The Enantioselective Total Synthesis of Natural (−)-Aphanorphine

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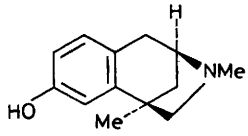
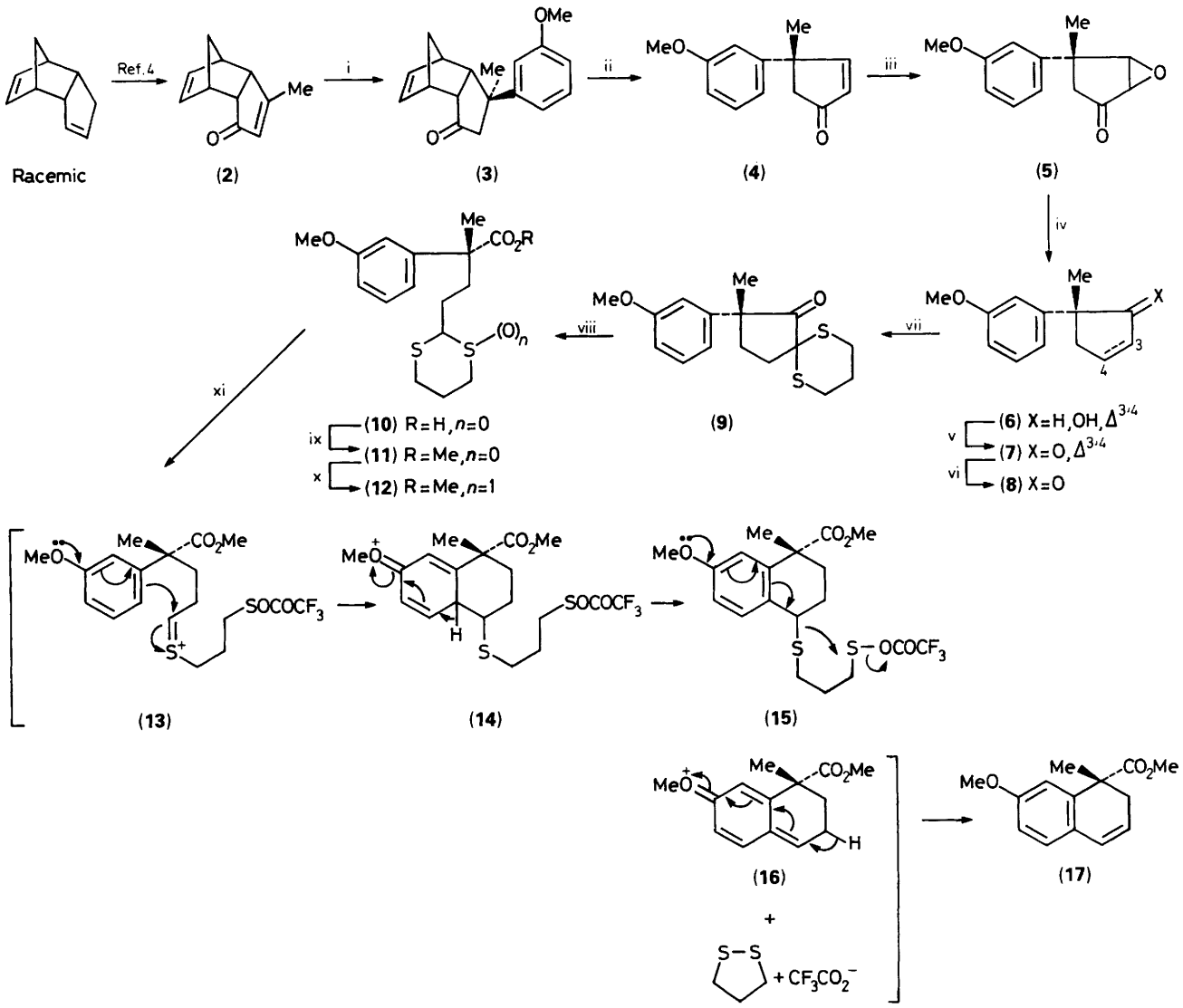
(−)-Aphanorphine, a novel 3-benzazepine alkaloid isolated from the freshwater blue–green alga *Aphanizomenon flos-aquae*, has been synthesized in an enantioselective fashion.

(−)-Aphanorphine[1] (**1**), isolated from the freshwater blue-green alga *Aphanizomenon flos-aquae*, possesses an interesting 3-benzazepine framework related to the natural narcotic alkaloid morphine and the synthetic analgesic pentazocine.[2] The relative stereochemistry of (**1**) was deduced spectroscopically and recently its absolute stereochemistry was determined unambiguously by the present authors[3] as (1*R*,4*R*) by synthesis of the (1*S*,4*S*)-antipode (ent-**1**) starting from (*S*)-*O*-benzylglycidol. We report herein the enantioselective total synthesis of natural (1*R*, 4*R*)-aphanorphine (**1**) starting from the known optically active dienone (**2**) whose asymmetric



(**1**)

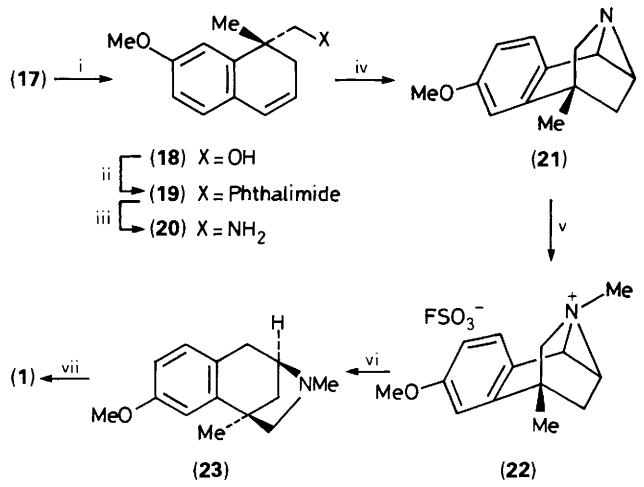


Scheme 1. *Reagents and conditions:*, i, 3-methoxyphenylmagnesium bromide (3.4 equiv.), CuBr·SMe_2 (10%), Me_3SiCl (TMSCl) (2.0 equiv.), hexamethylphosphoramide (HMPA) (2.2 equiv.), −70 °C to room temp., 2 h; ii, *o*-dichlorobenzene, 12 h, reflux; iii, 30% H_2O_2 (3.0 equiv.), NaOH (0.5 equiv.), MeOH, 0 °C to room temp., 2 h; iv, NH_2NH_2·HCl (3.0 equiv.), NEt_3 (4.5 equiv.), MeCN, 0 °C to room temp., 5 h; v, pyridinium chlorochromate (PCC), CH_2Cl_2, room temp., 4 h; vi, H_2, 10% Pd/C, EtOH, room temp., 8 h; vii, trimethylene dithiotosylate (2.0 equiv.), Bu^{t}OK (3.0 equiv.), tetrahydrofuran (THF), Bu^{t}OH, 0 °C; viii, KOH (4.0 equiv.), Bu^{t}OH, 60 °C, 12 h; ix, CH_2N_2, Et_2O; x, *m*-chlorobenzoic acid (MCPBA) (1.0 equiv.), $NaHCO_3$ (3.0 equiv.), −30 °C, 10 min; xi, TFAA (3.0 equiv.), toluene, 130 °C, 5 min.

synthesis from racemic cyclopentadiene dimer has already been established.[4,5]

Treatment of (+)-dienone (**2**) with 3-methoxyphenylmagnesium bromide in the presence of copper(I) bromide and trimethylsilyl chloride[6] gave the single 1,4-adduct (**3**) which, on thermolysis in *o*-dichlorobenzene,[4,5] afforded the enone (**4**)† {$[\alpha]_D^{29}$ + 105.2° (*c* 1.38, $CHCl_3$)} in 87% overall yield by retrograde Diels–Alder reaction. Conversion of (**4**) to the isomeric enone (**7**) was carried out by using the Wharton reaction.[7] Thus, epoxide (**5**) obtained from (**4**) as a mixture of diastereoisomers was treated with hydrazine monohydrochloride in acetonitrile[7] to give the allyl alcohol (**6**) which was then oxidized to (**7**) in 62% overall yield. After hydrogenation, ketone (**8**) {$[\alpha]_D^{27}$ + 83.2° (*c* 1.21, $CHCl_3$)} was transformed into the α-diketone monothioketal[8,9] (**9**) {$[\alpha]_D^{26}$ +39.5° (*c* 0.59, $CHCl_3$)} in 53% yield by treatment with trimethylene dithiotosylate[10] and potassium t-butoxide. When (**9**) was treated with potassium hydroxide in hot Bu^{t}OH facile ring cleavage[11] occurred to afford the acid (**10**) which gave the ester (**11**) {$[\alpha]_D^{28}$ −19.6° (*c* 1.20 $CHCl_3$)} in 79% overall yield on exposure to diazomethane. The monosulphoxide (**12**), obtained quantitatively as a mixture of diastereoisomers from (**11**) with *m*-chloroperbenzoic acid, underwent facile cyclization to furnish the dihydronaphthalene (**17**) {$[\alpha]_D^{27}$ −70° (*c* 0.97, $CHCl_3$)} in 55% yield as a single regioisomer upon brief treatment with trifluoroacetic anhydride (TFAA) in refluxing toluene (2 min).[3,12] We believe that the reaction proceeded through the involvement of the transient intermediates such as (**13**), (**14**), and (**15**) with removal of 1,2-dithiolane though we did not detect the latter compound. The ester (**17**) was

† Satisfactory analytical (combustion and/or high resolution mass) and spectral (IR, ^{1}H NMR, MS) data were obtained for all new isolable compounds.



Scheme 2. *Reagents and conditions:* i, $LiAlH_4$, THF, room temp., 20 min; ii, phthalimide (2.0 equiv.), Ph_3P (2.0 equiv.), $(Pr^iO_2CN)_2$ (2.0 equiv.), THF, room temp., 12 h; iii, $NH_2NH_2{\cdot}H_2O$ (3.0 equiv.), EtOH, reflux, 1 h; iv, $Pb(OAc)_4$ (1.6 equiv.), K_2CO_3 (6.2 equiv.), benzene, 60 °C to reflux, 20 min; v, FSO_3Me (1.0 equiv.), CH_2Cl_2, 0 °C, 5 min; vi, $LiAlH_4$, THF, room temp., 30 min; vii, BBr_3, CH_2Cl_2, −30 to 0 °C, 1 h.

reduced to the alcohol‡ (**18**) whose primary hydroxy group was replaced by a primary amino group by the Mitsunobu reaction[13] which provided the primary amine (**20**) *via* the imide (**19**) {$[\alpha]_D^{27}$ +61.1° (*c* 0.84, $CHCl_3$)} in 68% overall yield. Upon executing a Nagata reaction,[14] (**20**) yielded aziridine (**21**) as an unstable oil which was immediately exposed to methyl fluorosulphonate to give the ammonium salt (**22**). Treatment of (**22**) with lithium aluminium hydride allowed selective cleavage at the benzylic σ-bond to afford the penultimate intermediate (**23**) {$[\alpha]_D^{29}$ +8.46° (*c* 0.915, $CHCl_3$)} in 24% overall yield from (**20**). Finally, (**23**) was treated with boron tribromide to give (−)-aphanorphine§ (**1**) {m.p. 215—222 °C (lit.:[1] m.p. 223—229 °C), $[\alpha]_D^{22}$ −46.3° (*c* 0.22, HCl salt in H_2O) [lit.:[1] $[\alpha]_D^{25}$ −43.7° (*c* 0.47, HCl salt in H_2O)]} in 65% yield.

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‡ Optical purity of (**18**) was determined to be >98% enantiomeric excess (e.e.) by ^1H NMR (500 MHz) measurement of its methoxy(trifluoromethyl)phenylacetyl (MTPA) (*R*)- and (*S*)-ester. Optical purity of synthetic (−)-aphanorphine (**1**) was determined to be 99.1% e.e. by using a chiral HPLC column (Chiral Selector) which was kindly carried out by Dr. A. Ichida, Daicel Chemical Industries.

§ Identical with natural product (TLC, IR, and ^1H NMR spectra) kindly provided by Professor Y. Shimizu.