A Stereocontrolled Synthesis of (±)-1,6,7-Trideoxyforskolin

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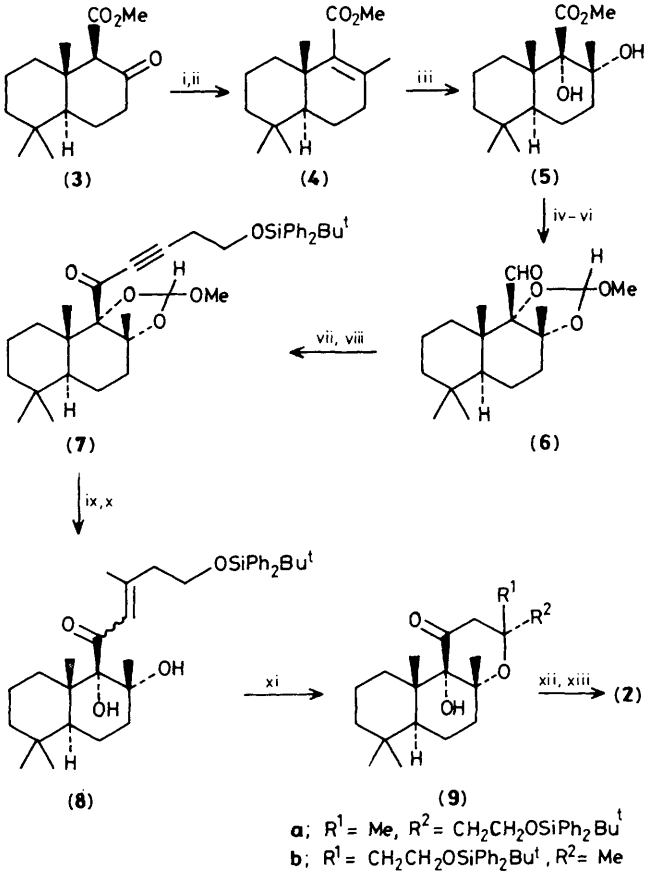
An efficient entry to c-ring annulation and subsequent elaboration in the synthesis of forskolin is described.

Forskolin (**1**),[1] a labdane diterpene isolated from the roots of the Indian herb *Coleus forskohlii* has been shown to exhibit strongly inotropic, antihypertensive, and bronchospasmolytic activity, and to activate adenylate cyclase by a direct stimulation of the catalytic component.[2] These interesting pharmacological properties coupled with the unique structure characterized by the presence of a tetrahydropyran-4-one moiety fused to a highly oxygenated *trans*-fused decalin system prompted us to embark upon an investigation directed towards the total synthesis of (**1**) and its analogues.

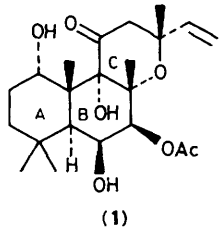
While several groups have reported synthetic approaches to the construction of the AB-ring system,[3] C-ring annulation and subsequent elaboration have not so far been reported. We report herein a stereocontrolled synthesis of (±)-1,6,7-trideoxyforskolin (**2**), wherein the regio- and stereo-selective construction of the C-ring has been established by two alternative approaches *via* (a) oxymercuration of the enone (**8**) by attack of the C-8 hydroxy group, or (b) oxymercuration of the ynone (**10**) followed by conjugate addition of a vinyl cuprate reagent.

The synthetic sequence based on the first approach is detailed in Scheme 1. Conversion of the *trans*-fused β-keto-ester (**3**), readily obtainable from β-ionone by a modification of the reported procedure,[4] into the enol phosphate followed by treatment with Me_2CuLi provided the α,β-unsaturated ester† (**4**) in 73% yield, which was oxidized with osmium tetroxide to afford the 8α,9α-diol (**5**) as the sole product in 78% yield. Orthoester formation followed by lithium aluminium hydride reduction and Collins oxidation furnished the aldehyde (**6**) in 73% overall yield from (**5**). An initial attempt at the elongation of the requisite carbon chain *via* addition of alkenyl-lithium reagents to (**6**) failed owing to considerable difficulties in the subsequent oxidation stage, whereas addition of 4-(t-butyldiphenylsiloxy)butynyl-lithium to (**6**) and subsequent oxidation with MnO_2 proceeded smoothly to give the ynone (**7**) in 62% yield. Conjugate addition of Me_2CuLi to (**7**) followed by hydrolysis afforded the enone (**8**) as an easily separable 1:1 mixture of (*E*)- and (*Z*)-isomers in 82% yield.

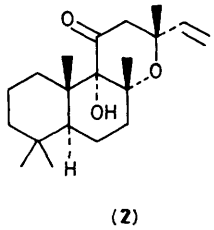
The crucial ring closure of (*E*)-(**8**) and (*Z*)-(**8**) with PhSeCl or $Hg(OCOCF_3)_2$ was found to proceed smoothly to give, after reductive work-up, the tetrahydropyran-4-one (**9**), with no trace of other cyclization products. The stereochemistry at the C-13 position in the oxyselenation was highly dependent on the geometry of the double bond [(**9a**):(**9b**) 82:12 from (*E*)-(**8**); 27:73 from (*Z*)-(**8**)]. In marked contrast, the oxymercuration resulted in the predominant formation of the desired (**9a**) as a kinetically controlled product, regardless of the starting alkene geometry [(**9a**):(**9b**) 80:20 from (*E*)-(**8**); 88:12 from (*Z*)-(**8**)]. These results can be explained as follows; both cyclizations proceed through chair-preferred transition states, wherein the oxyselenation involves the attack of the C-8 hydroxy group on an episelenonium ion, while the oxymercuration proceeds probably *via* a mercury-assisted carbocation allowing rotation about the C-12–C-13 bond.[5] The transformation of a protected 2-hydroxyethyl group at the C-13 position of (**9a**) to a vinyl group by Grieco's method[6] completed the synthesis of (**2**). Proof of the



Scheme 1. *Reagents:* i, NaH, $ClP(O)(OEt)_2$, tetrahydrofuran (THF), 30 °C, 79%; ii, Me_2CuLi, Et_2O, −40 to 0 °C, 92%; iii, OsO_4, pyridine (Py), then H_2S, 78%; iv, $HC(OMe)_3$, TsOH (Ts = tosyl), 95%; v, $LiAlH_4$, Et_2O, 96%; vi, CrO_3–2Py, CH_2Cl_2, 80%; vii, $Bu^tPh_2SiOCH_2CH_2C{\equiv}CLi$, THF, −70 to 25 °C, 78%; viii, MnO_2, benzene, 78%; ix, Me_2CuLi, Et_2O, −78 °C, 88%; x, THF–10% aq. HCl (50:1), then K_2CO_3, MeOH, 93%; xi, PhSeCl (2 equiv.), CH_2Cl_2, −78 to −40 °C, 3 h; Raney-Ni (W-2), MeOH, 77% or $Hg(OCOCF_3)_2$ (2 equiv.), CH_2Cl_2, −78 to −50 °C, 5 h, then LiI, Et_2O, Et_3N, 75%; xii, 10% aq. HCl–THF (1:2), 94%; xiii, o-$O_2NC_6H_4SeCN$, Bu^n_3P, THF; 0.1 M H_2O_2, CH_2Cl_2, 74%.

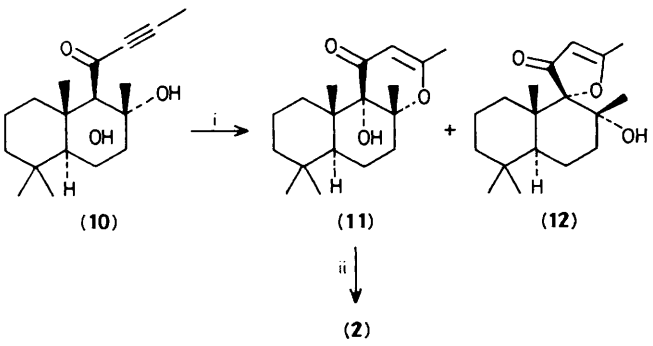


(**1**)



(**2**)

† All new compounds exhibited satisfactory spectroscopic and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.



Scheme 2. *Reagents:* i, $Hg(OCOCF_3)_2$, Et_3N, CH_2Cl_2, −78 °C, then LiI, Et_2O, Et_3N, 71% of (**11**) and 7% of (**12**); ii, $(CH_2{=}CH)_2Cu(CN)Li_2$ (3.5 equiv.), ether, 0 °C, 10 min, 80%.

stereochemistry at the C-13 position in (**2**) was established by comparison of its nuclear Overhauser effect between the C-8 and C-13 methyl groups with that of its C-13 epimer derived from (**9b**), which also substantiated the correctness of the stereochemical assignment for (**9a**) and (**9b**).

With the synthesis of (**2**) and its C-13 epimer realized, we then turned our attention to more effective construction of the c-ring, as outlined in Scheme 2. Treatment of the ynone (**10**) obtained from (**6**) by the foregoing procedure with $Hg(OCOCF_3)_2$ under Schwartz's condition[7] afforded in a regioselective manner the desired dihydropyran-4-one (**11**) in 71% yield along with 7% of the dihydrofuran-3-one (**12**). The key introduction of a vinyl group to (**11**) using the cuprate[8] $(CH_2{=}CH)_2Cu(CN)Li_2$ was found to occur exclusively from the less hindered α-face, so that the desired (**2**) could be obtained as a single isomer. This successful direct introduction of a vinyl group is of significance.[9]

Thus, a highly regio- and stereo-controlled synthesis of (±)-1,6,7-trideoxyforskolin (**2**) has been developed. The synthetic methodology can be applied to a total synthesis of forskolin (**1**) and its analogues.

We are grateful to Miss K. Sayama for her technical assistance. Partial financial support from the Japan Research Foundation for Optically Active Compounds and by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture is gratefully acknowledged.

Received, 12th August 1986; Com. 1159

References

1 S. V. Bhat, B. S. Bajwa, H. Dornauer, N. J. de Souza, and H.-W. Fehlhaber, *Tetrahedron Lett.*, 1977, 1669.
2 K. B. Seamon, W. Padgett, and J. W. Daly, *Proc. Natl. Acad. Sci. USA*, 1981, **78**, 3363; N. J. de Souza, A. N. Dohadwalla, and J. Reden, *Med. Res. Rev.*, 1983, **3**, 201; K. B. Seamon, *Annu. Rep. Med. Chem.*, 1984, **19**, 293; J. Lichey, T. Friedrich, M. Priesnitz, G. Biamino, P. Usinger, and H. Huckauf, *The Lancet*, 1984, **2**, 167.
3 P. R. Jenkins, K. A. Menear, P. Barraclough, and M. S. Nobbs, *J. Chem. Soc., Chem. Commun.*, 1984, 1423: K. C. Nicolaou and W. S. Li, *ibid.*, 1985, 421; F. E. Ziegler, B. H. Jaynes, and M. T. Saindane, *Tetrahedron Lett.*, 1985, **26**, 3307; P. G. Baraldi, A. Barco, S. Benetti, G. P. Pollini, E. Polo, and D. Simoni, *J. Chem. Soc., Chem. Commun.*, 1986, 757.
4 J. D. White, R. W. Skeean, and G. L. Trammell, *J. Org. Chem.*, 1985, **50**, 1939.
5 G. H. Schmid and D. G. Garratt, in 'The Chemistry of Double-Bonded Functional Groups,' ed. S. Patai, Wiley, London, 1977, Part 2, ch. 9.
6 P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, 1976, **41**, 1485.
7 M. Riediker and J. Schwartz, *J. Am. Chem. Soc.*, 1982, **104**, 5842.
8 B. H. Lipshutz, R. S. Wilhelm, and J. A. Kozlowski, *Tetrahedron*, 1984, **40**, 5005.
9 A. K. Saksena, M. J. Green, H.-J. Shue, and J. K. Wong, *J. Chem. Soc., Chem. Commun.*, 1985, 1748.