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Hypoiodite reactions of 1,9-dideoxyforskolin and its 6-acetyl-11-deoxo-11β-hydroxy derivative

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Abstract—Hypoiodite reactions of 1,9-dideoxyforskolin and its 6-acetyl-11-deoxo-11β-hydroxy derivative gave the corresponding C-20 oxido analogues. © 2001 Published by Elsevier Science Ltd.

The use of lead tetraacetate (LTA) and iodine for oxidative cyclisation of appropriate alcohols is an extremely powerful method for the preparation of tetrahydrofuran derivatives.[1] The hypoiodite reactions of 6β-hydroxy steroids afford 6β,19-ethers,[2] whereas 11β-hydroxy steroids give complex mixtures from which 11β,18-lactones and 11β,19-ethers and lactones can be isolated.[3] 1,9-Dideoxyforskolin[4] isolated from the Indian medicinal herb *Coleus forskohlii* is a potent nicotinic acetylcholine receptor blocker[5] and inhibits uterine contractions in rats.[6] 1,9-Dideoxyforskolin has five methyl groups ideally situated with reference to the 6-hydroxy and the 11-keto groups for remote functionalisation reactions. We report herein hypoiodite reactions of 1,9-dideoxyforskolin (**1**) and its 6-acetyl-11-deoxo-11β-hydroxy derivative (**4**) (Scheme 1).

Transesterification[7] of 1,9-dideoxyforskolin (**1**) followed by acetylation of the resulting compound **2** gave 6-acetyl-1,9-dideoxyforskolin (**3**), which was reduced with $NaBH_4$ to the 11β-hydroxy-derivative (**4**). Hypoiodite reaction[8] of compound **4** with LTA/I_2 gave a complex mixture from which three compounds, **5** (24%), **6** (12%) and **7** (6% yield) were isolated.

In order to overcome the difficulties faced during this separation, the crude product obtained after LTA/I_2 reaction was treated with silver acetate[8] to convert iodo-compounds to their corresponding acetates. Column chromatography of the product after silver acetate treatment gave compounds **5** (56%)[9] and **8** (17% yield) along with minor amounts of compounds **6** and **7** (combined yield <10%). Similarly the hypoiodite reaction, followed by silver acetate treatment of 1,9-dideoxyforskolin (**1**) gave, exclusively, compound **9** (87% yield).[10]

All the compounds were characterised by IR, UV, MS, ^1H NMR, ^{13}C NMR and 2D NOESY ^1H NMR spectral studies. In the 2D NOESY ^1H NMR spectrum of compound **5** (Fig. 1), both the C-20 protons showed a NOE with the C-19 protons, whereas only one of the C-20 protons displayed a NOE with the C-17 protons. Furthermore, the C-16 protons showed an NOE with the C-12 and C-14 protons, whereas the C-17 protons displayed an NOE with the C-20 and C-12 protons. Similarly, in the case of compound **9** the C-20 protons displayed a NOE with the C-17 and C-19 protons, the C-17 protons showed an NOE with the C-12, C-16 and C-20 protons and the C-19 protons displayed an NOE with the C-20 protons.

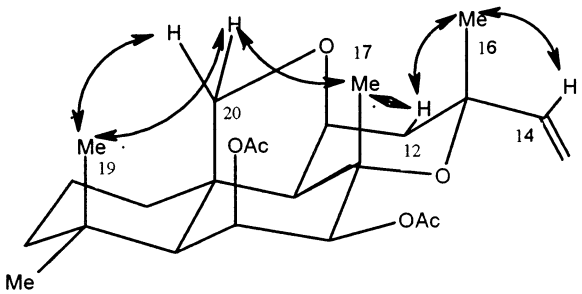

Figure 1. Selected NOESY interactions in compound **5**.

Keywords: hypoiodite reactions; 1,9-dideoxyforskolin.

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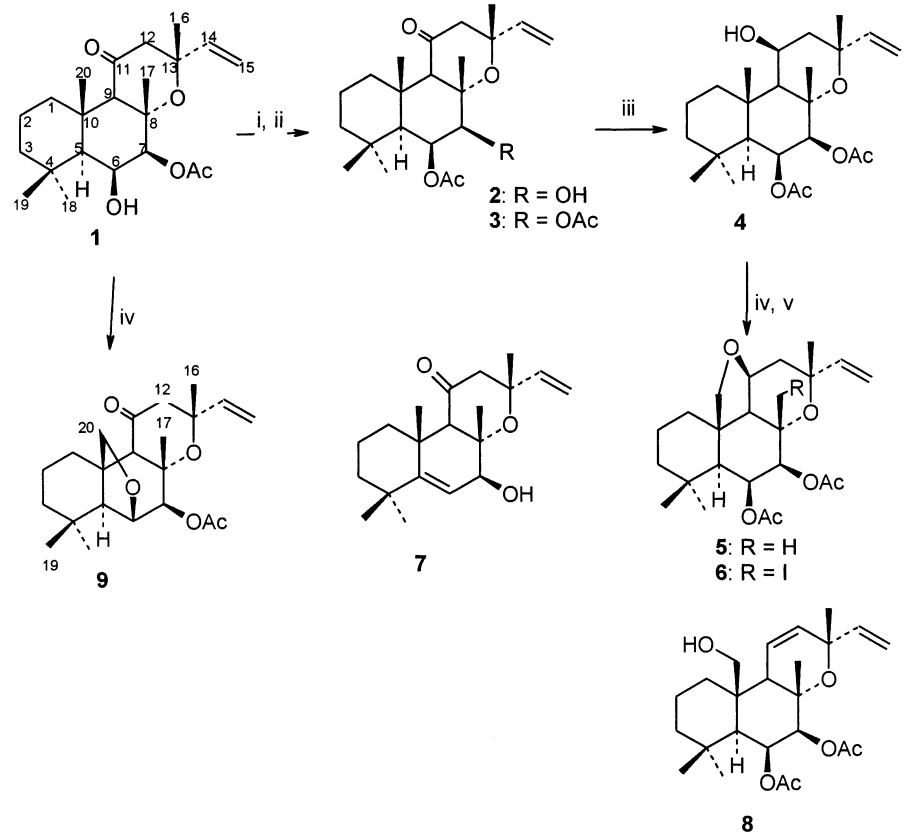

Scheme 1. *Reagents and conditions*: (i) basic alumina, C_6H_6; (ii) Ac_2O, pyridine; (iii) $NaBH_4$, MeOH; (iv) $Pb(OAc)_4$, I_2, $CaCO_3$, *hv*, cyclohexane; (v) AgOAc, aq. dioxane (90%) 65°C.

In summary, using hypoiodite reactions, 1,9-dideoxyforskolin and its 6-acetyl-11-deoxo-11β-hydroxy derivative were converted to the corresponding C-20 oxido analogues. In view of the important bioactivities of forskolin and 1,9-dideoxyforskolin the findings reported herein assume significance.

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9. Compound **5**: Mp 148–150°C; $[\alpha]_D^{30}$ +55.99 ($CHCl_3$, *c*, 1.0); FAB mass *m/z* 420 $[M]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 5.71 (1H, dd, $J=17.1$ and 10.2 Hz, 14-H), 5.66 (1H, dd, $J=1.9$ and 3.9 Hz, 6-H), 5.17 (1H, dd, $J=17.1$ and 1.0 Hz, 15-H), 4.92 (1H, dd, $J=10.2$ and 1.0 Hz, 15^1-H), 4.93 (1H, d, $J=3.9$ Hz, 7-H), 4.36 (1H, m, $W_{1/2}=7.5$ Hz, 11α-H), 4.07 (1H, d, $J=8.0$ Hz, 20-H), 3.80 (1H, d, $J=8.0$ Hz, 20^1-H), 2.29 (2H, m, 12-H), 2.07 (3H, s, OCOMe), 2.05 (3H, s, OCOMe), 1.92 (1H, d, $J=4.0$ Hz, 9-H), 1.78 (1H, d, $J=1.9$ Hz, 5-H), 1.73 (3H, s, 17-H), 1.25–2.0 (6H, m, 1-H, 2-H, 3-H), 1.21 (3H, s, 16-H), 0.89 (3H, s, 18-H) and 0.77 (3H, s, 19-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.12 (C-1), 28.49 (C-2), 37.08 (C-3) 34.02 (C-4), 39.36 (C-5), 69.81 (C-6), 73.09 (C-7), 76.79 (C-8), 40.94 (C-9), 43.99 (C-10), 71.94 (C-11), 46.06 (C-12), 69.36 (C-13), 146.73 (C-14), 111.90 (C-15), 31.34 (C-16), 22.94 (C-17), 33.75 (C-18), 31.84 (C-19), 73.40 (C-20), 170.59 (-O-CO-), 21.34 (-CO-$\underline{C}H_3$), 169.57 (-O-CO-) and 21.02 (-CO-$\underline{C}H_3$).
10. Compound **9**: $[\alpha]_D^{30}$ −5.89 ($CHCl_3$, *c*, 1.0); FAB mass *m/z* 376 $[M]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 5.94 (1H, dd, $J=17.2$ and 10.4 Hz, 14-H), 5.31 (1H, dd, $J=17.2$ and 1.0 Hz, 15-H), 5.11 (1H, dd, $J=10.4$ and 1.0 Hz, 15^1-H), 4.97 (1H, s, 7-H), 4.15 (1H, s, 6-H), 3.71 (2H, s, 20-H), 3.15 (1H, s, 9-H), 2.65 (2H, s, 12-H), 2.16 (3H, s,

OCOMe), 2.50 (1H, bd, $J=10$ Hz, 1α-H), 1.30–1.60 (5H, m, 1β-H, 2-H, 3-H), 1.54 (3H, s, 17-H), 1.27 (3H, s, 16-H), 0.96 (3H, s, 18-H) and 0.9 (3H, s, 19-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.94 (C-1), 27.69 (C-2), 32.31 (C-3), 32.14 (C-4), 39.21 (C-5), 68.86 (C-6), 79.18 (C-7), 81.66 (C-8), 39.41 (C-9), 44.49 (C-10), 205.19 (C-11), 49.78 (C-12), 79.32 (C-13), 146.88 (C-14), 112.55 (C-15), 30.97 (C-16), 22.90 (C-17), 33.66 (C-18), 32.11 (C-19), 75.06 (C-20), 170.43 (-O-CO-) and 21.26 (-CO-$\underline{C}H_3$).