Facile Syntheses of Aporphine Derivatives

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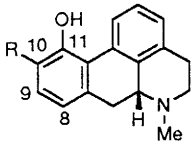
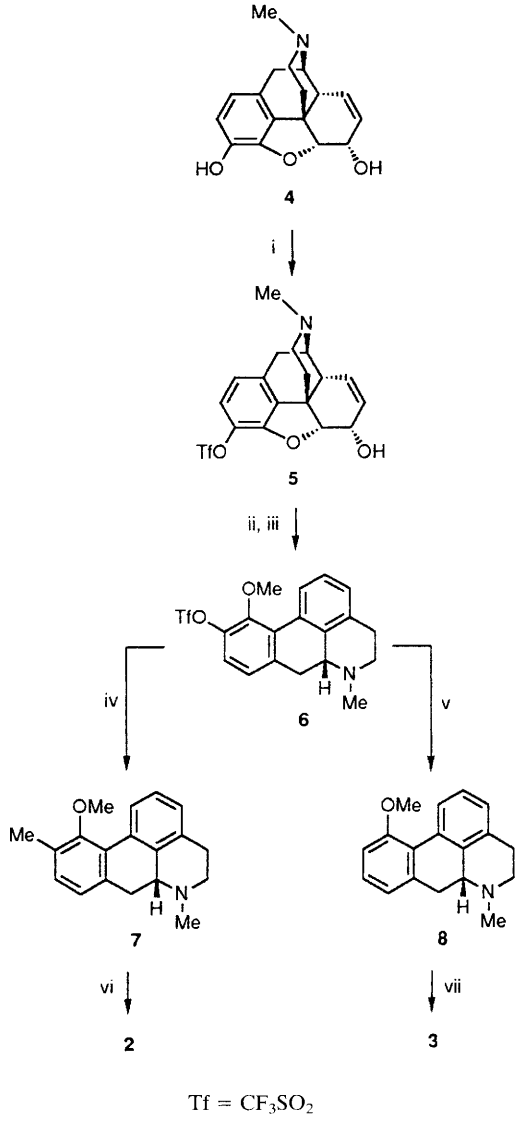
New and efficient synthetic routes, utilizing palladium-catalysed reactions, provide (*R*)-11-hydroxy-10-methylaporphine **2** and (*R*)-11-hydroxyaporphine **3** from natural morphine **4**.

(*R*)-Apomorphine **1** is a prototype dopamine (DA)-receptor agonist.[1] Recently, two derivatives of **1** have been shown to exhibit other interesting pharmacological profiles; (*R*)-11-hydroxy-10-methylaporphine **2** appears to be a 5-hydroxytryptamine (5-HT) receptor agonist with selectivity for 5-HT_{1A}-receptors[2] and (*R*)-11-hydroxyaporphine **3** has been characterized as a DA D_1-receptor antagonist.[3] These aporphine derivatives were synthesized from natural morphine **4** in seven and five steps, respectively, with low to moderate overall yields.[2–4] In this paper we report on two new, flexible and more efficient approaches producing **2** and **3** from **4** by use of palladium-catalysed synthetic methods (Schemes 1 and 2). The key-intermediate in both sequences is monotrifluoromethanesulfonate **5** {m.p. 123–124 °C, $[\alpha]_D^{21}$ −77.8 (*c* 1.0, MeOH)},† which is readily obtained from **4** by treatment with triethylamine and *N*-phenyltrifluoromethanesulfonimide in dichloromethane (CH_2Cl_2).[5] Treatment of **4** with the more reactive trifluoromethanesulfonic anhydride gave a very low yield of **5**.

In the first method (Scheme 1), monotrifluoromethanesulfonate **5** was converted to aporphine trifluoromethanesulfonate **6** {hydrochloride, m.p. 207–209 °C, $[\alpha]_D^{21}$ −48.0 (*c* 1.0, MeOH)} by an acid catalysed rearrangement[2,4,6] in concentrated methanesulfonic acid ($MeSO_3H$) followed by *O*-methylation of the C(11)-hydroxy group with diazomethane (CH_2N_2). Cross coupling of **6** with tetramethyltin [Me_4Sn] in the presence of tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$]‡ and lithium chloride (LiCl) in dimethylformamide (DMF) according to Stille *et al.*[7] gave 10-methyl-11-methoxyaporphine **7** {hydrochloride, m.p. 189–191 °C, $[\alpha]_D^{21}$ −179.0 (*c* 1.0, MeOH)}. The deoxygenated **8**[2–4] was obtained from **6** by treatment with formic acid (HCO_2H), triethylamine (Et_3N), palladium(II) acetate [$Pd(OAc)_2$] and 1,1′-bis(diphenylphosphino)ferrocene (dppf) in DMF.[5] Methoxy derivatives **7** and **8** were *O*-demethylated by treatment with aqueous



1; R = OH
2; R = Me
3; R = H
11; R = Ph

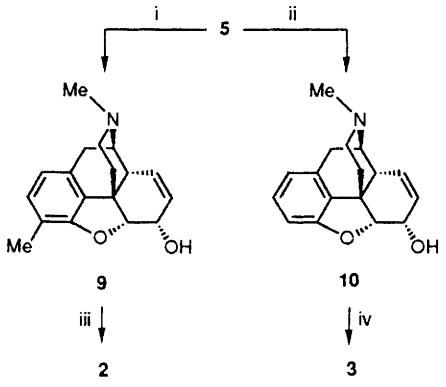


Tf = CF_3SO_2

Scheme 1 *Reagents and conditions*: i, **4**-monohydrate, *N*-phenyltrifluoromethanesulfonimide (1.2 equiv.), Et_3N (1.5 equiv.), CH_2Cl_2, room temp., N_2, 48 h, 90%; ii, $MeSO_3H$, N_2, 95 °C, 1.5 h; iii, CH_2N_2, Et_2O, $CHCl_3$, −15 °C, 12 h, (overall yield from **5** to **6**: 58%); iv, Me_4Sn (1.2 equiv.), LiCl (3.0 equiv.), $Pd(PPh_3)_4$ (0.030 equiv.), DMF, 100 °C, sealed tube, 16 h, 77%; v, HCO_2H (2.5 equiv.), Et_3N (3.8 equiv.), $Pd(OAc)_2$ (0.10 equiv.), dppf (0.15 equiv.), DMF, N_2, 60 °C, 22 h, 87%; vi, 48% aqueous HBr, N_2, 120 °C, 3 h, 89%; vii, same as vi, 74%

† All compounds gave satisfactory combustion analyses and IR, ^1H NMR (270 MHz) and ^{13}C NMR (67.5 MHz) spectroscopic data. *Selected data*: **3**·HCl: ^1H NMR δ (CD_3OD) 2.88 (t, 1H), 3.10 (m, 1H), 3.16 (s, 3H), 3.45 (m, 3H), 3.77 (m, 1H), 4.33 (m, 1H), 6.86 (d, 2H), 7.10 (t, 1H), 7.15 (d, 1H), 7.35 (t, 1H), 8.40 (d, 1H). **5**: ^1H NMR δ ($CDCl_3$) 1.90 (m, 1H), 2.11 (m, 1H), 2.28–2.40 (m, 2H), 2.44 (s, 3H), 2.62 (m, 1H), 2.70 (m, 1H), 3.09 (d, 1H), 3.39 (m, 1H), 4.21 (m, 1H), 5.02 (dd, 1H), 5.28 (m, 1H), 5.70 (m, 1H), 6.64 (d, 1H), 6.89 (d, 1H); ^{19}F NMR δ (84.5 MHz; $CDCl_3$) −73.9 (s, 3F); IR ν/cm^{-1} (KBr) 3550 (OH). **6**·HCl: ^1H NMR δ (CD_3OD) 2.93 (t, 1H), 3.10 (m, 1H), 3.19 (s, 3H), 3.42–3.65 (m, 3H), 3.68 (s, 3H), 3.83 (m, 1H), 4.51 (m, 1H), 7.32 (m, 3H), 7.44 (t, 1H), 8.25 (d, 1H); ^{19}F NMR δ (84.5 MHz; CD_3OD) −74.3 (s, 3F). **7**·HCl: ^1H NMR δ (CD_3OD) 2.32 (s, 3H), 2.83 (t, 1H), 3.14 (m, 1H), 3.18 (s, 3H), 3.41–3.63 (m, 3H), 3.50 (s, 3H), 3.81 (m, 1H), 4.42 (m, 1H), 7.07 (d, 1H), 7.16 (d, 1H), 7.24 (d, 1H), 7.40 (t, 1H), 8.36 (d, 1H). **9**: ^1H NMR δ ($CDCl_3$) 1.85 (m, 1H), 2.06 (m, 1H), 2.18 (s, 3H), 2.25–2.34 (m, 2H), 2.44 (s, 3H), 2.59 (m, 1H), 2.67 (m, 1H), 3.06 (d, 1H), 3.34 (m, 1H), 4.17 (m, 1H), 4.84 (d, 1H), 5.29 (m, 1H), 5.68 (m, 1H), 6.54 (d, 1H), 6.82 (d, 1H); IR ν/cm^{-1} (film) 3540 (OH).

‡ All palladium complexes used herein are commercially available.



Scheme 2 *Reagents and conditions*: i, Me_4Sn (1.2 equiv.), LiCl (3.0 equiv.), $Pd(PPh_3)_4$ (0.050 equiv.), DMF, 100 °C, sealed tube, 18 h, 88%; ii, HCO_2H (3.0 equiv.), Bu_3N (4.2 equiv.), dppp (0.15 equiv.), $(PPh_3)_2PdCl_2$ (0.060 equiv.), DMF, N_2, 80 °C, 18 h, 91%; iii, $MeSO_3H$, N_2, 95 °C, 1 h, 82%; iv, $MeSO_3H$, N_2, 95 °C, 15 min, 67%

48% hydrobromic acid (HBr) to give **2**§ and **3**¶ in overall yields of 36 and 34%, respectively.

In the second approach (Scheme 2) **5** was converted to **9** {m.p. 181–183 °C, $[\alpha]_D^{21}$ −195.0 (*c* 1.0, MeOH)} by a palladium-catalysed coupling with tetramethyltin as described above for compound **7**. Monotrifluoromethanesulfonate **5** was also used as a precursor in the preparation of 3-deoxymorphine **10**‖ by palladium-catalysed hydrogenolysis in accordance with the recently published procedure by Saá *et al.*;[8] tributylammonium formate (hydride donor), bis(triphenylphosphine)palladium(II) chloride $[PdCl_2(PPh_3)_2]$–1,3-bis(diphenylphosphino)propane $[(PPh_2)(CH_2)_3(PPh_2)]$ (catalytic system) and DMF. Acid catalysed rearrangements[2,4,6] of **9** and **10** afforded **2** and **3**, respectively. The overall yields in the second route were 65 and 55% for **2** and **3**, respectively.

It is apparent that the rearrangement of the morphine moiety to the aporphine structure occurs readily also in the absence of the 3-positioned morphine oxygen.** This conclusion was further corroborated by the facile acid-catalysed conversion of 3-deoxy-3-phenylmorphine†† to **11** {hydrochloride, m.p. 246–250 °C, $[\alpha]_D^{23}$ −52.0 (*c* 1.0 MeOH)} in 67% yield. Consequently, the methods presented here appear to be useful for production of an array of pharmacologically interesting 10-substituted derivatives of **2**.

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§ Optical rotation $[\alpha]_D^{21}$ −103.4 (*c* 1.0, MeOH), {lit.[2] $[\alpha]_{578}^{26.7}$ −85.2 (*c* 0.55, MeOH)}.

¶ Compound **3** has been reported as the hydrobromide.[3,4] Data for **3**·HCl: m.p. 270 °C; $[\alpha]_D^{22}$ −71.6 (*c* 1.0, MeOH).

‖ 3-Deoxymorphine **10**, obtained by this route, has been synthesized in eight steps and 16% overall yield from **4**.[9]

** We are not aware of any report on morphine to aporphine rearrangements of 3-deoxymorphine derivatives.

†† Prepared from **5** by cross coupling with phenylboronic acid in presence of $Pd(PPh_3)_4$, LiCl and 2 mol dm^{-3} aqueous Na_2CO_3 in refluxing dimethoxyethane (DME)–ethanol mixture under nitrogen atmosphere[10] in 80% isolated yield. M.p. 169–171 °C; $[\alpha]_D^{21}$ −49.0 (*c* 1.0, MeOH).