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

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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 isolated[1] from the blue-green alga *Aphanizomenon flos-aquae* and its absolute structure determined by synthesis,[2,3] has attracted considerable synthetic interest[4] owing to its unique structure resembling benzomorphan analgesics such as (–)-pentazocine[5] (**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.

(–)-aphanorphine (**1**)

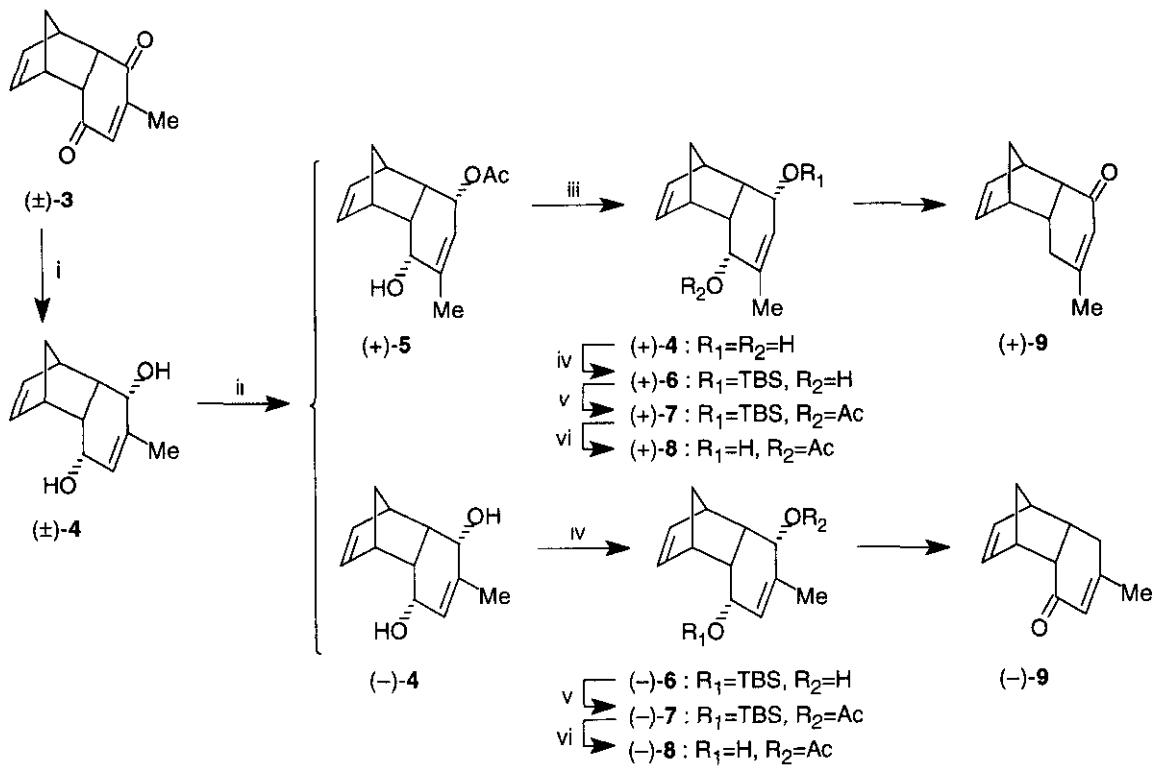
(–)-pentazocine (**2**)

Figure 1

We have recently developed[6] 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 adduct[7] [(±)-**3**] between toluquinone and cyclopentadiene, by employing lipase-mediated transesterification in an organic solvent[8] and a palladium-

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

mediated elimination reaction[9] 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 reported[9] recently (**Scheme 1**).



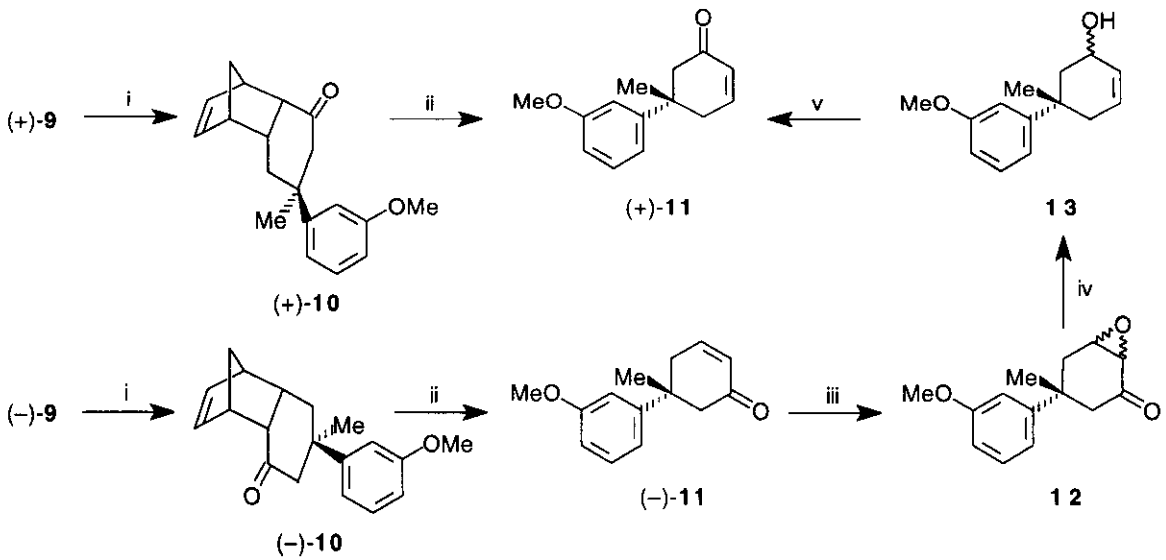
Scheme 1

Reagents and conditions: (i) $NaBH_4$-$CeCl_3 \cdot 7H_2O$, MeOH, 0 °C (~84%). (ii) vinyl acetate (4 equiv.), lipase LIP, THF-Et_3N (10:1), rt, 55 h [30% for (+)-**5** (>99% ee) and 42% for (–)-**4** (>99% ee)]. (iii) K_2CO_3, MeOH (98%). (iv) *t*-Bu(Me)$_2$SiCl, imidazole, DMF [92% for (+)-**6** and 87% for (–)-**6**]. (v) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2 [99% for (+)- and (–)-**7**]. (vi) Bu_4NF, 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 ketone[13] (**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° (*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° (*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° (*c* 1.1, $CHCl_3$), originated from the alcohol [(–)-**4**], afforded the enantiomeric (–)-5,5-disubstituted cyclohexenone [(–)-**11**], $[\alpha]^{29}_{D}$ –89.7° (*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 mangane(IV) dioxide in dichloromethane afforded the single enone [(+)-**11**], $[\alpha]^{27}_{D}$ +88.5° (*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,

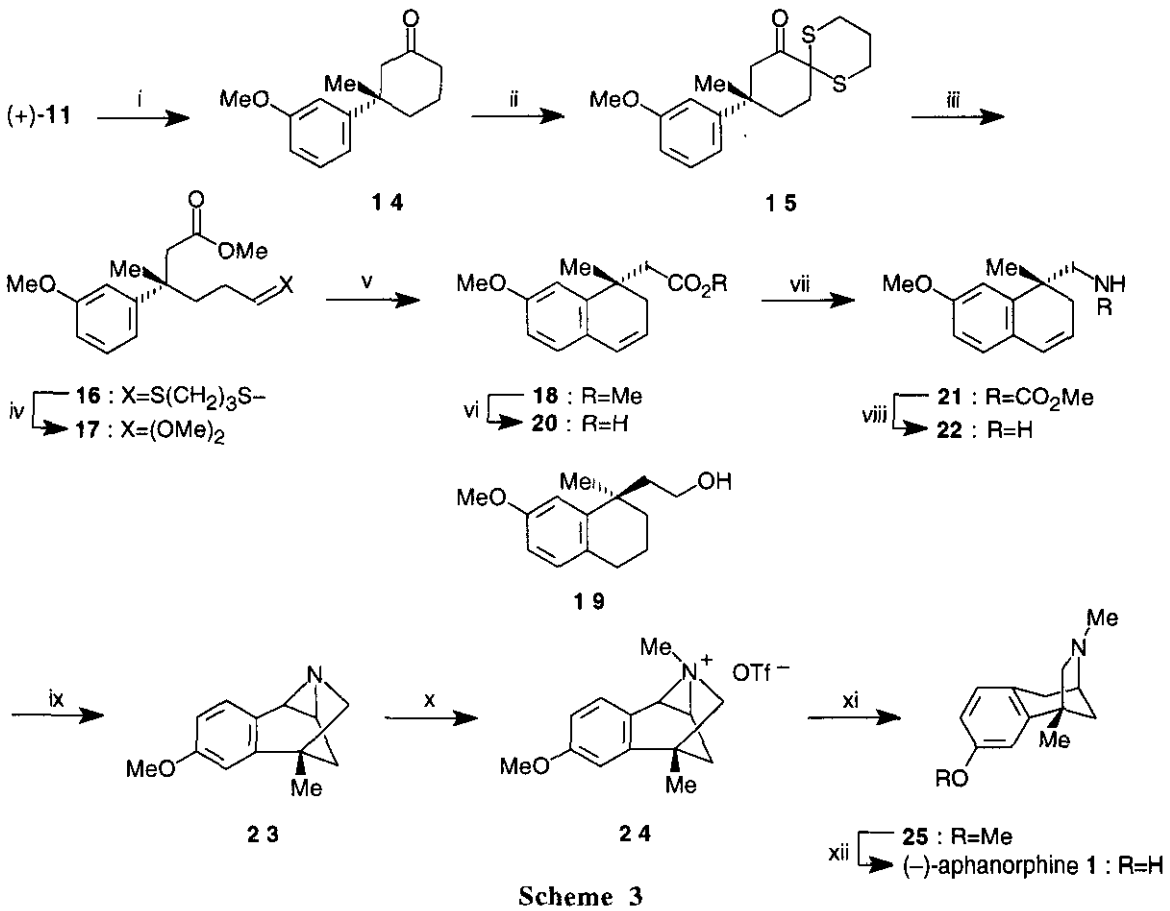


Scheme 2

Reagents and conditions: (i) 3-$MeOC_6H_4MgBr$ (3 equiv.), CuBr·Me_2S (10 mol %), Me_3SiCl (2 equiv.), HMPA (2 equiv.), THF, –78 °C ~ –30 °C ~ –78 °C then sat. NH_4Cl 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% H_2O_2 (3 equiv.), 5% NaOH (0.5 equiv.), 0 °C (92%). (iv) NH_2NH_2·HCl (3 equiv.), Et_3N (4 equiv.), sonication, rt, 2 h (64%). (v) MnO_2, CH_2Cl_2, 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° (*c* 1.1, $CHCl_3$), in 54% overall yield by sequential catalytic hydrogenation and regioselective α-thioketalization *via* the cyclohexanone (**14**), $[\alpha]^{25}_{D}$ +70.5° (*c* 0.7, $CHCl_3$). Alkaline cleavage[15] of **15** gave the dithiane (**16**), $[\alpha]^{29}_{D}$ +10.8° (*c* 1.1, $CHCl_3$), in 73% yield after esterification, which was converted to the dimethyl acetal (**17**), $[\alpha]^{28}_{D}$ +16.0° (*c* 1.0, $CHCl_3$), 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° (*c* 1.3,



Scheme 3

Reagents and conditions: (i) H_2, 10% Pd-C, MeOH (99%). (ii) $CH_2(CH_2STs)_2$, *t*-BuOK, *t*-BuOH-THF (2:7), –30 °C (54%). (iii) KOH (10 equiv.), *t*-BuOH, reflux then acid work up, CH_2N_2, CH_2Cl_2 (73%). (iv) $PhI(OCOCF_3)_2$ (2 equiv.), MeOH, rt (89%). (v) 2 N HCl (10 equiv.), THF, rt (92%). (vi) KOH (2 equiv.), 50% MeOH, reflux. (vii) $(PhO)_2P(O)N_3$, Et_3N, benzene, reflux then MeOH, reflux (79% from **18**). (viii) 50% aq. KOH-MeOH (1:1), reflux. (ix) $Pb(OAc)_4$ (2 equiv.), K_2CO_3 (10 equiv.), benzene, reflux. (x) MeOTf (1.5 equiv.), CH_2Cl_2, –15 °C. (xi) $LiAlH_4$ (2 equiv.), THF, –30 °C (47% from **21**). (xii) BBr_3 (2 equiv.), CH_2Cl_2, –78 °C (86%).

$CHCl_3$), in 92% yield. At this stage, the structure of **18** was confirmed by transforming its enantiomer (*ent*-**18**), $[\alpha]^{26}_D$ –7.6° (*c* 1.2, $CHCl_3$), obtained from (–)-**11** by employing the same procedure, into the known tetrahydronaphthalene[4c] (**19**), $[\alpha]^{25}_D$ +36.2° (*c* 0.7, $CHCl_3$) [lit.,[4c] $[\alpha]_D^{20}$ +36.2° (*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 azide[17] (DPPA) in benzene containing triethylamine, followed by methanol to give the carbamate (**21**), $[\alpha]^{30}_D$ +6.85° (*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 amine[3] (**22**) was exposed to lead(IV) tetraacetate[18] 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 hydride[3] in THF to give aphanorphine methyl ether (**25**), $[\alpha]^{28}_D$ +8.1° (*c* 1.2, $CHCl_3$) [lit., $[\alpha]^{29}_D$ +8.46° (*c* 0.91, $CHCl_3$)[2]; $[\alpha]^{21}_D$ +10.4° (*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 dichloromethane[3] to give (–)-aphanorphine (**1**), $[\alpha]^{29}_D$ –31.25° (*c* 1.3, MeOH); $[\alpha]^{30}_D$ –43.5° (*c* 0.7, H_2O) for the hydrochloride [lit., $[\alpha]^{23}_D$ –24.0° (*c* 0.33, MeOH)[4g]; $[\alpha]^{25}_D$ –43.7° (*c* 0.47, H_2O)[1] and $[\alpha]^{22}_D$ –46.3° (*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.

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