity,[1–12] and also from the synthetic challenge of constructing their quaternary benzylic carbon centers.[13–15] Both the natural[3–7,11,12] and unnatural[2,8,11,12] enantiomers have been prepared, although with **2** the unnatural isomer has been reported to be the more active and less toxic[9,10] isomer.



(-)-Aphanorphine **1**

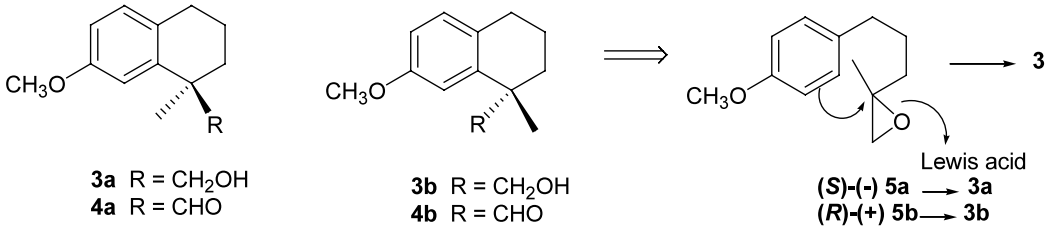


(+)-Eptazocine **2**

Fadel and Arzel[7] accomplished the formal syntheses of (−)-aphanorphine and (+)-eptazocine via a synthesis of alcohol **3a** (see Scheme 1), which was oxidized in 92% yield to the corresponding aldehyde **4a**. Shiotani[11,12] and co-workers synthesized (−)-aphanorphine from **3a**, and have accomplished a formal syntheses of (−)-eptazocine from the enantiomeric alcohol **3b**. Oxidation of the alcohols to the corresponding aldehydes (**4a** and **4b** in 90 and 88%, respectively) produced the compounds used to introduce the nitrogen functionality (e.g. via a Schiff's base) in the total synthesis.

2. Results

Shiotani's syntheses of alcohols **3a** and **b** required eleven steps for each of the enantiomers.[12] We wish to report the synthesis of both enantiomers by cyclizations that require only four steps each, and give very good ees (see the reaction envisaged for **5a** below). The epoxides used in the syntheses were prepared by Sharpless asymmetric osmylation of alkenes,[16] and transformation of the resulting diols into epoxides by Sharpless' method.[17,18] Isomer **3a** was prepared by cyclization of **5a**, and **3b** was obtained analogously from **5b**. The



Scheme 1. Retrosynthetic analysis of enantiomeric products.

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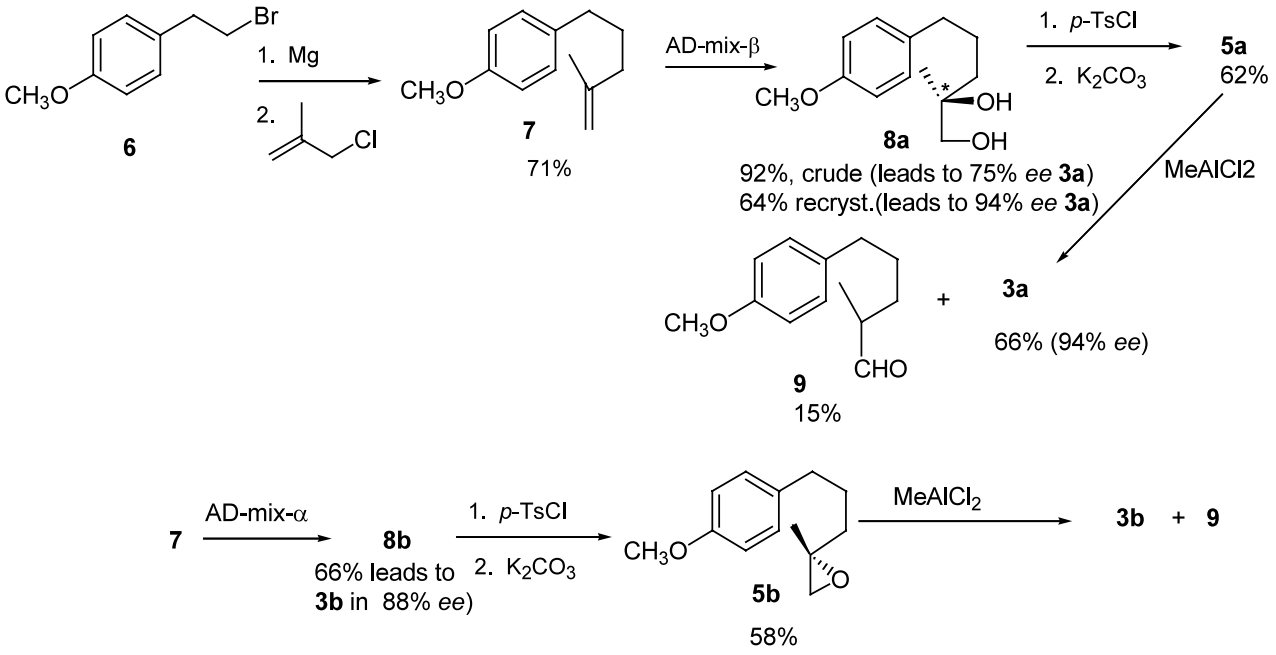


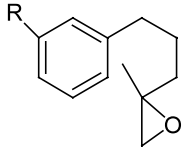
Scheme 2. Synthesis and cyclization of epoxides.

asymmetric syntheses show the generality and usefulness of the Sharpless methods (Scheme 2).[16,17]

We have carried out many epoxy-arene cyclizations before,[19–23] but never ones that involve optically active epoxides. The ees obtained suggest that this is a very good approach to asymmetric synthesis.

It is interesting that recrystallization of the diol (**8a** or **b**) was required for high enantiomeric purity. When the diol was used directly as it crystallized from the osmylation reaction (in 92% yield), the ee of cyclization product **3a** was 75%. However, when the diol was carefully recrystallized from 1:1 benzene/hexane, the yield was 66–76%, but the enantiomeric purity of the final alcohol product was much higher (94–95% ee—as determined by chiral GC on a β-cyclodextrin column). This also demonstrates that the enantiomeric purity of the epoxide is the key factor in determining the ee of the product. We were unable to determine the ee of the diol or the epoxide by any means attempted.

Earlier, we successfully completed a ring closure reaction at a racemic quaternary epoxide position (**10a**, R = H).[20] Julia and Labia[24] reported a cyclization of the racemic *meta*-substituted analog of **3** (**10b**), and observed that the reaction occured in 63% yield (with 21% aldehyde), but afforded equal amounts of *ortho* and *para* cyclization products. The *para* isomer does not result in this duality of isomers, although some aldehyde was formed during the cyclization reaction (21% with $MeAlCl_2$, see Section 3).



10a, R=H
10b, R=OCH_3

Corey and Sodeoka[25] reported that Me_2AlCl was a good catalyst to minimize rearrangements to carbonyl compounds in cyclizations of some epoxides at tertiary positions. In our earlier studies with **10a**, $SnCl_4$ did cause rearrangement to significant amounts of aldehyde (88%).[20] $MeAlCl_2$ did result in less aldehyde (a **3**:**9** ratio of 75:25) in our work with the enantiomers of **3**, but $BF_3{\cdot}OEt_2$ (25–29%) did too. Unfortunately our ees using $BF_3{\cdot}OEt_2$ for the cyclization reaction were lower (e.g. 78% ee) than those from $MeAlCl_2$-promoted reactions.

3. Experimental

The equipment used has been described earlier.[21] All the NMR spectra but those of **3a** (for which a Varian 400 MHz spectrometer was used) were obtained on a General Electric 300 MHz spectrometer (in $CDCl_3$). Perkin–Elmer 241 or a Jasco DIP 370 polarimeters were used for optical rotation measurements. ^{13}C NMR spectra are available to prove product identities and purities.

3.1. 2-Methyl-5-(*p*-methoxyphenyl)-1-pentene, 7

Using the methods of Julia and Labia[24] and Taylor, et al.,[20] a Grignard reagent was combined with 3-chloro-2-methylpropene. A sample of *p*-methoxyphenethyl bromide (4.4 g, 20.6 mmol) in dry THF (27 mL) was added with stirring to pure Mg (0.54 g, 22 mmol) turnings covered with THF (3 mL). After heating under reflux for 0.5 h, the mixture was cooled, and a solution

of 3-chloro-2-methylpropene (1.9 g, 21 mmol) was added dropwise. The resulting mixture was stirred for 16 h. After dropwise addition of H_2O (30 mL), ether (30 mL) and sat. NaCl (10 mL), the organic layer was collected and the aqueous layer was extracted with ether. The combined organic layers were extracted with sat. aqueous NaCl, dried ($MgSO_4$) and evaporated. Distillation of the product with a 1 inch Vigreux column gave four fractions, with the last two affording **7** (2.8 g, 14.7 mmol, 71%), bp 80–81°C (0.25 mmHg). Julia and Labia[24] obtained 63% yield in the preparation of the *meta* analog. The MS and NMR data matched those of the reported compound:[26] IR 3073 (m), 1613 (m), 1512, 1246, 1039, 887 (m) and 827 (m) cm^{-1}; ^1H NMR ($CDCl_3$), δ 1.71 (s, 3H), 1.7–1.8 (m, 2H), 2.04 (t, $J=7.8$ Hz, 2H), 2.54 (t, $J=7.8$ Hz, 2H), 3.77 (s, 3H), 4.7, (2 vinyl H, pseudo doublet), 7.1 and 6.8 (AB pattern, $\nu_{AB}=82$ Hz, $J_{AB}=8.8$ Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 22.3, 29.5, 34.5, 37.3, 55.2, 109.9, 113.7 (2C), 129.2 (2C), 134.6, 145.7 and 157.7; MS 190 (5, M^+), 134 (100), 121 (49). Anal calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.55; H, 9.51%.

3.2. (2*S*)-1,2-Dihydroxy-2-methyl-5-(*p*-methoxyphenyl)-pentane, 8a

Prepared by asymmetric osmylation with AD-mix-β: a mixture of *t*-butanol (18.5 mL), H_2O (22.5 mL), and AD-mix-β (6.77 g) was cooled in an ice water bath, and **7** (0.910 g, 4.8 mmol) was added dropwise to the stirred mixture. After stirring for 5.5 h, TLC (3:1 hexane:EtOAc) showed no alkene remained, and sodium sulfite (7.5 g) was slowly added to the cooled mixture. After stirring for 45 min, the product was extracted twice with CH_2Cl_2 and once with ether. The combined organic extracts were washed with sat. NaCl and dried ($MgSO_4$). The evaporated mixture was dissolved in benzene (3 mL), and hexane (3 mL) was added. On cooling overnight, crystals formed, which were isolated by vacuum filtration. After drying under high vacuum at room temperature, the product was isolated as a solid (1.04 g, 93%); mp 55.2–57.4°C $[\alpha]_D^{27}$ −5.0 (*c* 1.05, $CHCl_3$); IR 3400 (br), 1613 (m), 1512, 1246,1038, 831 (m) and 810 (m) cm^{-1}; ^1H NMR (with 400 MHz NMR) ($CDCl_3$), δ 1.14 (s, 3H), 1.4–1.5 (m, 2H), 1.5–1.7 (m, 2H), 2.0 (s, 2OH), 2.56 (t, $J=7.5$ Hz, 2H), 3.4 (AB pattern, $\nu_{AB}=20$ Hz, $J_{AB}=10.8$ Hz, 2H), 3.78 (s, 3H), 6.95 (AB pattern, $\nu_{AB}=108$ Hz, $J_{AB}=8$ Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 23.6, 26.2, 35.7, 38.5, 55.6, 70, 73.2, 114 (2C), 129.4 (2C), 134.5, 157.9.4. A purified sample showed a mp of 59.1–60.4°C, but the sample was hygroscopic, and so C,H analysis was not attempted. Crude diol afforded a final product (**3a** or **b**) that was typically 75% ee (rather than 90–95% ee). When the diol was carefully recrystallized from 1:1 benzene:hexane, the **3a** or **b** ultimately produced was 94–95% ee.

3.3. (2*R*)-1,2-Dihydroxy-2-methyl-5-(*p*-methoxyphenyl)-pentane, 8b

Prepared as above using AD-mix-α. The product was recrystallized from benzene/hexane, mp 54–57.5°C, and the sample (not rigorously dried) showed $[\alpha]_D^{21}$ +3.6 (*c* 2.7, $CHCl_3$). A 1.04 g sample of **7** gave **8b** (0.956 g, 92%). The compound gave the same spectral data as **8a**.

3.4. Racemic 1,2-epoxy-2-methyl-5-(*p*-methoxyphenyl)-pentane, 5

Prepared by MCPBA epoxidation of **7** (as described for other epoxide preparations)[19–21] by adding **7** (1.38 g, 7.26 mmol) in CH_2Cl_2 (12 mL) to an ice-cooled solution of MCPBA (1.86 g, 70%, 7.5 mmol)) in CH_2Cl_2 (20 mL), and stirring for 50 min. Standard workup[19] (dilution with petroleum ether, filtration of MCBA, and washes with 20% $NaHSO_3$, 5% sodium bicarbonate and 10% NaCl)[21] left product that distilled at 72–78°C (0.01–0.02 mmHg), or rotary TLC (3.5:1 hexanes:EtOAc) gave racemic **5** (0.821 g, 55%), 98% pure; IR 1613 (m), 1512, 1244, 831 (m) and 812 (m) cm^{-1}: ^1H NMR ($CDCl_3$), δ 1.3 (s, 3H), 1.51–1.7 (m, 4H), 2.56 (2m, 4H), 3.78 (s, 3H), 6.95 (AB pattern, $\nu_{AB}=79.4$ Hz, $J_{AB}=8.7$ Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 20.9, 27.1, 34.9, 36.2, 53.7, 55.2, 56.7, 113.8 (2C), 129.2 (2C), 134.2, 157.9. Anal calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.52; H, 8.89%. The product was used to verify the identity and purity of the *R*- and *S*-enantiomers below.

3.5. (2*S*)-1,2-Epoxy-2-methyl-5-(*p*-methoxyphenyl)-pentane, 5a

Was prepared from **8a** and purified by the procedures detailed below, $[\alpha]_D^{21}$ −6.8 (*c* 0.58, $CHCl_3$), mass spectrum, exact mass *m*/*z* calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1312.

3.6. (2*R*)-1,2-Epoxy-2-methyl–5-(p-methoxyphenyl)-pentane, 5b

The diol **8b** (0.66 g, 2.95 mmol) was dissolved in dry pyridine (3.5 mL), and *p*-toluenesulfonyl chloride (0.57 g, 3 mmol) was added in three portions over 15 min to the ice/water-cooled solution. The reaction vial was tightly sealed and kept in the refrigerator for 5.5 h. The pyridine hydrochloride crystals were removed by filtration, and the filtrate was added to H_2O (75 mL) and the resulting mixture was extracted twice with ether. The combined ethereal extract was washed twice with 10% HCl, once with 5% $NaHCO_3$ and sat. NaCl and dried ($MgSO_4$). The product was dissolved in MeOH (6 mL), and K_2CO_3 (1.04 g, 7.5 mmol) and the mixture was stirred for 5.5 h. Filtration left material that was dissolved in ether (30 mL), and the aqueous layer was extracted with ether, and the combined ethereal extract was washed with sat. NaCl and evaporated. The residue was purified by rotary chromatography using 3:1 (or 3.5:1) hexane:EtOAc, giving 0.3769 g of **5b** (62%), $[\alpha]_D^{20}$ +6.3 (*c* 0.66, $CHCl_3$), mass spectrum, exact mass *m*/*z* calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1307. Chiral GC did not separate the enantiomers.

3.7. Cyclizations of epoxides

3.7.1. Racemic alcohols. Racemic **5** (0.253 g, 1.2 mmol) was dissolved in dry CH_2Cl_2 (21 mL-distilled under N_2

from calcium hydride). The mixture was cooled under N_2 with a dry ice/acetone bath, and $MeAlCl_2$ (1 M solution in hexane, 0.52 mL, 0.52 mmol) was added dropwise via syringe. After 30 min at −78°C, 5% HCl (70 mL) was added dropwise to the mixture over 15 min, and ether (50 mL) was added. The aqueous layer was washed with ether, and the combined ethereal extract was washed with 5% $NaHCO_3$ and brine and dried ($MgSO_4$). Rotary silica chromatography with 3:1 hexane:EtOAc produced racemic alcohol **3** (0.158 g, 62%): IR 3400 (br), 1611 (m), 1503, 1497, 1240, 1038, 806 (m), 736 (w) and 702 (w) cm^{-1}: ^1H NMR ($CDCl_3$), δ 1.23 (s, 3H), 1.4 (br, OH), 1.45–1.6 (m, 1H), 1.65–1.9 (m, 2H), 1.9–2.1 (m, 1H), 2.7 (t, $J=6.4$ Hz, 2H), 3.64 (AB pattern, $\nu_{AB}=86$ Hz, $J_{AB}=10.7$ Hz, 2H), 3.78 (s, 3H), 6.71 (dd, $J=8.3$, 2.9 Hz, 1H), 6.83 (d, $J=2.9$ Hz, 1H), 7.01 (d, $J=8.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.6, 26.6, 29.8, 33.4, 39.5, 55.2, 71.7, 111.5, 112.2, 130.2, 130.4, 142.3, 157.9: mass spec. 206 (12), 175 (100), 129 (15), 128 (14), 125 (15), 115 (15).

3.8. (*R*)-(C1)-1,2,3,4-Tetrahydro-7-methoxy-1-methyl-1-naphthalenemethanol, 3a

Was made by combining **5a** (29 mg) in dry CH_2Cl_2 (2 mL) at −78°C under N_2 with $MeAlCl_2$ (1 M in hexane, 70 μL). The mixture was stirred 30 min, and then 5% HCl (8 mL) and ether (30 mL) were added. The resulting aqueous layer was extracted with ether (20 mL), and the combined ethereal extract was extracted with 5% $NaHCO_3$ and dried ($MgSO_4$). Column chromatography (4.5:1 hexane:EtOAc) gave 19.2 mg (66%) of **3a**, 89.5% ee $[\alpha]_D^{22}$ −18.3 (*c* 1.1, $CHCl_3$), lit.[12] $[\alpha]_D^{26}$ −16.5 (*c* 0.36, $CHCl_3$) and lit.[7] $[\alpha]_D^{20}$ −20 (*c* 1, $CHCl_3$). When recrystallized (from 1:1 benzene:hexane) **8a** was used to make epoxide **5a**, the ee of the cyclization product **3a** was 94–95%.

3.9. (*S*)-(C1)-1,2,3,4-Tetrahydro-7-methoxy-1-methyl-1-naphthalenemethanol, 3b

A sample of **5b** (123.4 mg) was dissolved in dry CH_2Cl_2 (8 mL), and the solution was cooled to −78°C. $MeAlCl_2$ (1 M in hexane, 230 μL) was added and the cooled mixture was stirred for 42 min. TLC showed the reaction was over, and 5% HCl (25 mL) was added over 15 min, and then at room temperature, ether (30 mL) was added. The aqueous layer was extracted with ether, and the combined ethereal extract was washed with 5% $NaHCO_3$ and sat. NaCl and dried ($MgSO_4$). Rotary TLC gave 9.3 mg of aldehyde **9** (below) and 81.6 mg (66%) of **3b**, 88% ee, $[\alpha]_D^{20}$ +18.1 (*c* 0.85, $CHCl_3$), lit.[12] $[\alpha]_D^{24}$ +16.6 (*c* 3.4, $CHCl_3$). Capilliary GC showed the fractions collected were pure, and this was the preferred method of purification. The crude product was analysed by GC and found to be 84% alcohol and 14% aldehyde (2% total impurity). Recrystallized diol led to **3b** with a higher ee (90–94%).

3.10. 2-Methyl-5-(*p*-methoxyphenyl)pentanal, 9

IR 2772 (w), 1724 (s), 1613, 1514, 1246, 831 (m), and 812 (m) cm^{-1}: ^1H NMR ($CDCl_3$), δ 1.08 (d, $J=7.3$ Hz, 3H), 1.3–1.8 (m, 4H) 2.4 (q of d, $J=7$ and 2 Hz, 1H), 2.57 (t, $J=7.3$ Hz, 2H), 3.78 (s, 3H), 6.84 and 7.07 (AB pattern, $\nu_{AB}=77.6$ Hz, $J_{AB}=9$ Hz, 4H), 9.6 (d, $J=2$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13, 29, 30, 35, 46, 55, 114 (2C), 129 (2C), 134, 158, 205: mass spec. 206 (15), 134 (12), 121 (100), 128 (13). Anal calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.22; H, 8.74%: mass spectrum, exact mass m/z calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1303.

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