## SYNTHESIS OF THE FORSKOLIN SKELETON VIA ANIONIC OXY-COPE REARRANCEMENT

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Summary: The forskolin prototype 14 has been elaborated in 9 steps from 2,4,4-trimethylcyclohexenone (5), the entire ring system materializing during oxyanionic Cope rearrangement of alcohol 10.

The intense scrutiny presently being accorded forskolin (1),<sup>1</sup> a highly oxygenated labdane diterpene isolated from the roots of *Coleus forskolii*,<sup>2</sup> stems in large part from its broncho-spasmolytic, antihypertensive, and inotropic activity,<sup>3</sup> as well as its demonstrated ability to activate adenylate cyclase<sup>4</sup> and reduce intraocular pressure in man.<sup>5</sup> The unique structure of 1 and its fascinating pharmacological properties have elicited the attention of synthetic chemists worldwide. Preliminary approaches have appeared having as their basis intramolecular Diels-Alder<sup>6</sup> and nitrile oxide cycloadditions.<sup>7</sup> Strategies involving radical cyclization,<sup>8</sup> a tandem Michael-aldol sequence,<sup>9</sup> and ring C annulation<sup>10</sup> have also shown promise.

We became interested in 1 in the context of a program designed to expand the synthetic utility of oxyanionic [3,3] sigmatropy.<sup>11</sup> As part of the relevant retrosynthetic analysis (eq 1), the need arose to develop a route to ketone 3, to explore the feasibility of conjoining a 2-lithiodihydropyran (or equivalent) to this substrate, and to elucidate the proclivity of the potassium alkoxide of 2 for Cope rearrangement. Furthermore, the use of optically pure 4 should allow for kinetic resolution<sup>11</sup>g and arrival at natural forskolin. The prototype experiments reported herein provide a successful test of the overall process.



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Scheme I shows the synthetic route to 3. Thus, application of the Sakurai reaction<sup>12</sup> to 5 led smoothly (89%) to 6, whose double bond could be oxidatively cleaved without need for carbonyl protection when treated with RuCl<sub>3</sub> in the presence of NaIO<sub>4</sub> (92%).<sup>13</sup> The fact that 7 was a mixture of diastereomers proved inconsequential since subsequent cyclization by means of hot PPA in acetic acid furnished only 8 (91%). The steric driving force underlying exo orientation of the secondary methyl group in 8 is obvious. Conversion of 8 to the desired enol ether 3 mandates selective enolization to give the thermodynamically more stable enolate followed by 0-methylation. While the latter step proved easy to accomplish, considerable experimentation was required to achieve regioselective deprotonation perhaps due to the highly hindered environment about this proton. The actual course of events is intimately linked to the nature of the base and the solvent. The best conditions involved use of potassium hexamethyldisilazide in 1,2-dimethoxyethane containing HMPA at -20°C. Subsequent addition of methyl triflate afforded in 62% yield a 7:1 mixture of 3 and 9. These isomers are readily separable chromatographically.

Scheme I



Exposure of 3 to 2-lithiodihydropyran<sup>14</sup> resulted in the formation of 10 and its epimer in a ratio of 1.5:1 (90%). Although this product distribution is lower than desired, a more

bulky nucleophile such as 4 is expected to foster greater levels of 1,2-addition from the less sterically encumbered direction. $^{15}$ 

Oxy-Cope rearrangement of the potassium salt of 10 required heating to  $70^{\circ}$ C in THF solution containing 18-crown-6 for 20 min. During this time, the initially formed enolate equilibrated completely<sup>16</sup> as reflected, for example, in the isolation of 11 (79%) following addition of phenylselenenyl chloride. This finding proved to be highly suited to our objectives, since elimination to give 12 provided a substrate capable only of unidirectional enolization. In actuality, the deprotonation-methylation of 12 furnished 13 (39%) and 14 (52%). The co-formation of 13, a compound easily converted back to 12 with 10% hydrochloric acid in THF at 25°C (100%), is presumed to reflect the fact that the new angular methyl group in 14 must necessarily be subject to serious 1,3-diaxial Me-Me interaction as it is being formed. That methyl capture had indeed occurred on the convex face as desired was convincingly established by difference NOE studies at 300 MHz.

Selective reduction of the conjugated double bond in 14 cannot be accomplished by dissolving metal reduction. The cis nature of the B/C ring fusion causes its  $C_8$ -O bond to be axially disposed and subject to more rapid cleavage under these conditions. In contrast, high chemoselectivity can be achieved by catalytic hydrogenation over 10% Pd-C in 0.1 N

Scheme II



ethanolic KOH solution.<sup>17</sup> The exclusive product was shown to be 15 (84%) by COSY and NOE analyses at 500 MHz.<sup>18</sup> Dreiding molecular models reveal that prior establishment of a trans relationship between the substituents at C-8 and C-9 (see 14) as demanded by forskolin imparts considerable conformational rigidity and predisposes to Cg-0 bond equatorially. Epimerization at C-9 is, of course, critically dependent on the presence of an OR substituent in 2 and the compounds derived therefrom. The likelihood that this structural modification will permit appropriate control of stereochemistry is currently being assessed.

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## References and Notes

(1) de Souza, N. J.; Dohadwalla, A. N.; Reden, J. Medicin. Res. Revs. 1983, 3, 201.
(b) Seamon, K. B. Ann. Rep. Medicin. Chem. 1984, 19, 293.

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

(3) (a) Lichey, A.; Friedrich, T.; Priesnitz, M.; Biamino, G.; Usinger, P.; Huckauf,
H. The Lancet 1984, 2, 167. (b) Bhat, S. V.; Dohadwalla, A. N.; Bajwa, B. S.; Dadkar, N.
K.; Dornauer, H.; de Souza, N. J. J.Med. Chem. 1983, 26, 486.

(4) Seamon, K. B.; Padgett, W.; Daly, J. W. Proc. Natl. Acad. Sci. 1981, 78, 3363.

(5) Caprioli, J.; Sears, M. The Lancet 1983, 1, 958.

(6) (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, 3307.
(d) Bold, G.; Chao, S.; Bhide, R.; Wu, S.-H.; Patel, D. V.; Shih, C. J. Ibid. 1987, 1973.

(7) Baraldi, P. G.; Barco, A., Benetti, S.; Pollini, G. P.; Polo, E.; Simoni, D. J. Chem. Soc., Chem. Commun. 1986, 757.

(8) Hutchinson, J. H.; Pattenden, G.; Myers, P. L. Tetrahedron Lett. 1987, 1313.

(9) Koft, E. R.; Kotnis, A. S.; Broadbent, T. A. Tetrahedron Lett. 1987, 2799.

(10) Hashimoto, S.; Sonegawa, M.; Sakata, S.; Ikegami, S. J. Chem. Soc., Chem. Commun. 1987, 24.

(11) (a) Paquette, L. A.; Andrews, D. R.; Springer, J. P. J. Org. Chem. 1983, 48, 1147.
(b) Paquette, L. A.; Colapret, J. A.; Andrews, D. R. Ibid. 1985, 50, 201. (c) Paquette, L. A.; Learn, K. S. J. Am. Chem. Soc. 1986, 108, 7873. (d) Paquette, L. A.; Romine, J. L.; Lin, H.-S. Tetrahedron Lett. 1987, 31. (e) Paquette, L. A.; Learn, K. S.; Romine, J. L. Synth. Commun. 1987, 17, 369. (f) Paquette, L. A.; Pierre, F.; Cottrell, C. E. J. Am. Chem. Soc. 1987, 109, in press. (g) Paquette, L. A.; DeRussy, D. T.; Cottrell, C. E. submitted for publication.

(12) Hosomi, A.; Sakurai, H. J. Am. Chem. Soc. 1977, 99, 1673.

(13) Carlsen, P. H. J.; Sharpless, K. B. J. Org. Chem. 1981, 46, 3936.

(14) Boeckman, R. K., Jr., Bruza, K. J. Tetrahedron Lett. 1977, 4187.

(15) The smaller vinylmagnesium bromide adds to 3 predominantly (2:1) from the direction syn to the gem-dimethyl group.

(16) This phenomenon has been observed previously under less forcing conditions, although not with such striking exclusivety.<sup>11g</sup>

(17) McQuillin, F. J.; Ord, W. O. J. Chem. Soc. 1959, 2902.

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