Tetrahedron Letters,Vol.28,No.21,pp 2339-2342,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

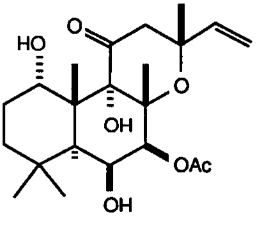
RECONSTITUTION OF FORSKOLIN FROM A RING C DIHYDROPYRAN-4-ONE DEGRADATION PRODUCT THEREOF

Frederick E. Ziegler* and Burton H. Jaynes

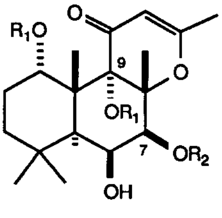
Sterling Chemistry Laboratory
Yale University
New Haven, Connecticut 06511 USA

Abstract: Dihydropyran-4-one **2b**, derived from the known degradation product **2a** of forskolin **1**, has been successfully converted into forskolin by a photochemical route.

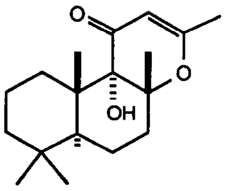
Forskolin (1)[1] has been the subject of intense interest among synthetic organic chemists[2] owing to its significant physiological activity.[3] Our synthetic efforts in this area have been directed toward a ring C dihydropyran-4-one of generic structure **2**, which was anticipated to undergo conjugate addition of a vinyl anion equivalent. Thus, we were disheartened when a report from the Schering Laboratories appeared noting that dihydropyran-4-one **2a**, prepared by degradation of forskolin, failed to react with $(CH_2{=}CH)_2Cu(CN)Li_2$.[4] Cuprates have been added successfully in a conjugate fashion to monocyclic dihydropyran-4-ones,[5] and recently Ikegami has succeeded in adding $(CH_2{=}CH)_2Cu(CN)Li_2$ to the model system **3** with α-face attack.[2f] In the interim, we have developed a photochemical route to forskolin from dihydropyran-4-one **2b**.[6]



1



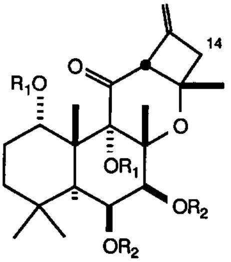
2a, R_1 = CO, R_2 = Ac
b, R_1 = CO, R_2 = H



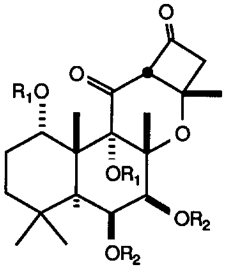
3

Irradiation of dihydropyran-4-one **2b** in the presence of allene[7] (450W-Hanovia lamp, Pyrex filter, 1:1 Et_2O/THF, N_2, -55°C, 3.5 h) provided a single photoadduct **4a** (96% yield; NMR (250 MHz, $CDCl_3$, partial) δ 5.05 (m, 2H, vinyl H), 1.57, 1.52, 1.51, 1.28, 1.06 (s, 5 x 3H); IR ($CHCl_3$) 3587, 1746, 1719 cm^{-1}; HRMS (EI) m/z 406.1989 (calcd, 406.1992)). While neither the regiochemistry nor the stereochemistry could be assessed at this juncture,[8] the former was established by chemical transformation. The vicinal diol **4a** was protected as its cyclic carbonate ($COCl_2$, CH_2Cl_2, pyridine, cat. DMAP;

0°C, then 25°C for 14 h) affording bis-carbonate **4b** (IR ($CHCl_3$) 1811, 1758, 1719 cm^{-1}) in 97% yield. Ozonolysis of **4b** (O_3, CH_2Cl_2, $PhCH_2OH$, -78°C; DMS) gave rise to a mixture (~10:1) of cyclobutanone **5** (NMR (250 MHz, $CDCl_3$, partial) δ 3.88 (dd, 1H, $J_{AB,AX}$=18.9, 2.0 Hz, C_{14}-H), 3.31 (dd, 1H, $J_{AB,BX}$=18.9, 3.9 Hz, C_{14}-H)) and benzyl ester **6a**.[9] Haller-Bauer cleavage[10] of diketone **5** (CH_2Cl_2, pyridine, DMAP, 25°C, 3.25 h) gave benzyl ester **6a** (NMR (250 MHz, $CDCl_3$, partial) δ 5.32 (d, 1H, J_{AB}=12.2 Hz, benzylic H), 5.12 (d, 1H, J_{AB}=12.2 Hz, benzylic H), 3.55 (d, 1H, J=16.1 Hz, C_{12}-H), 2.91 ((d, 1H, J=14.2 Hz, C_{14}-H), 2.69 (d, 1H, J=14.2 Hz, C_{14}-H), 2.61 (d 1H, J=16.1 Hz, C_{12}-H); IR(CCl_4) 1815, 1771, 1729 cm^{-1})) in 60% yield. The choice of a benzyl group in ester **6a** was dictated by a need to have functionality at C_{15} that could be reduced to a primary alcohol in the presence of the C_{11} carbonyl group. Attempts to hydrolyze selectively methyl ester **6b** were accompanied by removal of the carbonate protecting groups, while thiolester **6c** underwent preferential reduction of the C_{11} carbonyl group with $LiAl($*tert*-$BuO)_3H$.



4

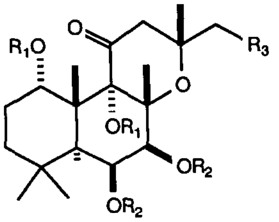


5

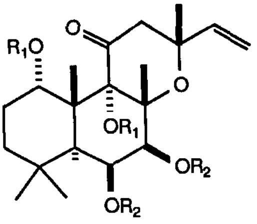
a, R_1 = CO, R_2 = H
b, R_1 = R_2 = CO

The cleavage reaction established the regiochemistry of the photoaddition, but the issue of stereochemistry required transformation to forskolin for confirmation. Accordingly, benzyl ester **6a** was hydrogenolyzed (Pd/C, EtOAc, 25°C, atm. pressure) to afford crude carboxylic acid **6d** (IR ($CHCl_3$) 1810, 1751, 1729 cm^{-1}) which was selectively reduced (BH_3·THF, 25°C, 11.5 h) to alcohol **6e** (IR ($CHCl_3$) 3563 (br.) 1811, 1748 cm^{-1}; HRMS (EI) m/z 438.1901 (calcd, 438.1890)) in 41% yield for the two steps. Elimination of the elements of water from the β-hydroxyethyl side chain of alcohol **6e** was accomplished by the Grieco protocol using o-$NO_2PhSeCN$/n-Bu_3P (19 h, 25°C; 30% H_2O_2, THF, 9.5 h, 25°C) with the proviso that pyridine, and not THF,[11] be used in the derivatization reaction. The resultant bis-carbonate **7a**[1b] (NMR (250 MHz, $CDCl_3$, partial) δ 6.07 (dd, J=17.2, 10.7 Hz, vinyl H), 5.28 (d, J=17.2 Hz, vinyl H), 5.11 (m, 2H, C_6-H, vinyl H); IR ($CHCl_3$) 1810, 1757, 1730 cm-1) served as an initial point of comparison with forskolin. A sample of forskolin (containing 25% of 9-deoxyforskolin) was deacetylated (K_2CO_3/MeOH, 0.75 h, 25°C) affording 7-deacetyl forskolin **7b**, which was readily separated on silica gel from 7-deacetyl-9-deoxyforskolin. Treatment of 7-

deacetyl forskolin with phosgene/pyridine[1b] provided bis-carbonate 7a that was identical (tlc, 250 MHz NMR) with the material from the photochemical route. Moreover, the sample of the bis-carbonate from the photochemical route gave upon hydrolysis (NaOH, MeOH, 25°C, 12 h) 7-deacetyl forskolin which was converted into forskolin by selective acetylation[1a] (Ac_2O, pyridine, 25°C, 15 h, 88%).



6a, $R_1 = R_2 = CO$, $R_3 = CO_2CH_2Ph$
b, $R_1 = R_2 = CO$, $R_3 = CO_2Me$
c, $R_1 = CO$, $R_2 = H$, $R_3 = COSPh$
d, $R_1 = R_2 = CO$, $R_3 = CO_2H$
e, $R_1 = R_2 = CO$, $R_3 = CH_2OH$



7a, $R_1 = R_2 = CO$
b, $R_1 = R_2 = H$

Acknowledgments:

This work was supported by grant CA-39976 from the National Cancer Institute. BHJ expresses his gratitude for the receipt of a Dox Fellowship (1986). We thank Mr. Dan Pentek, Yale University Chemical Instrumentation Center, for recording the high resolution mass spectra. We are most grateful to Dr. Michael Green, Schering (Bloomfield), for a generous gift of forskolin and for many valuable discussions.

References and Notes:

1. a) Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; deSouza, N. J.; Fehlhaber, H.-W. *Tetrahedron Lett.* **1977**, 1669; b) Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; deSouza, N. J. *J. Chem. Soc., Perkin Trans. I*, **1982**, 767.

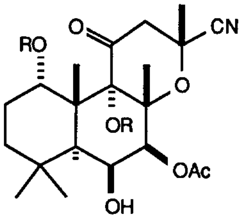
2. a) Jenkins, P. R.; Menear, K. A.; Barraclough, P.; Nobbs, M. S. *J. Chem. Soc., Chem. Commun.*, **1984**, 1423; b) Nicolaou, K. C.; Li, W. S. *ibid.*, **1985**, 421; c) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *Tetrahedron Lett.* **1985**, 26, 3307; d) Kulkarni, Y. S.; Snider, B. B. *Org. Prep. and Proced. Int.*, **1986**, 18, 7; e) Baraldi, P. G.; Barco, A. ; Benetti, S.; Pollini, G. P.; Polo, E.; Simoni, D. *J. Chem. Soc., Chem. Commun.*, **1986**, 757; f) Hashimoto, S.; Sonegawa, M.; Sakata, S.; Ikegami, S. *ibid.*, **1987**, 24; g) Hrib, N. J. *Tetrahedron Lett.*, **1987**, 28, 19.

3. a) Seamon, K. B.; Padgett, W.; Daly, J. W. *Proc. Natl. Acad. Sci.*, **1981**, 78, 3363; b) Bhat, S. V.; Dohadwalla, A. N.; Bajwa, B. S.; Dadkar, N. K.; Dornauer, H.; deSouza, N. J. *J. Med. Chem.*, **1983**, 26, 486. c) Caprioli, J.; Sears, M. *Lancet*, **1983**, 1, 958.

4. Saksena, A. K.; Green, M. J.; Shue, H.-J.; Wong, J. K. *J. Chem. Soc., Chem. Commun.*, **1985**, 1748.

5. Wratten, S. J.; Meinwald, J. *Tetrahedron Lett.*, **1980**, 21, 3163; Wallace, T. W. *ibid.*, **1984**, 25, 4299; Kubo, I.; Matsumoto, T.; Wagner, D. L.; Shoolery, J. N. *Tetrahedron Lett.*, **1985**, 26, 563.

6. Dihydropyran-4-one **2a** was prepared as described in ref. 4 and U. S. Patent 4,517,200 (Schering). Under seemingly identical conditions, both dihydropyran-4-one **2a** and nitrile **i** (NMR (250 MHz, $CDCl_3$) δ 5.28 (d, 1H, J=3.9 Hz, C_7-H), 5.19 (t, J=2.6 Hz, C_1-H), 4.55 (m, 1H, C_6-H), 3.35 (d, 1H, J=19.4 Hz, C_{12}-H), 2.92 (d, 1H, J=19.4 Hz, C_{12}-H), 2.21 (s, 3H, OAc), 1.1-2.2 (m, 5H), 1.74, 1.71, 1.57, 1.27, 1.06 (s, 5 x 3H); IR($CHCl_3$) 2958 (br.) 1760, 1737 cm^{-1} (CN not visible); Anal. $C_{22}H_{29}O_8N$) were formed in a 2:3 ratio. Both compounds were converted to dihydropyran-4-one **2b** upon exposure to K_2CO_3/MeOH (25°C, 30 min.).



i, R = CO

7. For a recent report of a photoaddition of acetylene to a dihydropyran-4-one see, Fetizon, M.; Khac, D. D.; Tho, N. D. *Tetrahedron Lett.*, **1986**, 26, 1777.

8. Allene photoadditions to α,β-unsaturated enones prefer head-to-head, syn stereochemistry, Eaton, P. *Tetrahedron Lett.*, **1964**, 3695; b) Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.*, **1964**, 86, 5570. However, head-to-tail products can be appreciable, c) Crabbe, P.; Garcia, G. A.; Rius, C. *Tetrahedron Lett.*, **1972**, 2951.

9. Ozonolysis in methanol gave a preponderance of cyclobutanone **5** over methyl ester **6b**.

10. See ref. 8a and Ziegler, F. E.; Reid, G. R.; Studt, W. L.; Wender, P. A. *J. Org. Chem.*, **1977**, 42, 1991.

11. Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.*, **1976**, 41, 1485.

(Received in USA 18 February 1987)