Synthesis of 12-Bromo-, 12-Chloro- and 12-Fluoro-forskolin

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The synthesis of 12-bromo- and 12-chloro-forskolin was accomplished by TBAF promoted halogenation of suitably protected silyl enol ethers, while reaction of a lithium enolate with acetyl hypofluorite gave 12-fluoroforskolin.

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]

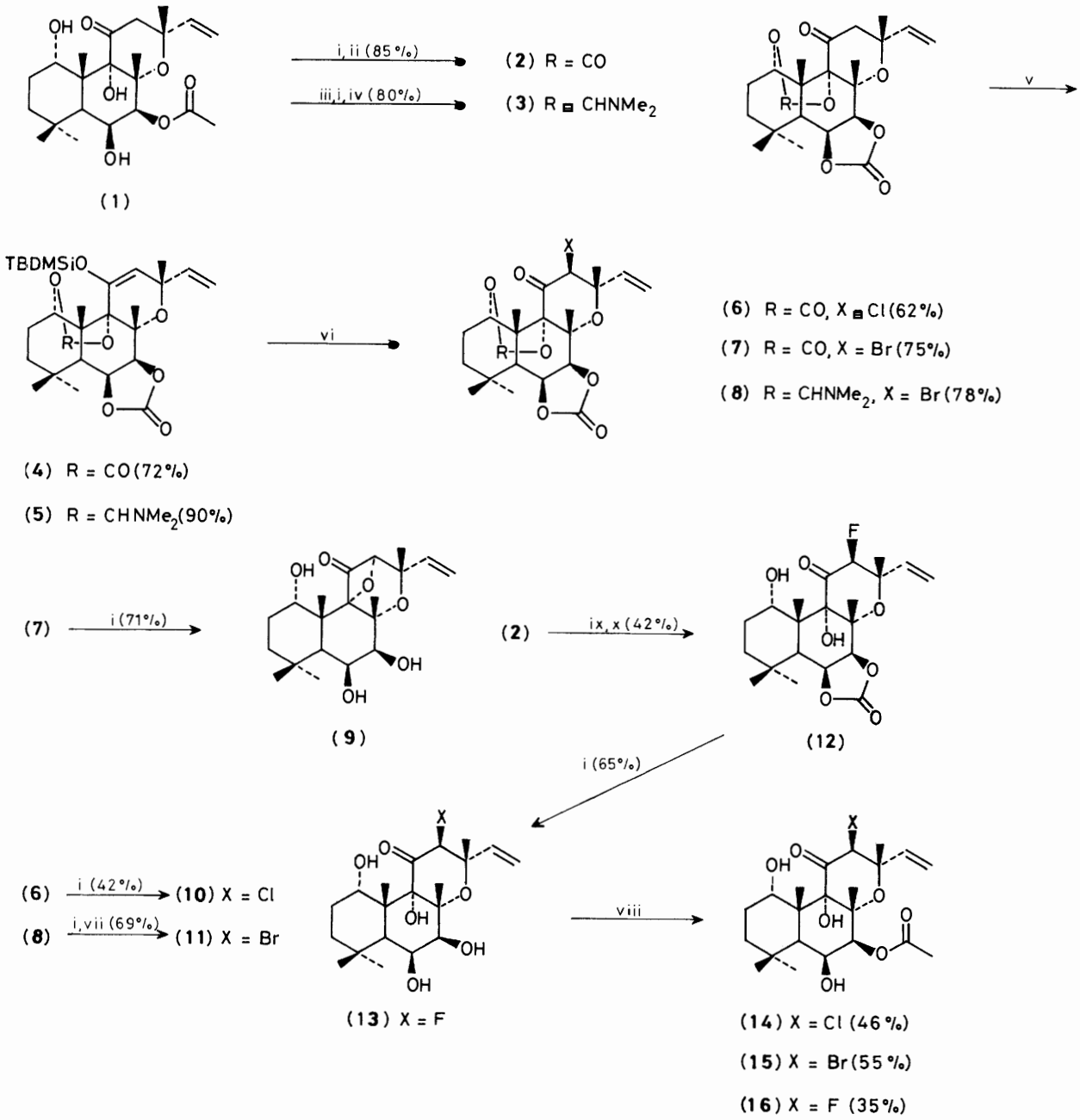
Halogenations α to carbonyl groups are well known and can, in certain cases, impart desirable biological properties to molecules. In particular, fluorinations α to an existing carbonyl group have been shown to improve the biological activity of steroids[3] and of prostaglandins.[4] For this reason it was decided to examine the synthesis of some 12-halogenated forskolins.

It was expected that competition from halogenation of the double bond would be a problem, and initial attempts (pyridinium bromide perbromide, HOAc; NBS,† H_2SO_4, Bu^{t}OH with a protected enol acetate) showed that such was indeed the case. However, enol ethers, such as those recently reported for 9-deoxyforskolin,[5] proved to be viable intermediates for the synthesis of 12-halogenated forskolins. We report here the details of this work.

Mild basic hydrolysis of (**1**) (see Scheme) gave a tetraol (desacetylforskolin), which was protected as the dicarbonate, (**2**).[6] Reaction of (**2**) with LiN(TMS)$_2$† in THF † in the presence of TBDMS † chloride gave the stable crystalline silyl enol ether, (**4**).‡ While treatment of (**4**) with NCS † in CH_2Cl_2 slowly gave

† THF = tetrahydrofuran, TMS = trimethylsilyl, TBDMS = t-butyldimethylsilyl, TBAF = tetrabutylammonium fluoride, NCS = *N*-chlorosuccinimide, NBS = *N*-bromosuccinimide, DMF = dimethylformamide.

‡ Selected spectral data: (**4**) m.p. 175—177 °C; $\nu_{max.}$ 1 810 and 1 750 cm^{-1}; (Varian XL-200, $CDCl_3$) 0.27 (s, 6 H, Me_2Si), 0.95 (s, 9 H, Me_3CSi), 1.12, 1.22 (s, 3 H, CH_3), 1.41 (s, 6 H, 2 × Me), 1.62 (s, 3 H, Me), 1.2—1.7 (m, 2 H, 3-H), 1.79 (d, 1 H, *J* 2 Hz, 5-H), 1.8—2.2 (m, 2 H, 2-H), 4.82 (d, 1 H, *J* 4 Hz, 7-H), 4.91 (s, 1 H, 12-H), 5.08 (d, 1 H, *J* 11 Hz, 15-H), 5.08 (m, 1 H, 6-H), 5.17 (dd, 1 H, *J* 1, 18 Hz, 15′-H), 5.48 (m, 1 H, 1-H), and 6.02 (dd, 1 H, *J* 11, 18 Hz, 14-H); (**7**) m.p. 218 °C (decomp.); $\nu_{max.}$ 1 815 and 1 770, 1 750sh cm^{-1}; δ 1.12, 1.24, 1.54, 1.57, 1.60 (s, 3 H, CH_3), 1.3-1.7 (m, 2 H, 3-H), 1.79 (d, 1 H, *J* 2 Hz, 5-H), 1.8—2.0 (m, 1 H, 2β-H), 2.0—2.3 (m, 1 H, 2α-H), 4.80 (m, 1 H, 1-H), 5.01 (d, 1 H, *J* 4 Hz, 7-H), 5.10 (m, 1 H, 6-H), 5.26 (d, 1 H, *J* 11 Hz, 15-H), 5.28 (s, 1 H, 12-H), 5.50 (dd, 1 H, *J* 1, 18 Hz, 15′-H), and 6.07 (dd, 1 H, *J* 11, 18 Hz, 14-H); (**9**) m.p. 148—150 °C; $\nu_{max.}$ 1 810 cm^{-1}; δ 1.04, 1.23, 1.31, 1.50, 1.57 (s, 3 H, Me), 1.2—1.7 (m, 2 H, 3-H), 1.80 (d, 1 H, *J* 2 Hz, 5-H), 1.8—2.1



Scheme. *Reagents and conditions.* i, K_2CO_3, MeOH, H_2O; ii, Im_2CO (2 equiv), Et_3N, toluene reflux; iii, MeO_2CHNMe_2, 55 °C; iv, Im_2CO (1 equiv), Et_3N, toluene reflux; v, $LiN(TMS)_2$, TBDMSiCl, THF, 5 °C; vi, NXS, TBAF, THF, −65 °C; vii, HOAc, MeOH, H_2O; viii, Ac_2O, pyridine; ix, $LiN(TMS)_2$, THF, evaporate, then THF solution added to $MeCO_2F$, $CFCl_3$, HOAc, −65 °C; x, $NaHCO_3$, THF, H_2O.

the 12-chlorodicarbonate, (**6**), treatment with TBAF† in THF at −65 °C in the presence of NCS gave rapid conversion into (**6**), uncontaminated with products of double bond halogenation. Deprotection gave the 12-β-chlorotetraol, (**10**), which was converted into 12-β-chloroforskolin (**14**) by selective acetylation.[6]

(m, 2 H, 2-H), 2.24 (br s, 1 H, OH), 2.58 (br s, 1 H, OH), 3.90 (m, 1 H, 1-H), 4.16 (d, 1 H, *J* 4 Hz, 7-H), 4.44 (m, 1 H, 6-H), 4.98 (s, 1 H, 12-H), 5.21 (dd, 1 H, *J* 1, 11 Hz, 15-H), 5.35 (dd, 1 H, *J* 1, 18 Hz, 15′-H), 5.44 (br s, 1 H, OH), and 5.90 (dd, 1 H, *J* 11, 18 Hz, 14-H); (**11**) m.p. 133—135 °C; $\nu_{max.}$ 1 737 cm^{-1}; δ 1.09, 1.30, 1.55, 1.57, 1.64 (s, 3 H, Me), 1.1—1.18 (m, 3 H, 2β-H and 3-H), 2.18 (d, 1 H, *J* 2 Hz, 5-H), 2.2—2.4 (m, 1 H, 2α-H), 2.36 (br s, 3 H, 3 × OH), 4.34 (d, 1 H, *J* 4 Hz, 7-H), 4.42 (m, 1 H, 1-H), 4.52 (m, 1 H, 6-H), 5.18 (dd, 1 H, *J* 1, 11 Hz, 15-H), 5.46 (dd, 1 H, *J* 1, 19 Hz, 15′-H), 5.93 (s, 1 H, 12-H), 6.10 (dd, 1 H, *J* 11, 19 Hz, 14-H), and 7.05 (br s, 1 H, OH); (**15**) m.p. 203 °C (decomp.); $\nu_{max.}$ 1 740 cm^{-1}; δ 1.06, 1.28, 1.47, 1.58, 1.64 (s, 3 H, Me), 1.1—1.8 (m, 3 H, 2β-H and 3-H), 1.96 (br s, 1 H, OH), 2.12 (d, 1 H, *J* 2 Hz, 5-H), 2.2—2.4 (m, 2 H, 2α-H and OH), 2.20 (s, 3 H, COMe), 4.42 (m, 1 H, 1-H), 4.50 (m, 1 H, 6-H), 5.10 (dd, 1 H, *J* 1, 11 Hz, 15-H), 5.48 (dd, 1 H, *J* 1, 19 Hz, 15′-H), 5.75 (d, 1 H, *J* 4 Hz, 7-H), 5.93 (s, 1 H, 12-H), 6.06 (dd, *J* 11, 19 Hz, 14-H), and 7.00 (br s, 1 H, OH); (**16**) m.p. 263—265 °C; $\nu_{max.}$ 1 740 cm^{-1}; δ 1.05, 1.28 (s, 3 H, Me), 1.32 (d, 3 H, $J_{H,F}$ 6 Hz, Me), 1.60, 1.68 (s, 3 H, Me), 1.1—1.8 (m, 2 H, 3-H), 1.8—2.0 (m, 3 H, 2β-H and 2 × OH), 2.18 (s, 3 H, COMe), 2.2—2.4 (m, 1 H, 2α-H), 2.23 (d, 1 H, *J* 2 Hz, 5-H), 4.42 (m, 1 H, 1-H), 4.48 (m, 1 H, 6-H), 5.10 (dd, 1 H, *J* 1, 11 Hz, 15-H), 5.44 (dd, 1 H, *J* 1, 19 Hz, 15′-H), 5.69 (d, 1 H, *J* 4 Hz, 7-H), 5.84 (d, 1 H, $J_{H,F}$ 51 Hz, 12-H), 6.02 (dd, 1 H, *J* 11, 19 Hz, 14-H), and 6.80 (br s, 1 H, OH).

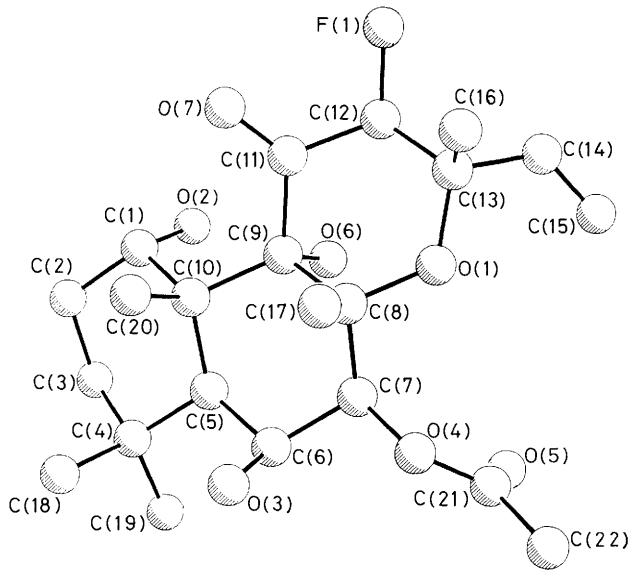


Figure. Computer drawn plot of the molecular structure of (**16**)

An analogous reaction with NBS gave the 12-bromodicarbonate, (**7**).* Attempted deprotection, however, gave the oxetanone, (**9**).*† It was reasoned that, in order to avoid the formation of (**9**), it would be necessary to avoid exposing the 9-hydroxy group to basic conditions in the presence of the labile bromine. Accordingly, desacetylforskolin was protected at the 1,9-positions as the acid labile DMF‡ acetal, (**3**), which underwent analogous transformations to the silyl enol ether (**5**) and 12-bromo derivative, (**8**). Sequential deprotection, first with base and then with acid gave the 12-β-bromotetraol, (**11**)‡ and 12-β-bromoforskolin, (**15**),* after selective acetylation as before.

To prepare 12-β-fluoroforskolin (**16**), (**2**) was treated with $LiN(TMS)_2$ at room temperature, after which the mixture was evaporated. The residue solid enolate was then redissolved in THF and added to a solution of acetyl hypofluorite in HOAc–$CFCl_3$ as described by Rozen and Brand.[8] Although the initially formed fluorodicarbonate proved difficult to separate from uncharged (**2**) by flash chromatography, selective hydrolysis with aqueous $NaHCO_3$ in THF gave the more easily purified monocarbonate, (**12**) [$\nu_{max.}(CHCl_3)$ 1 810 and 1 745 cm^{-1}], which was deprotected (**13**) and acetylated to give (**16**).*

An *X*-ray analysis of (**16**) established the β-orientation of the fluorine.§ A computer drawing, generated from the X-ray co-ordinates, is shown in the Figure.

The β-orientation of (**15**) was established by the ease with which the oxetanone (**9**) was formed.[7] ^1H N.m.r. evidence further established the β-configuration at the 12-position of (**14**), (**15**), and (**16**): in each case, the 12-α-proton displayed a large downfield shift,¶ due to the interaction with a 9-α-OH group.[9] Examination of models reveals that the steric demands of the 1,9-carbonate and the double bond may be sufficient to account for the observed selectivity for halogenation on the β-face of the molecules. The biological activity of these new compounds is currently under evaluation.

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* As footnote † on p. 1544.

† For the synthesis of some steroid oxetanones and a discussion of the stereochemistry of the precursor bromohydrins, see ref. 7.

‡ As footnote ‡ on p. 1544.

§ *Crystal data* for $C_{22}H_{33}FO_7$, F_c = 428.6, orthorhombic space group $P2_12_12_1$, a = 8.106(2), b = 9.267(2), c = 29.709(6) Å, V = 2 231.7(7) $Å^3$, Z = 4, d = 1.27 g/cm^3, R = 0.038 for 1 665 observed reflections having $3° < 2\Theta < 114°$ with Cu-K_α radiation, λ = 1.541 78 Å. Data were collected by an ω-scan technique on a Nicolate R3m diffractometer. The structure was solved by direct methods using SHELXTL software. Atomic co-ordinates, bond lengths and angles and thermal parameters are available on request from the Cambridge Crystallographic Data Centre. [See 'Instructions for Authors (1989)', *J. Chem. Soc., Perkin Trans. 1*, 1989, Issue 1.]

¶ Compared with the corresponding 4-β-halogenobicyclo[4.2.0]octan-3-ones, for example (ref. 10, $DCCl_3$, values in parentheses), these compounds exhibited a downfield shift >1 p.p.m.: (**14**) δ 5.72 (4.37); (**15**), δ 5.91 (4.45); (**16**), δ 5.84 (4.79).