

A NEW SYNTHESIS OF (-)-APHANORPHINE BY AN ENANTIOCONVERGENT TACTIC†

Masahiro Shimizu, Takashi Kamikubo, and Kunio Ogasawara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

Abstract — A new route to (-)-aphanorphine, isolated from the blue-green alga *Aphanizomenon flos-aquae*, has been devised by employing an enantioconvergent tactic making use of both enantiomeric starting materials.

(-)-Aphanorphine (**1**), which was isolated¹ from the blue-green alga *Aphanizomenon flos-aquae* and its absolute structure determined by synthesis,^{2,3} has attracted considerable synthetic interest⁴ owing to its unique structure resembling benzomorphan analgesics such as (-)-pentazocine⁵ (**2**) (**Figure 1**). We report here a new enantiocontrolled synthesis of (-)-aphanorphine (**1**) employing an enantioconvergent tactic which allows enantioconvergent transformation of both enantiomers of the starting materials into the single chiral target molecule.

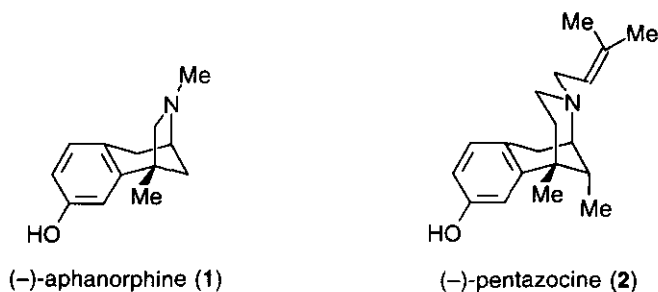
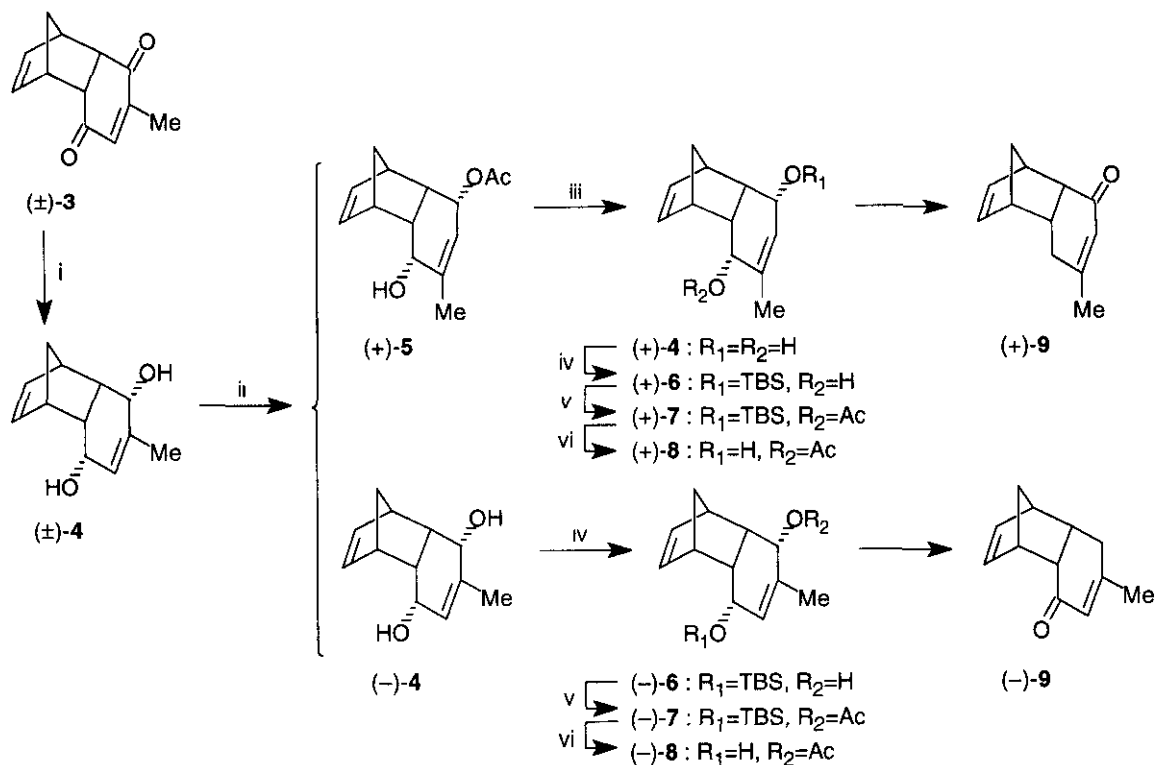


Figure 1

We have recently developed⁶ a synthesis of both enantiomers of the tricyclic dienone (**9**) in optically pure form from the racemic *endo*-diol [(±)-**4**], obtained from the Diels-Alder adduct⁷ [(±)-**3**] between toluquinone and cyclopentadiene, by employing lipase-mediated transesterification in an organic solvent⁸ and a palladium-

† Dedicated to the memory of the late Professor Shun'ichi Yamada.

mediated elimination reaction⁹ as the key steps. Thus, the *endo*-diol [(±)-4], obtained from [(±)-3] with sodium borohydride-cerium(III) chloride,¹⁰ furnished the (+)-acetate [(+)-5] and the (-)-alcohol [(-)-4] on treatment with vinyl acetate in THF containing triethylamine (10%) in the presence of lipase LIP (*Pseudomonas* sp. TOYOBO).¹¹ Both of the products after transformation into the corresponding monoacetate (8) afforded the corresponding enone (9) without difficulty in the palladium-mediated elimination reaction which we reported⁹ recently (Scheme 1).



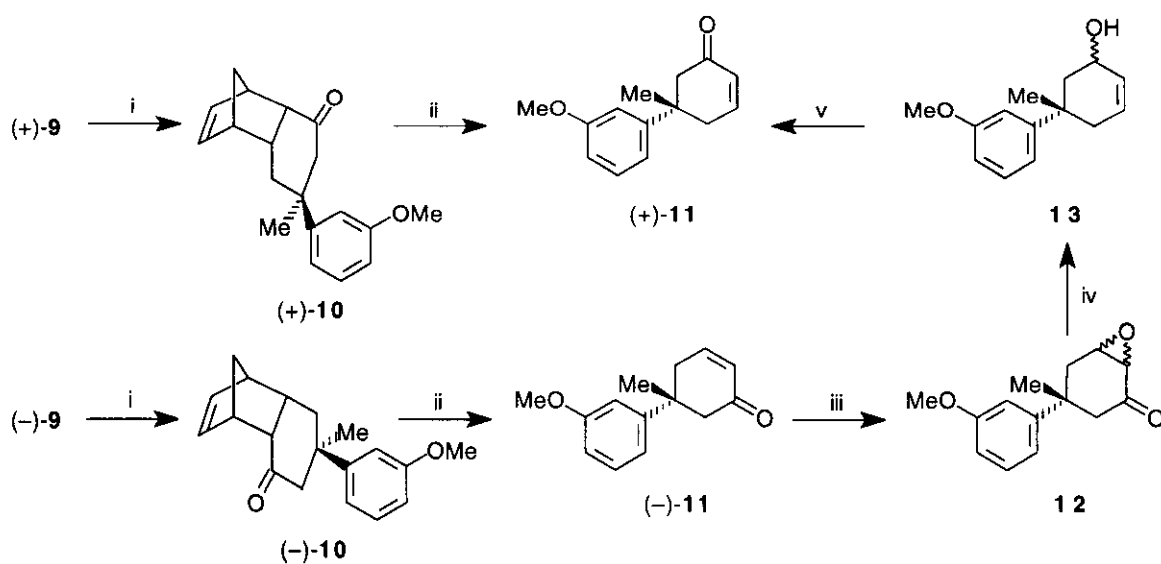
Scheme 1

Reagents and conditions: (i) NaBH₄-CeCl₃·7H₂O, MeOH, 0 °C (~84%). (ii) vinyl acetate (4 equiv.), lipase LIP, THF-Et₃N (10:1), rt, 55 h [30% for (+)-5 (>99% ee) and 42% for (-)-4 (>99% ee)]. (iii) K₂CO₃, MeOH (98%). (iv) *t*-Bu(Me)₂SiCl, imidazole, DMF [92% for (+)-6 and 87% for (-)-6]. (v) Ac₂O, Et₃N, DMAP (cat.), CH₂Cl₂ [99% for (+)- and (-)-7]. (vi) Bu₄NF, THF [94% for (+)- and 92% for (-)-8].

In order to transform both the (+)- and (-)-enones (9) into (-)-aphanorphine (1), they (both >99% ee) were treated, respectively, with 3-methoxyphenylmagnesium bromide in the presence of chlorotrimethylsilane and a catalytic amount of a copper(I) bromide-dimethyl sulfide complex in THF containing hexamethylphosphoric triamide (HMPA) (2 equiv.).¹² The corresponding enantiomeric ketone¹³ (10) having a quaternary benzylic stereogenic center was obtained stereoselectively by convex-face addition in good yields after hydrolytic

workup. Thermolysis of the (+)-ketone [(+)-**10**], $[\alpha]^{29}_D +210.3^\circ$ (*c* 1.2, CHCl_3), originated from the acetate [(+)-**5**], in refluxing diphenyl ether afforded the (+)-5,5-disubstituted cyclohexenone [(+)-**11**], $[\alpha]^{25}_D +89.4^\circ$ (*c* 1.1, CHCl_3), in 81% yield within 30 min by retro-Diels-Alder reaction. On the same treatment, the enantiomeric (–)-ketone [(–)-**10**], $[\alpha]^{25}_D -212.8^\circ$ (*c* 1.1, CHCl_3), originated from the alcohol [(–)-**4**], afforded the enantiomeric (–)-5,5-disubstituted cyclohexenone [(–)-**11**], $[\alpha]^{29}_D -89.7^\circ$ (*c* 1.1, CHCl_3), in a comparable 80% yield. Under these conditions both enantiomers of **11** thus obtained retained their original chiral integrity which was confirmed by hplc analysis using a chiral column (CHIRALCEL OD, elution with *i*-PrOH/hexane, 2.0:100).

So as to make the synthesis enantioconvergent, chirality inversion of the (–)-enone [(–)-**11**] was next carried out by employing the Wharton rearrangement.^{6,14} Thus, (–)-**11** was first treated with alkaline hydrogen peroxide to give the epoxy ketone (**12**) in 92% yield as a diastereomeric mixture. The mixture was next treated with hydrazine hydrochloride in the presence of triethylamine under sonication to give the allyl alcohol (**13**) in 64% yield as an inseparable mixture. Oxidation of the mixture (**13**) with manganese(IV) dioxide in dichloromethane afforded the single enone [(+)-**11**], $[\alpha]^{27}_D +88.5^\circ$ (*c* 1.1, CHCl_3), in 90% yield without losing the original optical purity of the enantiomeric precursor [(–)-**11**] [>99% ee by hplc using a chiral column (CHIRALCEL OD,

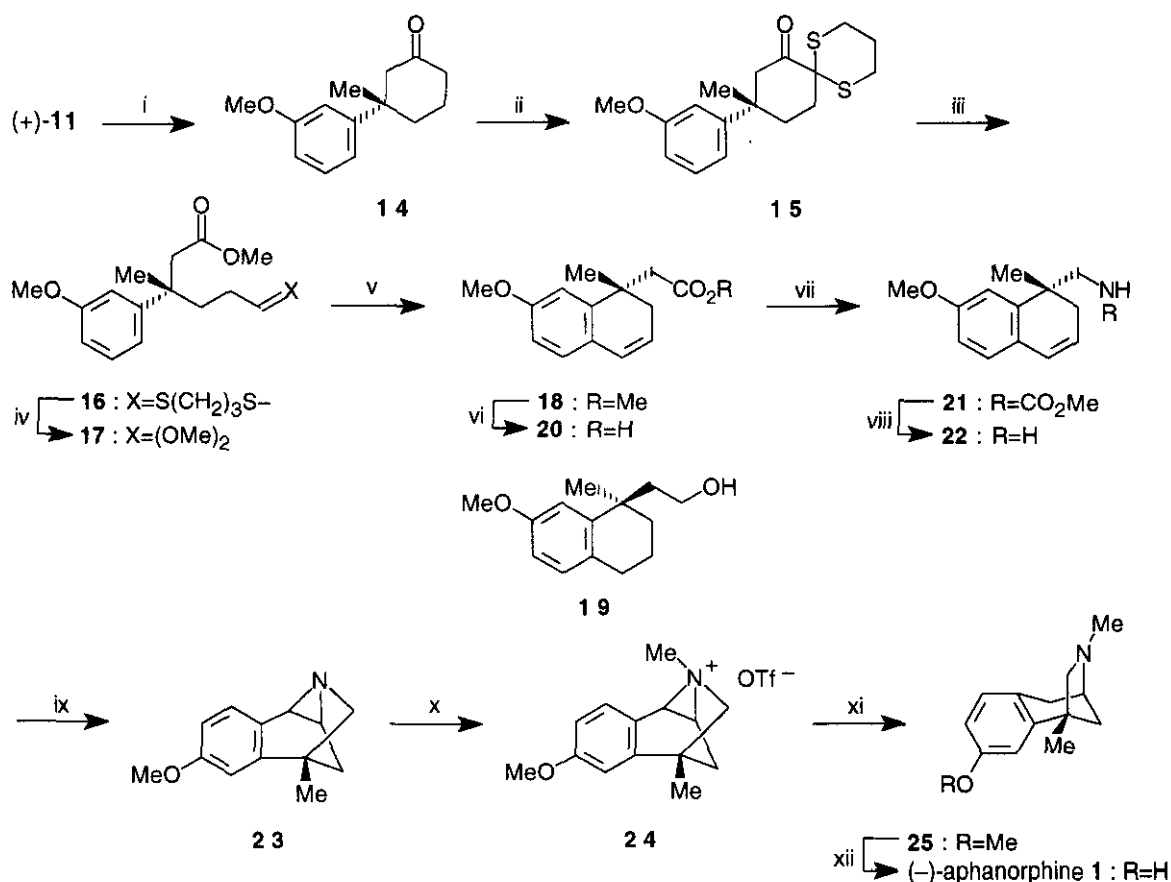


Scheme 2

Reagents and conditions: (i) 3-MeOC₆H₄MgBr (3 equiv.), CuBr·Me₂S (10 mol %), Me₃SiCl (2 equiv.), HMPA (2 equiv.), THF, –78 °C ~ –30 °C ~ –78 °C then sat. NH₄Cl then 10% HCl, 0 °C [83% for (+)-**10** and (–)-**10**]. (ii) diphenyl ether, reflux, 30 min [81% for (+)-**11** and 80% for (–)-**11**]. (iii) 30% H₂O₂ (3 equiv.), 5% NaOH (0.5 equiv.), 0 °C (92%). (iv) NH₂NH₂·HCl (3 equiv.), Et₃N (4 equiv.), sonication, rt, 2 h (64%). (v) MnO₂, CH₂Cl₂, rt (90%).

i-PrOH/hexane, 2.0:100)] (Scheme 2).

Having established the enantiomerization procedure, (+)-**11** was transformed into the α -diketone monothioketal,¹⁵ $[\alpha]^{27}_D +116.5^\circ$ (*c* 1.1, CHCl₃), in 54% overall yield by sequential catalytic hydrogenation and regioselective α -thioketalization *via* the cyclohexanone (**14**), $[\alpha]^{25}_D +70.5^\circ$ (*c* 0.7, CHCl₃). Alkaline cleavage¹⁵ of **15** gave the dithiane (**16**), $[\alpha]^{29}_D +10.8^\circ$ (*c* 1.1, CHCl₃), in 73% yield after esterification, which was converted to the dimethyl acetal (**17**), $[\alpha]^{28}_D +16.0^\circ$ (*c* 1.0, CHCl₃), in 89% yield on exposure to bis(trifluoroacetoxy)iodobenzene in methanol.¹⁶ When **17** was stirred with 2 N HCl (10 equiv.) overnight in THF at room temperature,^{4b} a clean reaction occurred to give the dihydronaphthalene (**18**), $[\alpha]^{30}_D +7.0^\circ$ (*c* 1.3,



Scheme 3

Reagents and conditions: (i) H₂, 10% Pd-C, MeOH (99%). (ii) CH₂(CH₂STs)₂, *t*-BuOK, *t*-BuOH-THF (2:7), -30 °C (54%). (iii) KOH (10 equiv.), *t*-BuOH, reflux then acid work up, CH₂N₂, CH₂Cl₂ (73%). (iv) PhI(OCOCF₃)₂ (2 equiv.), MeOH, rt (89%). (v) 2 N HCl (10 equiv.), THF, rt (92%). (vi) KOH (2 equiv.), 50% MeOH, reflux. (vii) (PhO)₃P(O)N₃, Et₃N, benzene, reflux then MeOH, reflux (79% from **18**). (viii) 50% aq. KOH-MeOH (1:1), reflux. (ix) Pb(OAc)₄ (2 equiv.), K₂CO₃ (10 equiv.), benzene, reflux. (x) MeOTf (1.5 equiv.), CH₂Cl₂, -15 °C. (xi) LiAlH₄ (2 equiv.), THF, -30 °C (47% from **21**). (xii) BBr₃ (2 equiv.), CH₂Cl₂, -78 °C (86%).

CHCl_3), in 92% yield. At this stage, the structure of **18** was confirmed by transforming its enantiomer (*ent*-**18**), $[\alpha]^{26}_{\text{D}} -7.6^\circ$ (*c* 1.2, CHCl_3), obtained from (–)-**11** by employing the same procedure, into the known tetrahydronaphthalene^{4c} (**19**), $[\alpha]^{25}_{\text{D}} +36.2^\circ$ (*c* 0.7, CHCl_3) [lit.,^{4c} $[\alpha]^{20}_{\text{D}} +36.2^\circ$ (*c* 1.8, CHCl_3)], used as the key intermediate for the synthesis of an analgesic (–)-eptazocine,^{4c,4g} by sequential catalytic hydrogenation and hydride reduction.

To render the side chain appropriate for the construction of (–)-aphanorphine (**1**), the ester (**18**) was first converted to the acid (**20**) which was then treated with diphenylphosphoryl azide¹⁷ (DPPA) in benzene containing triethylamine, followed by methanol to give the carbamate (**21**), $[\alpha]^{30}_{\text{D}} +6.85^\circ$ (*c* 0.9, CHCl_3), in 79% overall yield. After saponification of the carbamate (**21**) with 50% potassium hydroxide in methanol (1:1), the resulting primary amine³ (**22**) was exposed to lead(IV) tetraacetate¹⁸ in benzene in the presence of potassium carbonate to give the unstable aziridine (**23**). Without purification, **23** was treated with methyl trifluoromethanesulfonate in dichloromethane to give the ammonium triflate (**24**) which, after evaporation of the solvent, was immediately treated with lithium aluminum hydride³ in THF to give aphanorphine methyl ether (**25**), $[\alpha]^{28}_{\text{D}} +8.1^\circ$ (*c* 1.2, CHCl_3) [lit., $[\alpha]^{29}_{\text{D}} +8.46^\circ$ (*c* 0.91, CHCl_3)²; $[\alpha]^{21}_{\text{D}} +10.4^\circ$ (*c* 1.24, CHCl_3)^{4g}], in 47% overall yield by reductive cleavage of the benzylic carbon-nitrogen bond. Overall yield of the penultimate (**25**) from **21** was 47% in four steps. Finally, **25** was treated with boron tribromide in dichloromethane³ to give (–)-aphanorphine (**1**), $[\alpha]^{29}_{\text{D}} -31.25^\circ$ (*c* 1.3, MeOH); $[\alpha]^{30}_{\text{D}} -43.5^\circ$ (*c* 0.7, H_2O) for the hydrochloride [lit., $[\alpha]^{23}_{\text{D}} -24.0^\circ$ (*c* 0.33, MeOH)^{4g}; $[\alpha]^{25}_{\text{D}} -43.7^\circ$ (*c* 0.47, H_2O)¹ and $[\alpha]^{22}_{\text{D}} -46.3^\circ$ (*c* 0.22, H_2O)² for the hydrochloride], in 86% yield (Scheme 3).

In summary, an enantioconvergent tactic for the synthesis of (–)-aphanorphine (**1**) has been developed making use of both enantiomeric starting materials obtained by lipase-mediated kinetic transesterification.

ACKNOWLEDGEMENTS

We thank Professor Yuzuru Shimizu, Department of Pharmacognosy and Environmental Health Sciences, The University of Rhode Island, for an authentic natural (–)-aphanorphine and Professor Shunsaku Shiotani, Department of Chemistry, Toyama University, for kind suggestions and spectroscopic data. We also thank Mr. Shinji Tarama, Toyobo Co., Osaka, for a donation of lipase LIP and the Japan Society for the Promotion of Science for Japanese Junior Scientists for a fellowship (to T. K.).

REFERENCES

1. N. Gulavita, A. Hori, 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. (a) T. Honda, A. Yamamoto, Y. Cui, and M. Tsubuki, *J. Chem. Soc., Perkin Trans. 1*, 1992, 531. (b) A. I. Meyers, W. Schmidt, and B. Santiago, *Heterocycles*, 1995, **40**, 525. (c) A. N. Hulme, S. S. Henry, and A. I. Meyers, *J. Org. Chem.*, 1995, **60**, 1265. (d) A. Fadel and P. Arzel, *Tetrahedron: Asymmetry*, 1995, **6**, 893. (e) M. Node, H. Imazato, R. Kurosaki, Y. Kawano, T. Inoue, K. Nishide, and K. Fuji, *Heterocycles*, 1996, **42**, 811. (f) K. O. Hallinan and T. Honda, *Tetrahedron*, 1995, **51**, 12211. (g) S. Shiotani, H. Okada, K. Nakamata, T. Yamamoto, and F. Sekino, *Heterocycles*, 1996, **43**, 1031.
5. For a pertinent review, see: D. C. Palmer and M. J. Strauss, *Chem. Rev.*, 1977, **77**, 1.
6. T. Kamikubo, M. Shimizu, and K. Ogasawara, *Enantiomer*, in press.
7. K. Alder, F. H. Flock, and H. Beumling, *Chem. Ber.*, 1960, **93**, 1896.
8. For a pertinent monograph, see: C. -H. Wong and G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Pergamon, Oxford, 1994.
9. (a) S. Takano, Y. Higashi, T. Kamikubo, M. Moriya, and K. Ogasawara, *Synthesis*, 1993, 948. (b) S. Takano, M. Moriya, T. Kamikubo, K. Hiroya, and K. Ogasawara, *Tetrahedron Lett.*, 1993, **34**, 8485. (d) M. Moriya, T. Kamikubo, and K. Ogasawara, *Synthesis*, 1995, 187.
10. J. -L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226; A. L. Gemal and J. -L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.
11. Cf. F. Theil, J. Weidner, S. Ballschuh, A. Kunath, and H. Schick, *Tetrahedron Lett.*, 1993, **34**, 305; T. Sugahara, Y. Kuroyanagi, and K. Ogasawara, *Synthesis*, 1996, 1101.
12. Y. Horiguchi, S. Matsuzawa, E. Nakamura, and I. Kuwajima, *Tetrahedron Lett.*, 1986, **27**, 4025.
13. Satisfactory spectral (IR, ^1H NMR, and MS) and analytical (combustion and high resolution MS) data for all new compounds isolated.
14. Cf. T. Sugahara and K. Ogasawara, *Tetrahedron Lett.*, 1996, **37**, 7403.
15. For a pertinent review, see: S. Takano and K. Ogasawara, *J. Syn. Org. Chem. Jpn.*, 1977, **35**, 795.
16. G. Stork and K. Zhao, *Tetrahedron Lett.*, 1989, **30**, 287.
17. T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203.
18. W. Nagata, S. Hirai, K. Kawata, and T. Aoki, *J. Am. Chem. Soc.*, 1967, **89**, 5045.

Received, 26th November, 1996