Enantiocontrolled Synthesis of (+)-Aphanorphine from (*R*)-*O*-Benzylglycidol: Assignment of Absolute Configuration

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Aphanorphine, a novel 3-benzazepine alkaloid isolated from the freshwater blue–green alga *Aphanizomenon flos-aquae*, has been synthesized in the antipodal forms starting from (*R*)-*O*-benzylglycidol to establish the absolute configuration of the natural product as (1*R*, 4*R*).

Aphanorphine[1] (**1**), isolated from the freshwater blue–green alga *Aphanizomenon flos-aquae*, possesses an interesting 3-benzazepine framework closely related to the natural narcotic alkaloid, morphine (**2**) and the synthetic benzomorphane analgesic,[2] pentazocine (**3**). Since neither its absolute configuration nor its synthesis has been established,† we began an enantiocontrolled synthesis in order to assign the absolute structure as well as to provide a sample for pharmacological testing using the known chiral γ-lactone[3] (**5**), readily accessible in about 40% overall yield *via* a four-step sequence of reactions from (*R*)-*O*-benzylglycidol[4] (*R*)-(**4**), as starting material.

Treatment of (**5**) with diphenyl disulphide and tri-n-butylphosphine[5] afforded the sulphide‡ (**6**), $[\alpha]_D^{22}$ +22.6° (*c* 1.09, $CHCl_3$), in 91% yield. Oxidation of (**5**) with *m*-chloroperbenzoic acid (1 equiv.) followed by treating the resulted sulphoxide (**6**) with trifluoroacetic anhydride (3 equiv.) in refluxing toluene[6] furnished the tricyclic lactone (**9**) as a mixture of epimers (3 : 1), in 88% yield, presumably *via* the intervention of a Pummerer type intermediate such as (**8**). Upon refluxing with the complex generated from methylamine hydrochloride and trimethylaluminium[7] in benzene, (**9**) afforded the amide (**10**), in 77% yield, which was reduced to the secondary amine (**11**), in 72% yield, with lithium aluminium hydride. The amine (**11**), which consisted of two epimers, was treated with sodium in liquid ammonia to give the single amino-alcohol (**12**), $[\alpha]_D^{24}$ −9.5° (*c* 0.506, $CHCl_3$), in 90% yield. Although we have not found optimal conditions yet, when (**12**) was refluxed with thionyl chloride in benzene concurrent cyclization occurred to give *O*-methylaphanorphine (**14**), $[\alpha]_D^{27}$ −7.40° (*c* 0.35, $CHCl_3$), in 30% yield in a single step without

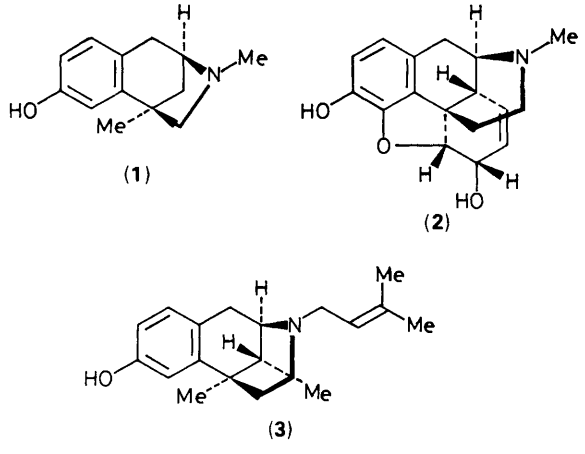
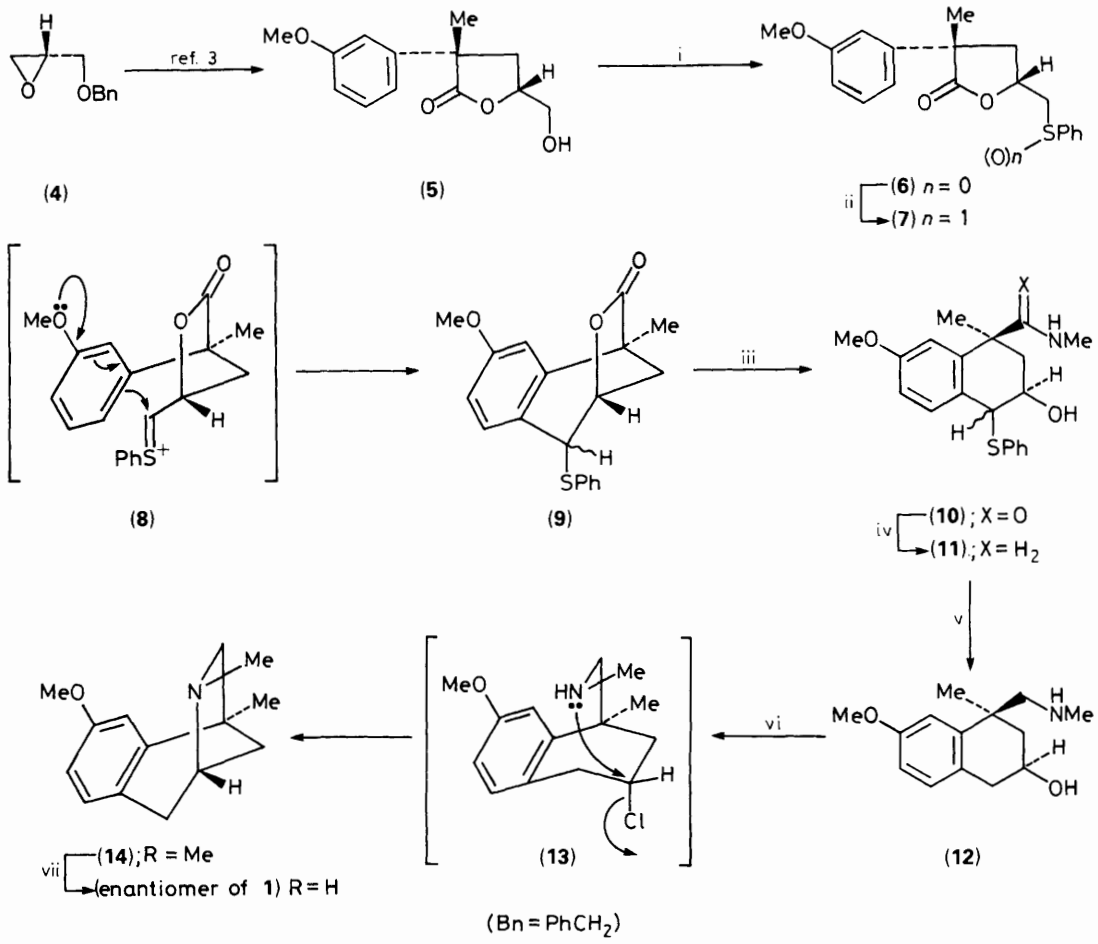


Figure 1

† Asymmetric synthesis starting from dicyclopentadiene has recently been completed by employing a fundamentally different method which led to the same stereochemical conclusion: S. Takano, K. Inomata, T. Sato, M. Takahashi, and K. Ogasawara, to be published.

‡ Satisfactory analytical and spectral data were obtained for all new compounds.



Scheme 1. *Reagents and conditions*: i, $(PhS)_2$ (1.5 equiv.), Bu^n_3P (1.5 equiv.), pyridine, 60 °C, 11 h; ii, *m*-chloroperbenzoic acid (mCPBA) (1.1 equiv.), $NaHCO_3$ (3.0 equiv.), CH_2Cl_2, −30 °C, 2.5 h, then trifluoroacetic anhydride (3.0 equiv.), toluene, reflux, 10 min; iii, $MeNH_2$·HCl (2.2 equiv.), Me_3Al (2.2 equiv.), benzene, reflux, 1.5 h; iv, $LiAlH_4$ (9.0 equiv.), tetrahydrofuran (THF), reflux, 12 h; v, Na (6.0 equiv.), liq. NH_3; vi, $SOCl_2$ (1.5 equiv.), benzene, reflux, 10 min, then sat. aq. $NaHCO_3$, room temp., 2 h; vii, BBr_3 (2.2 equiv.), −78 to −10 °C, 3 h.

forming the expected chloride (**13**). Finally, (**14**) was treated with boron tribromide to give aphanorphine [enantiomer of (**1**)], m.p. 215—222 °C (lit.[1] m.p. 223—229 °C), $[\alpha]_D^{22}$ +37.5° (*c* 0.16, MeOH), in 65% yield. T.l.c., i.r., ^1H n.m.r. (500 MHz, hydrochloride in D_2O), and mass spectra of the synthetic material were identical with those of the natural product.§

The specific optical rotation of the hydrochloride of the synthetic material was $[\alpha]_D^{27}$ +40.1° (*c* 0.12, H_2O), whereas $[\alpha]_D^{25}$ − 43.7° (*c* 0.47, H_2O) was reported for the hydrochloride of the natural product,[1] indicating that they are enantiomers. With correlation to the absolute configuration of the starting (*R*)-*O*-benzylglycidol (*R*)-(**4**), the synthetic material can be specified as (1*S*, 4*S*) and, therefore, the natural aphanorphine (**1**) should have (1*R*,4*R*)-configuration as shown in Figure 1. Since we have established the preparation[8] of (*S*)-*O*-benzylglycidol (*S*)-(**4**), aphanorphine (**1**) in its natural form may also be obtained by employing the present procedure.

§ At present, we are unable to find any suitable n.m.r. chiral shift reagents or chiral h.p.l.c. columns which allow assessment of the optical purity of the final product.

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