Syntheses of 12-Oxygenated Forskolins

Nicholas J. Hrib

Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey 08876, U.S.A.

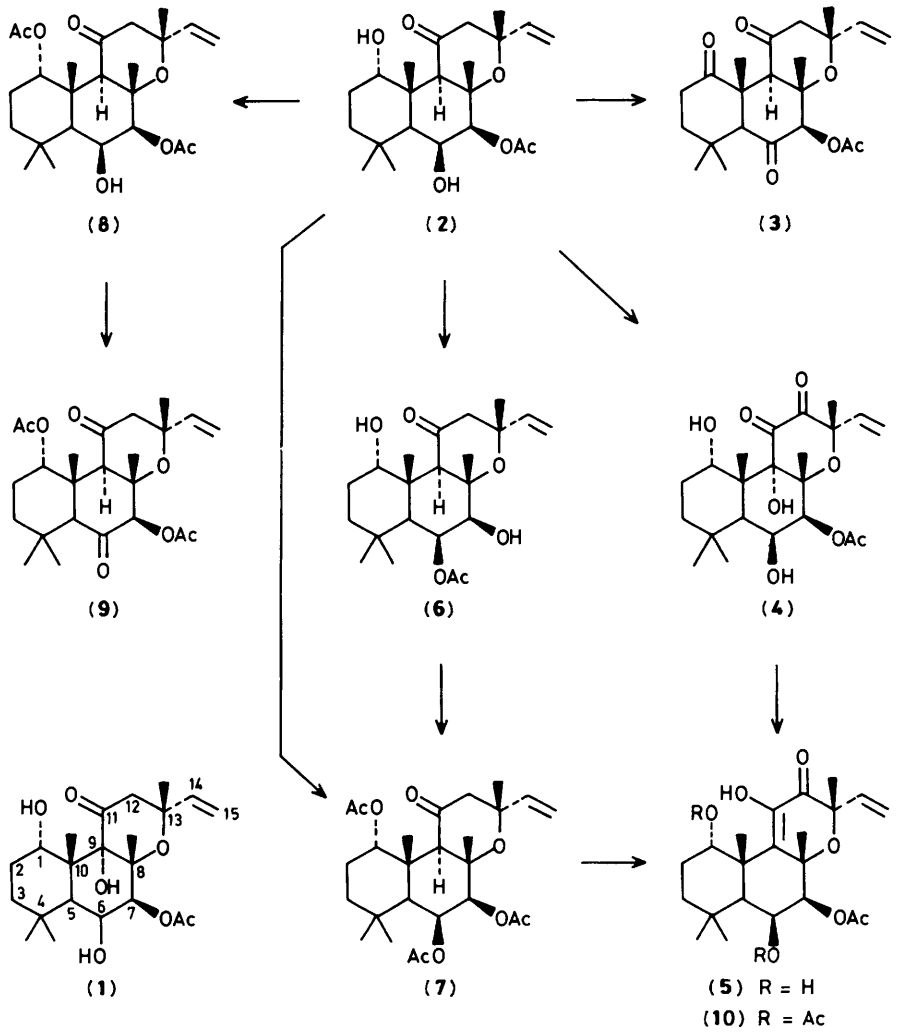
The preparation of selectively oxygenated forskolin derivatives has been achieved with reagent, solvent, and steric environment as key factors in selectivity of the oxidation.

Forskolin (**1**), a biologically active diterpene isolated from *Coleus forskohlii*, has generated considerable interest as a target for total or partial synthesis of the natural product itself and of potentially active analogues as well.[1,2]

We described in a previous paper the successful conversion of 9-deoxyforskolin (**2**) into forskolin *via* a stereo- and regio-selective hydroxylation sequence.[3] We were also interested in developing procedures which would allow direct hydroxylation at C-9 with or without further functionalization of the forskolin framework. This paper describes some of the results of these studies, including the preparation of the previously unknown 12-oxygenated derivatives of both forskolin and 9-deoxyforskolin.

The carbon framework of 9-deoxyforskolin proved surprisingly resistant to a number of oxidizing agents such as lead tetra-acetate,[4] molecular oxygen with various catalysts,[5] or halogenating agents.[6] Benzeneseleninic anhydride has been reported to effect α-hydroxylation of ketones in the presence of strong base.[7] However, under these conditions [$(PhSeO)_2O$, NaH, toluene, reflux] the only product we could obtain from 9-deoxyforskolin was the triketone (**3**) (40%).† The utilization of selenium dioxide[8] as an oxidizing agent

† Selected spectral data: (**3**) i.r. ($CHCl_3$): $\nu_{max.}$ 1735s and 1715s cm^{-1}; ^1H n.m.r. (Varian XL-200; $CDCl_3$); δ 6.08 (1H, dd, *J* 12 and 18 Hz, 14-H), 5.30 (3H, m, 2 × 15-H, 7-H), 3.92 (1H, s, 5-H), 3.15 (1H, dt, *J* 4 and 10 Hz), 2.95 (1H, J_{AB} 18 Hz, 12-H), 2.58 (1H, J_{AB} 18 Hz, 12-H), 2.25 (3H, s, Ac), 2.20 (1H, m), 1.50 (3H, s, Me), 1.45 (3H, s, Me), 1.35 (3H, s, Me), 1.24 (3H, s, Me), 1.00 (3H, s, Me), and 1.84—1.2 (2H, m); *m/z* 390 (M^+, EI, 17 eV); m.p. 127—129 °C; (**4**) i.r. ($CHCl_3$): $\nu_{max.}$ 1740s, and 1730s cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 7.40 (1H, s, 1-OH), 6.00 (1H, dd, *J* 12 and 18 Hz, 14-H), 5.55 (2H, m, 15-, 7-H), 5.18 (1H, dd, *J* 2 and 12 Hz, 15-H), 4.68 (1H, m, 1-H), 4.50 (1H, m, 6-H), 2.20 (3H, s, Ac), 1.74 (3H, s, Me), 1.54 (3H, s, Me), 1.28 (3H, s, Me), 1.07 (3H, s, Me), and 2.4—1.0 (7H, m); *m/z* 406 (M^+ −18, 17 eV); m.p. 185—187 °C (decomp.); (**5**) i.r. ($CHCl_3$): $\nu_{max.}$ 1742s and 1665m cm^{-1}. ^1H n.m.r. ($CDCl_3$); δ 5.90 (1H, dd, *J* 9 and 18 Hz, 14 H), 5.30 (3H, m, 2 × 15-H, 7-H), 4.70 (1H, m, 1-H), 4.58 (1H, m, 6-H), 2.22 (3H, s, Ac), 1.91 (3H, s, Me), 1.6 (3H, s, Me), 1.57 (3H, s, Me), 1.28 (3H, s, Me), 1.06 (3H, s, Me), and 2.30—1.0 (m, 8H); *m/z* 408 (M^+, 17 eV); m.p. 89—91 °C.



provided us with the first clear evidence of functionalization at the saturated C-9 and C-12 positions. Thus, treatment of 9-deoxyforskolin with this reagent (SeO_2, pyridine, toluene, reflux) proceeded cleanly, affording as the only product 12-oxoforskolin (**4**) (91%). The choice of solvent was critical in this case; no reaction occurred utilizing toluene, tetrahydrofuran, or dioxane alone.

In addition to standard ^1H n.m.r., i.r., mass spectral, and elemental analyses,† 12-oxoforskolin (**4**) was characterized by its ^{13}C n.m.r. spectrum which showed two ketone carbonyl carbon signals (δ 199.2 and 186.3) as well as a signal attributed to an ester carbonyl (δ 169.6).

Interestingly, forskolin itself was unstable under these conditions, suggesting that C-12 might be the site of initial oxidation. This hypothesis is supported by the observation that reduction of (**4**) (Zn, HOAc, room temp.) provided as sole product 12-oxo-9-deoxyforskolin (**5**)† in 94% yield. The ^{13}C n.m.r. spectrum of this compound revealed that the 11-ketone was completely enolized (one ketone carbonyl carbon signal at δ 193.6, two new sp^2 carbon signals at δ 141.2 and 137.3). These two compounds comprise the first examples of 12-oxygenated forskolin derivatives.

In the course of these studies we also prepared a series of selectively protected acetyl derivatives of 9-deoxyforskolin, which were also subjected to oxidative conditions. Since the 6-acetyl-7-de-acetyl derivative (**6**) is not accessible *via* direct acylation, treatment of (**2**) with base [$LiN(SiMe_3)_2$, tetrahydrofuran, 0 °C][3] resulted in a clean 7 → 6 acyl migration to provide (**6**) (80%).[9] Exposure of this compound to acetic anhydride (Ac_2O, pyridine, reflux) produced the fully acetylated derivative (**7**) (75%), while under identical conditions 9-deoxyforskolin gave only the 1,7-diacetyl derivative (**8**) (87%). Alternatively, (**7**) could be prepared directly from (**2**) under acidic conditions (Ac_2O, cat. $HClO_4$, 85%).

While exposure of the 1,7-diacetyl derivative (**8**) to benzeneseleninic anhydride [$(PhSeO)_2O$, NaH, toluene, reflux] provided the diketone (**9**) (47%), under these conditions the fully protected derivative (**7**) gave a complex mixture of products. However, treatment of (**7**) with selenium dioxide (SeO_2, pyridine, reflux) provided the enolic ketone (**10**) (84%) as sole product, the result of oxidation at the 12-position only. Apparently, the presence of an acetate moiety in the 1-position is sufficient to render the already hindered 9-position inaccessible to further oxidative attack.

In conclusion, we have developed methodology to prepare the hitherto unknown 12-oxygenated derivatives of forskolin with or without concomitant functionalization at the 9-position. The biological activity of these new compounds is currently under evaluation.

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