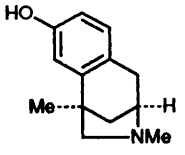
Synthesis of (±)-Aphanorphine *via* an Aminylium Ion Intermediate

Toshio Honda,* Atsunori Yamamoto, Yingshe Cui† and Masayoshi Tsubuki
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

A facile synthesis of (±)-aphanorphine **1** was achieved *via* the aminylium ion intermediate as a reactive species.

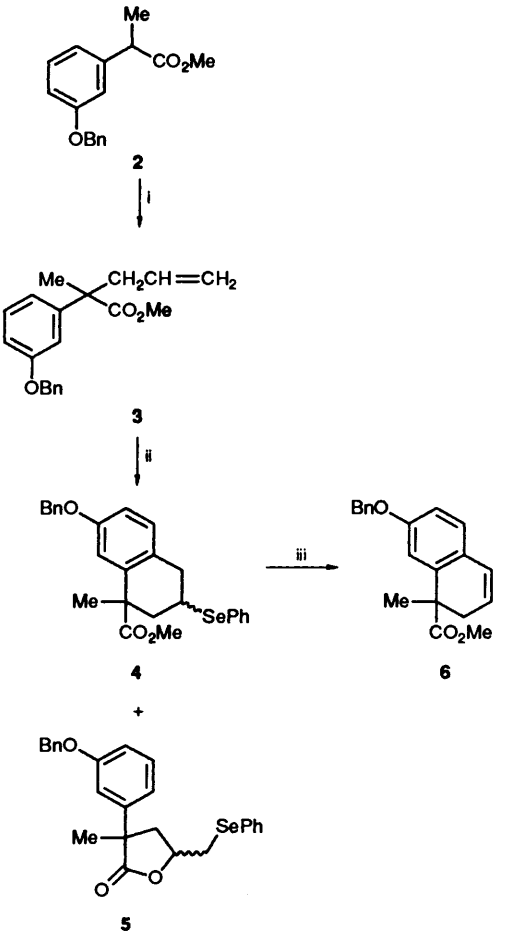
Aphanorphine **1**[1] was isolated from the freshwater blue-green alga *Aphanizomenon flos-aquae* as a marine natural product and its absolute configuration was determined by its total synthesis to be **1** by Takano and his co-workers.[2,3] Owing to its novel structure and potential analgesic activity, the synthesis of aphanorphine and its derivatives continues to attract interest. We describe herewith a facile synthesis of (±)-aphanorphine by utilizing an aminylium ion-promoted cyclisation reaction as a key step.



1

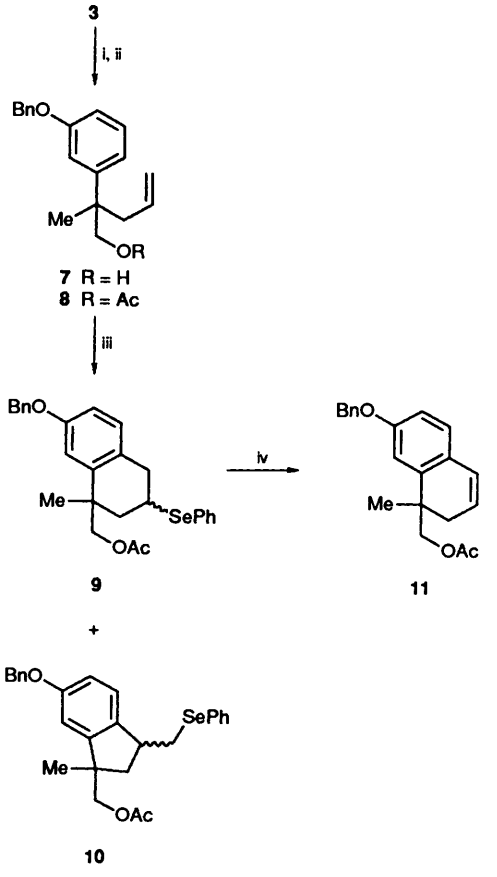
The ester **2** was allylated with allyl bromide in dry tetrahydrofuran (THF)–hexamethylphosphoric triamide (HMPA) in the presence of lithium di-isopropylamide (LDA) at −78 °C to give the ester **3** in 85% yield. First, arene-alkene cyclisation of **3** mediated by benzeneselenenyl chloride[4,5] which usually afforded the tetralin derivative, was investigated under a variety of reaction conditions. Disappointingly, the desired cyclisation product **4** was isolated as a minor product in 8% yield, the major product, isolated in 65% yield, being established as the five-membered lactone **5**. Furthermore, a similar cyclisation of the acetate **8**, derived by reduction of **3** with lithium aluminium hydride, followed by acetylation of the resulting alcohol **7** in the customary manner, afforded the desired product **9** and the five-membered compound **10** in 25 and 27.5% yields respectively. Oxidative elimination of the phenylselenenyl groups in **4** and **9** using sodium periodate gave the corresponding olefins, **6** and **11**, in 48 and 86% yields respectively. Since the reactivities obtained here for the cyclisation of **3** or **8** were quite different from those previously observed by us[4] in the synthesis of a benzomorphan derivative, we turned our attention to explore the aldehyde **13** as a precursor for the synthesis of a 1,2-dihydronaphthalene skeleton.

Thus, the ester **2** was treated with 2-(2-bromoethyl)-1,3-dioxolane in THF–HMPA in the presence of LDA to give the dioxolane **12** in 92% yield. Exposure of **12** to toluene-*p*-sulphonic acid in methanol gave rise to the aldehyde **13**, whose dehydration reaction on treatment with a catalytic amount of toluene-*p*-sulphonic acid in refluxing benzene provided the desired cyclisation product **6** in 93% yield from **12**. Conversion of the ester function of **6** into the *N*-methylamino group was achieved by three-steps as follows. Reduction of **6** with lithium aluminium hydride gave the alcohol **14** in 92% yield, identical with the sample obtained by hydrolysis of the acetate **11**, which on Swern oxidation with oxalyl chloride and dimethyl sulphoxide afforded the aldehyde **15** in 79% yield from **6**. Condensation of the aldehyde **15** with methylamine in methanol, followed by reduction with sodium borohydride gave the expected amine **16** in 82% yield. It is recognized[6] that carbon–nitrogen bond formation can be accomplished by using a *N*-chloro compound on treatment with some metal species such as $TiCl_3$ or Ag_2O, and the later metal in our hands[7] usually afforded the desired cyclisation product in better yield. Thus, the carbon–nitrogen bond-forming reaction was achieved *via* the aminylium ion intermediate[7] generated by reaction of the amine **16** with *N*-chlorosuccinimide in dichloromethane, followed by treatment of the resulting *N*-chloro compound with silver oxide in aqueous THF at reflux to provide the cyclization product **17** in 83% yield as a single isomer. The stereochemistry of the benzylic hydroxy group was tentatively assigned to be *trans* to the amino group based on its NMR spectrum, although its stereogenic centre was removed at a later stage of this

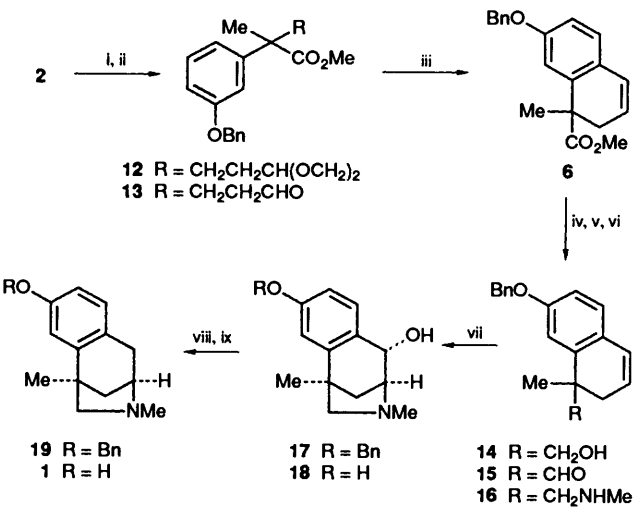


Scheme 1 *Reagents and conditions:* i, LDA, allyl bromide, THF–HMPA, −78 °C; ii, PhSeCl, CH_2Cl_2, −78 to 25 °C; iii, $NaIO_4$, MeOH–THF–H_2O, 25 °C

† Visiting Scientist by Sasakawa Scholarship from Department of Pharmacy, Yanbian Medical College, People's Republic of China.



Scheme 2 *Reagents and conditions:* i, LAH, THF, 25 °C; ii, Ac_2O, Py; iii, PhSeCl, CH_2Cl_2, −78 to 25 °C; iv, $NaIO_4$, MeOH–THF–H_2O, 25 °C



Scheme 3 *Reagents and conditions:* i, LDA, $BrCH_2CH_2CH(OCH_2)_2$, THF–HMPA, −78 °C; ii, *p*-TsOH, MeOH, 25 °C; iii, *p*-TsOH, benzene, reflux; iv, LAH, THF, 25 °C; v, Swern oxidation; vi, $MeNH_2$, MeOH, 25 °C then $NaBH_4$, MeOH; vii, NCS, CH_2Cl_2, 0 °C then Ag_2O, THF–H_2O, reflux; viii, Et_3SiH, TFA, 25 °C; ix, 10% Pd–C, H_2, EtOH

synthesis. Since the basic skeleton of aphanorphine was thus constructed, removal of the hydroxy and benzyl groups was then investigated to complete its total synthesis.

Catalytic reduction of **17** over 10% palladium–carbon under a hydrogen atmosphere afforded the phenolic alcohol **18** in quantitative yield, whose further reduction with triethylsilane in trifluoroacetic acid (TFA)[8] provided (±)-aphanorphine **1**, m.p. 189–191 °C, in 28% yield. (±)-Aphanorphine was more efficiently synthesised from **17** by reduction with triethylsilane in TFA, followed by debenzylation of benzylaphanorphine **19** over 10% palladium–carbon under a hydrogen atmosphere in quantitative yield from **17**. The spectroscopic data of the synthetic compound were identical with those of the authentic sample provided by Takano and Ogasawara.

Experimental

Cyclization of **16** *into* **17**.—*N*-Chlorosuccinimide (310 mg, 2.35 mmol) was added to a stirred solution of the amine **16** (570 mg, 1.95 mmol) in CH_2Cl_2 (30 cm^{-3}) at 0 °C. After the stirring had been continued for 10 min at the same temperature, the mixture was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and evaporated to give the *N*-chloro compound as a colourless oil which, without purification, was used in the next reaction. A mixture of the above *N*-chloro compound and Ag_2O (660 mg, 2.38 mmol) in THF–H_2O (1:1, v/v; 30 cm^{-3}) was heated at reflux for 9 h. The reaction mixture was filtered to remove the insoluble material and the filtrate was evaporated to give a residue, which was taken up in chloroform. The organic layer being washed with water, dried (Na_2SO_4) and evaporated to give a brown oil, which was subjected to column chromatography on silica gel. Elution with chloroform–methanol (9:1, v/v) afforded the cyclised product **17** (499 mg, 83%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3550br and 1605; $\delta(CDCl_3)$ 1.48 (3 H, s, Me), 1.74 (1 H, dd, *J* 5.5 and 11.6, CH), 1.96 (1 H, d, *J* 11.6, CH), 2.46 (1 H, d, *J* 9.2, CH*H*NMe), 2.53 (3 H, s, NMe), 2.71 (1 H, d, *J* 9.2, C*H*HNMe), 3.25 (1 H, dd, *J* 3.3 and 6.0, C*H*NMe), 4.62 (1 H, d, *J* 3.3, C*H*OH), 5.04 (2 H, s, CH_2Ph), 6.82–6.88 (3 H, m, ArH) and 7.31–7.44 (5 H, m, Ph); *m/z* 309 (M^+).

Acknowledgements

We thank Profs. S. Takano and K. Ogasawara, Pharmaceutical Institute, Tohoku University for the generous gift of aphanorphine.

References

1 N. Gulavita, Y. Shimizu, P. Laszlo and J. Clardy, *Tetrahedron Lett.*, 1988, **29**, 4381.
2 S. Takano, K. Inomata, T. Sato and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1989, 1591.
3 S. Takano, K. Inomata, T. Sato, M. Takahashi and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1990, 290.
4 T. Kametani, M. Nishimura, Y. Suzuki and T. Honda, *Heterocycles*, 1986, **24**, 1791.
5 E. Edstom and T. Livinghouse, *J. Am. Chem. Soc.*, 1986, **108**, 1334.
6 L. Stella, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 337 and references cited therein.
7 T. Kametani, Y. Suzuki and T. Honda, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1373.
8 C. T. West, S. J. Donnelly, D. A. Kooistra and M. P. Doyle, *J. Org. Chem.*, 1973, **38**, 2675.

Paper 1/06043K
Received 29*th November* 1991
Accepted 6*th January* 1992