Tetrahedron Letters,Vol.28,No.1,pp 19-22,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

A SYNTHESIS OF FORSKOLIN. HYDROXYLATION OF 9-DEOXYFORSKOLIN.

Nicholas J. Hrib
Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey 08876

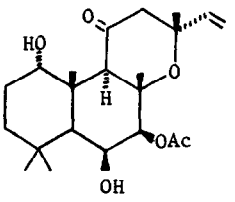
Summary: A synthesis of forskolin has been achieved via a unique hydroxylation reaction on 9-deoxyforskolin.

Forskolin (1), a labdane diterpene isolated from the roots of Coleus forskohlii, shows a positive inotropic effect and is active as an antihypertensive and in the lowering of intraocular pressure[1,2].

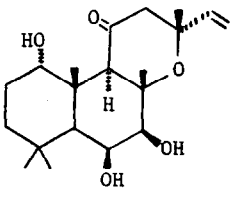
From the same plant source another diterpene, 9-deoxyforskolin (2), is isolated[3]. This compound differs from forskolin only in lacking the α-hydroxyl group at C-9; however, its activity is much reduced. A procedure for the chemical conversion of (2) to the more active compound forskolin (1) would serve a dual purpose; it would increase the supply of forskolin itself, and would generate useful knowledge for the synthesis of new forskolin analogues or the total synthesis of forskolin itself.

Two possible routes were undertaken to achieve this conversion. The more straight forward one, involving direct treatment of 9-deoxyforskolin with various oxidizing reagents, would have the advantage of brevity. However, an alternate and regioselective route was also planned whereby a suitably protected 9-deoxyforskolin derivative would first be converted to a 9,11-enol ether, enol acetate or silyl enol ether. This compound would then be treated with oxidizing reagents. We report here the successful conversion of 9-deoxyforskolin to forskolin via regio-and stereospecific hydroxylation of an enol ether intermediate. Our results on direct oxidations of 9-deoxyforskolin will be presented in a subsequent paper.

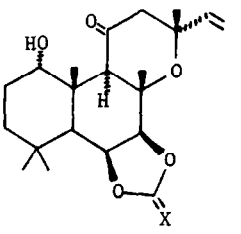
Our first attempts to trap the 9,11-enolate of 2 with trimethylsilyl chloride did not succeed, due to the lability of the trimethysilyl enol ether formed. However, stable crystalline 9,11-enol ethers (Table 1) were obtained utilizing tert-butyldimethylsilyl chloride or dimethyl sulfate as the trapping agent. The conditions for this reaction are rather specific (ketone in THF solution added to a stirred suspension of KH (5 eq.) and trapping agents (3 eq.) in THF under N_2, at RT). When 9-deoxyforskolin itself was the substrate, concomitant acetyl migration and trapping of the 7-alkoxide often occurred (viz. 11-13). Further studies with these compounds revealed that, while the tert-butyldimethylsilyl group rendered the 9-position sterically inaccessible, the methyl enol ether could be stereospecifically oxidized. We then considered the use of a suitable protecting group for the 6,7-functionality, ideally locking the 6-and 7-hydroxyls in a ring which should render the α-face of the molecule even more accessible. Thus, compound 2 was cleaved (K_2CO_3, aqueous CH_3OH) to yield the triol (3), which was further converted to either the acetonide (4) (2,2-dimethoxypropane, catalytic PPTS, reflux, 64%) or the carbonate (5) (1,1'-carbonyldiimidazole, toluene,



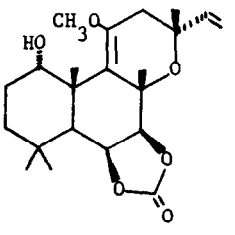
2



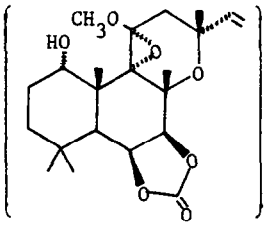
3



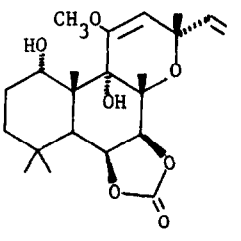
4, X=$(CH_3)_2$
5, X=O



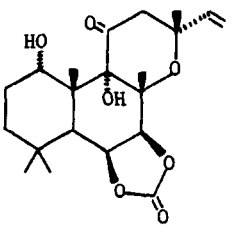
6



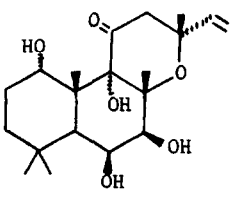
7



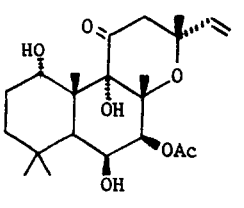
8



9



10



1, Forskolin

triethylamine, reflux, 62%) under relatively mild conditions. For convenience of protection and deprotection, we chose the 6,7-carbonate (5) as the subject of our initial investigations. The methyl enol ether (6) was obtained regiospecifically and in good yield from 5, (potassium hydride, dimethyl sulfate, anhydrous THF, N_2, 62%). The β-face of 6 is quite hindered by the presence of the axial methyl groups as well as the carbonate ring; however, we expected the α-face would be open to electrophilic attacks.

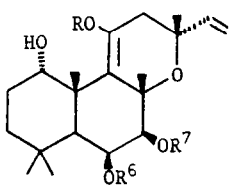
As expected, oxidation of this key intermediate (6) (m-chloroperbenzoic acid, CH_2Cl_2, K_2CO_3, 71%)[5] resulted in stereo- and regiospecific epoxidaton of the enol ether (in the presence of the 14,15-olefin) to produce the α-epoxide (7). Furthermore, under the reaction conditions, ring opening of 7 occurred to provide, in one pot, the desired 9-hydroxy enol ether (8) stereospecifically and in good yield.

Facile hydrolysis of enol ether 8 (3:1 1N HCl:THF, 95%) provided the known ketone 9[6]. The synthesis was completed by removal of the protecting group of 9 (K_2CO_3, aq. CH_3OH, 90%) to afford 7-desacetylforskolin (10), and its subsequent, selective acetylation[6] at the 7-OH to provide 1. The synthetic forskolin so obtained is identical to the natural product by ^{1}H-NMR, IR, MS as well as TLC properties.

The seven-step route proceeds in 12% (unoptimized) overall yield, and is amenable to scale-up. The product can also be obtained from the acetonide (4) using slightly different reaction conditions.

In conclusion, the synthesis of forskolin from 9-deoxyforskolin has been achieved. The versatile intermediates and methodology developed during the course of this work can be employed in the synthesis of new forskolin analogues.

Table 1. Enol Ether Derivatives



No.	R	R^6	R^7	mp[a]	Yield (%)[b]
6	CH_3	-CO-		123-125°	62
11	CH_3	Ac	CH_3	76-79°	60
12	$tBu(Me)_2Si$	Ac	$tBu(Me)_2Si$	189-191°	45
13	$tBu(Me)_2Si$	Ac	H	58-60°	25

a. Mp's are uncorrected.
b. Yields of isolated products.

References:

1. N. J. deSouza, A. N. Dohadwalla and J. Reden, Med. Res. Rev., 3 (2), 201-219 (1983).
2. J. Caprioli, M. Sears, L. Bausher, D. Gregory and A. Mead, Inves. Ophth. and Vis. Sci., 25 268-277 (1984).
3. S. V. Bhat, A. N. Dohadwalla, B. S. Bajwa, N. K. Dadkar, H. Dornauer and N. J. deSouza, J. Med. Chem., 26 486-492 (1983).
4. S. V. Bhat, B. S. Bajwa, H. Dornauer, N. J. deSouza and H.-W. Fehlhaber, Tetrahedron Lett., (19) 1669-1672 (1977).
5. C. L. Stevens and J. Tazuma, J. Amer. Chem. Soc., 76, 715 (1954). For examples of epoxidations of silyl enol ethers, see: A. Hassner, R. H. Reuss and H. W. Pinnick, J. Org. Chem., 40, 3427 (1975).
6. S. V. Bhat, B. S. Bajwa, H. Dornauer and N. J. deSouza J. Chem. Soc. Perk. I, 767-771 (1982).
7. Spectral data on new compounds.

(5): IR ($CHCl_3$): γ1800 (s); 1715 (s). NMR ($CDCl_3$): δ5.96 (1H, dd, J = 10 and 18 Hz, 14-H); 5.10 (3H, m, 15-H's and 6-H); 4.77 (1H, d, J = 8 Hz, 7-H); 4.41 (1H, m, 1-H); 3.35 (1H, s, 9-H); 2.65 (2H, AB, J = 18 and 40 Hz, 12-H's); 2.18 (1H, m, 5-H); 1.46 (3H, s, CH_3); 1.36 (3H, s, CH_3); 1.30 (3H, s, CH_3); 1.15 (3H, s, CH_3); 1.08 (3H, s, CH_3); 1.8-0.95 (5H, m).

MS: 378 ($M^{\ddagger}$, EI, 17 ev). mp 78-80°.

Analysis: Calculated for $C_{21}H_{30}O_6$: 66.64%C, 7.99%H;

Found: 66.38%C, 8.31%H.

(6): IR ($CHCl_3$): γ1800 (s). NMR ($CDCl_3$): δ5.8 (1H, dd, J = 10 and 18 Hz, 14-H); 5.08 (3H, m, 15-H's and 6-H); 4.72 (1H, d, J = 8 Hz, 7-H); 4.38 (1H, m, 1-H); 3.60 (3H, s, CH_3O); 2.96 (1H, d, J=4 Hz, 5-H); 2.42 (2H, AB, J = 16 and 28 Hz, 12-H's); 1.52 (3H, s, CH_3); 1.39 (3H, s, CH_3); 1.30 (3H, s, CH_3); 1.16 (3H, s, CH_3); 1.07 (3H, s, CH_3); 2.15-1.0 (5H, m). MS: 392 ($M^{\ddagger}$, EI, 17 ev). mp 123-125°.

Analysis: Calcualted for $C_{22}H_{32}O_6$: 67.32%C, 8.22%H;

Found: 66.92%C, 8.44%H,

(8): IR ($CHCl_3$): γ1800 (s). NMR ($CDCl_3$): δ6.0 (1H, dd, J = 12 and 18 Hz, 14-H); 5.2 (3H, m), 4.7 (3H, m) 3.62 (3H, s, CH_3O); 2.55 (1H, d, J = 6 Hz); 2.0 (2H, m); 1.60 (3H, s; CH_3); 1.43 (3H, s, CH_3), 1.20 (6H, s, two CH_3's); 1.12 (3H, s, CH_3); 1.6-0.8 (5H, m). MS: 408 ($M^{\ddagger}$, EI, 17 ev). mp 242-244°.

Analysis: Calculated for $C_{22}H_{32}O_7 \cdot 0.5H_2O$: 63.29%C, 7.96%H;

Found: 63.14%C, 8.41%H

Acknowledgements:

We would like to thank Mr. Marc N. Agnew and Ms. Anastasia Rizwaniuk of the Physical Methods Group, H-RPI, for spectral data, and Drs. R. Kosley, G. Shutske and Mr. R. Cherill for helpful discussions.

(Received in USA 4 September 1986)