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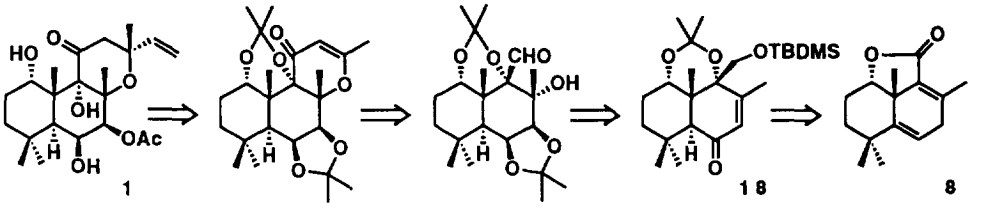
Total Synthesis of Forskolin - Part I

Bernard Delpech, Daniel Calvo+ and Robert Lett*

Unité Mixte CNRS - Roussel Uclaf
93235 Romainville (France)

Abstract : A new total synthesis of forskolin **1** has been achieved and this note describes the synthesis of the *trans* fused enone **18** as a key-intermediate. Key steps are: 1) the intramolecular Diels-Alder reaction of **7** to afford the tricyclic lactone **8** (48-56%); 2) a stereospecific and regiospecific one-pot conversion of $\mathbf{11_A}$ into **12** (94%) with $LiBH_4/BF_3$-THF at room temperature. The scheme allows a very early stereospecific introduction of the required 1α and 9α OH and their specific protection with respect to the end of forskolin synthesis.

Forskolin **1**, a labdane diterpene isolated from the roots of *Coleus forskohlii* [1], interacts specifically with the catalytic subunit of adenylate cyclase; it is therefore a unique tool for studying both the biochemistry and the regulation of adenylate cyclase, or the physiological functions of cAMP [2]. It has been shown to have a very promising biological and medicinal potential, mainly in the cardiovascular area, for its positive inotropic action and blood pressure lowering properties [3]. Hence a considerable interest has been raised in its total synthesis [4-6], synthetic approaches and chemical modifications [7]. We now report the completion of a new total synthesis of forskolin, according to the following retrosynthetic scheme [8].



1 **18** **8**

The key-intermediate enone **18** was prepared according to Scheme I and its further elaboration into forskolin **1** is described in the accompanying note [9]. Several points are worth some comments:

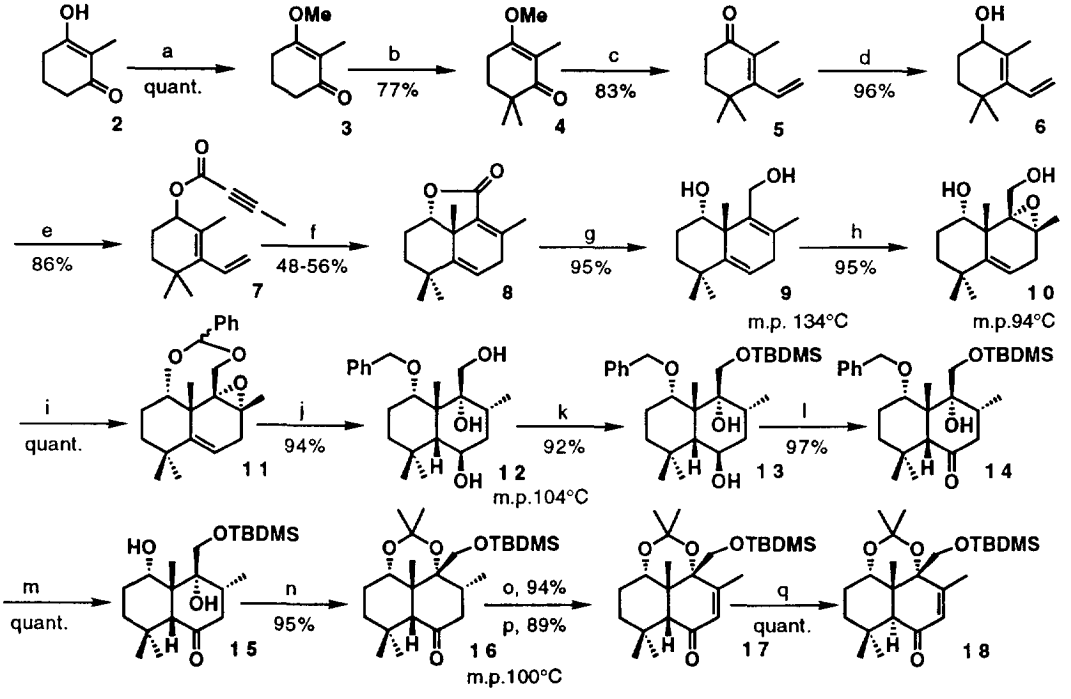
- the sequential gem-dimethylation of **3** was achieved under kinetic conditions [10] and required no intermediate work-up or isolation after the first alkylation; after medium pressure chromatography on silicagel (cyclohexane 9/AcOEt 1, 1‰ NEt_3), **4** was obtained in 77% yield (0.2 molar scale); the isolated monomethylation product (7%) was realkylated separately to give **4** (90%).

- the intramolecular Diels-Alder of **7** was reported to give **8** in only poor yield in several previous approaches [11]. Corey and coworkers developped alternative different sequences for converting the dienol **6** into the dienic lactone **8**, either racemic [6a] or optically active [6b]. The IMDA **7** -> **8** proved to be a difficult reaction and we observed competitive reactions, depending on the conditions, leading to the triene **19** and

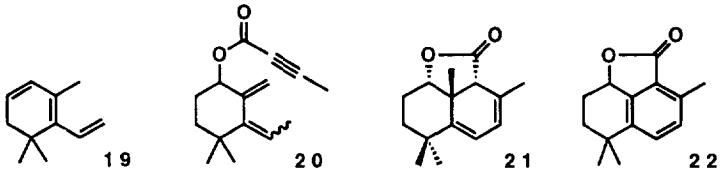
dedicated with respect and gratitude to the memory of Professor Alain Horeau (1909-1992)
+ deceased September 2nd, 1993.

derived products, the ene reaction product **20**, the thermodynamic isomeric lactone **21**, and in too harsh thermic conditions the aromatisation product **22**. Traces of oxygen had also to be excluded in order to avoid the autoxidation of the dienic lactone **8** to form the dienic 7- hydroperoxide or 7-ketone. All attempts of Lewis acid catalyzed IMDA of **7** failed completely. After some experimentation, we could however obtain **8**, almost reproducibly (48-56%), either by heating a solution of **7** in anhydrous *n*-decane (1.3-1.7 M, reflux under argon, 14h) in a carefully cleaned and neutralized glassware on a 2-3g scale, or in a clean stainless steel autoclave (iPr_2O/*n*-butyl glycidyl ether 20/1, BHT 10% mol, 180°C, 20-24h) on a 15-22g scale.

Scheme I

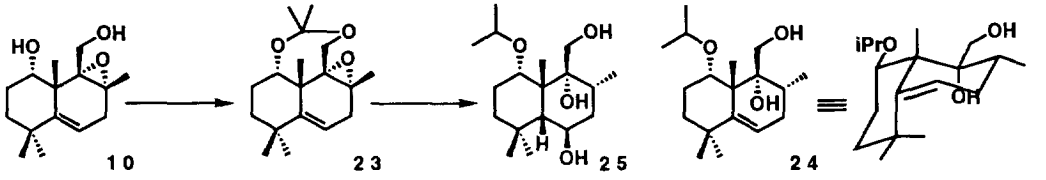


a) K_2CO_3, Me_2SO_4, acetone, reflux; b) LDA (1 eq)/THF/-78°, then CH_3I (1.05 eq)/-78° to +10° (reverse addition), followed by LDA (1eq)/-78°C and further CH_3I (1.1 eq) (reverse addition, -78° to 0°); c) vinylMgBr/THF, -78°to r. tp. , then aqueous work-up and extraction, followed by aq H_2SO_4/acetone/r. tp.; d) $LiAlH_4/Et_2O$; e) tetrolic acid /DCC/DMAP/CH_2Cl_2; f) see text; g) $LiAlH_4/Et_2O$; h) tBuOOH/VO(acac)$_2$/CH_2Cl_2; i) and j) see text; k) TBDMSCl (1.05 eq)/DMF/imidazole/r.tp.; l) CrO_3-py$_2$/CH_2Cl_2; m) H_2,Pd/C, EtOH, r. tp.; n) 2-methoxy propene/CCl_4/ $POCl_3$/r. tp.; o) LDA/THF/-78°, followed by PhSeCl quench at -78° (reverse addition); p) 30% H_2O_2/CH_2Cl_2-pyridine/r. tp.; q) basic Al_2O_3/toluene/100°.

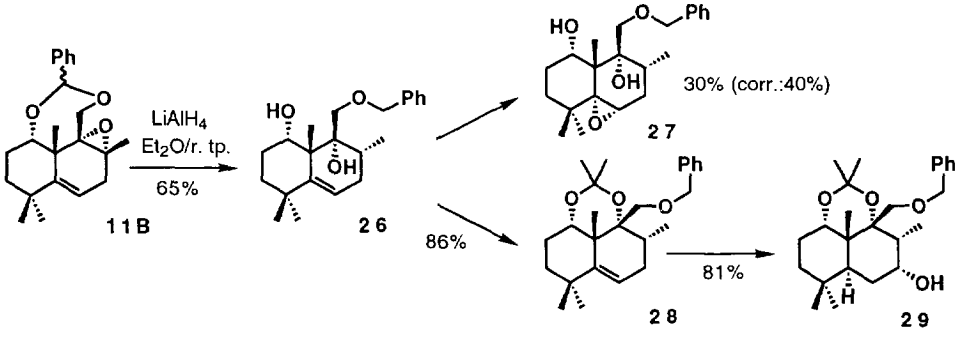


Due to the easy isomerization of the adduct **8** into the thermodynamic isomer **21**, even with weak bases, and its high sensitivity to autoxidation, **8** was reduced into the diol **9** (95%) which was converted into the epoxide **10** (95%) with tBuOOH/VO(acac)$_2$ in a highly regio- and stereoselective reaction. Attempted selective glycolations (OsO_4, $KMnO_4$, WO_3/H_2O_2) of the diol **9** were unsuccessfull, as were hydroborations (BH_3-THF) of **10** or of the acetonide **23**, in strong contrast with the easy selective hydroboration of a related dienic diester [12]. The acetonide **23** could however be efficiently converted into **25** (83%) with $LiBF_4/BH_3$/THF at

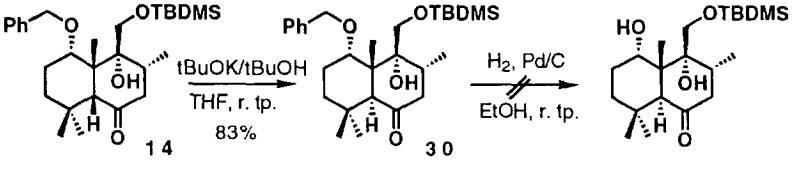
room temperature; the intermediate was shown to be **24**, the double bond of which in contrast was easily hydroborated (BH_3-THF, r.tp.). The stereochemistry of the hydroboration might be explained by the conformation of **24** in solution which is drawn below, determined by ^1H NMR (*quasi-cis* ring fusion).



Hence, the same conditions were applied to the benzals **11**. Ketalization in thermodynamic conditions (Ph $CH(OMe)_2$ / $POCl_3$ or pTsOH) yielded a nearly 1/1 mixture of the two diastereoisomers of which only the less polar one underwent the precedent desired transformation; thus **12** was obtained from $\mathbf{11_A}$ in 94% yield (on a 9g scale) either with $LiBF_4$ / BH_3-THF or $LiBH_4$ / BF_3-Et_2O in THF at room temperature [13, 14]. In contrast, the most polar diastereoisomer $\mathbf{11_B}$ was completely inert in the same conditions [16] and heating gave complex reactions. Kinetic ketalization conditions were found to favour the useful diastereoisomer $\mathbf{11_A}$, affording the mixture of benzals in a quantitative yield (PhCH(OMe)$_2$ / CCl_4, reflux, 20h); chromatography on silicagel (*n*-hexane 4 / iPr_2O 1) gave pure $\mathbf{11_A}$ (78%) and $\mathbf{11_B}$ (20%); $\mathbf{11_B}$ could be equilibrated nearly quantitatively into a 1/1 mixture of $\mathbf{11_A}$ and $\mathbf{11_B}$ (PhCH(OMe)$_2$ / CCl_4 / MeCOCl / MeOH / r.tp.), and hence recycled. On the other hand, reaction of $\mathbf{11_B}$ with $LiAlH_4$ / Et_2O, at r.tp., afforded **26** (65%) which yielded, with BH_3-THF (12 days, r. tp.) and subsequent work-up with H_2O_2/NaOH, the 5α, 6α-epoxide **27** [17] (30%) and some starting material was still recovered (24%). Hydroboration of the acetonide **28** in the same conditions was also very sluggish (1M BH_3-THF, 8 days, r. tp.) and gave **29** (81%), resulting from the isomerization in those conditions of the 5,6 hindered double bond into the 6,7 olefin which is then hydroborated with a high regio- and stereoselectivity by the α face. These results considered together are quite demonstrative and intriguing concerning the factors which govern the hydroboration of such substrates.



We then completed the sequence leading to the enone **18**, in which the 1α and 9α OH groups were protected as early as possible as an acetonide which was planned to be kept throughout the synthesis towards forskolin. These reactions deserve no special comment, apart from the fact that hydrogenolysis of the benzyl ether proved to be very difficult for the *trans* fused compound **30** whereas it was quite easy for the *cis* isomer **14**, thus affording **15** in quantitative yield.



Protection of the 1α, 9α-diol **15** as an acetonide (2-methoxy propene / $POCl_3$ 1% v/v in CCl_4, r. tp.) gave **16** in 95% yield and it was further shown that no epimerization at the 5-position occurred at all in those conditions. Subsequent conversion into the *cis* enone **17** was effected in high yield; the *cis* fused structure

was proved unambiguously by further chemistry and complete equilibration of **17** into **18**, (tBuOK/tBuOH-THF, r. tp., 83%) or better [18](basic Al_2O_3 / toluene / 100°C, quant.). The *trans* enone **18** was further elaborated into forskolin [8,9].

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14. 0.15 M $\mathbf{11_A}$ in THF; Molar ratio $\mathbf{11_A}$/ $LiBH_4/BF_3$-Et_2O = 1/5/6.5; 20°C, 10 days, under argon. Work-up of the hydroboration with ethylene glycol, followed by addition of 3N NaOH and 30% H_2O_2, at r. tp., was found to considerably improve the yield of **12** and minimize the formation of the 6-boronic acid[15]. Conversion to the ethylene glycol ester facilitates the oxidation in such a hindered situation, as mentioned by Brown, H. C. *Organic Syntheses via Boranes*, Wiley: 1975; p.108, note 2.
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19. *cis* -fused enone **17**:
    ^1H NMR ($CDCl_3$, 300 MHz, δ/TMS): -0.03 (s, 3H) and 0.00 (s, 3H), MeSi; 0.82 (s, 9H), tBu; 1.14 (s, 3H), Me; 1.16 (s, 3H), Me; 1.43 (s, 3H), Me; 1.45 (s, 3H), Me; 1.47 (s, 3H), Me; 1.99 (broad s, 3H), 8-Me; 2.33 (broad s, 1H), H_5; 3.40 (d, 1H, 10 Hz) and 3.81 (d, 1H, 10 Hz), H_{11}; 3.75 (dd, 1H, 6 and 8 Hz), H_1; 5.99 (broad s, 1H), H_7.
    I. R. ($CHCl_3$): C=O 1656 cm^{-1}; U. V. (EtOH): ε_{238} = 7100; 230nm (infl.); ε_{320} = 76.
    MS (EI, 70 eV): *m/z* 422 ($M^{\cdot+}$), 407 (M^+ - CH_3), 365 (M^+ - tBu), 307 (M^+ - TBDMS).
20. *trans*-fused enone **18**:
    ^1H NMR ($CDCl_3$, 300 MHz, δ/TMS): 0.05 (s, 3H) and 0.07 (s, 3H), MeSi; 0.84 (s, 9H), tBu; 1.03 (s, 3H), Me; 1.16 (s, 3H), Me; 1.27 (s, 3H), Me; 1.41 (s, 3H), Me; 1.43 (s, 3H), Me; 1.94 (broad s, 3H), 8-Me; 2.96 (broad s, 1H), H_5; 3.73 (d, 1H, 10 Hz) and 4.22 (d, 1H, 10 Hz), H_{11}; 3.99 (m, 1H), H_1; 5.77 (broad s, 1H), H_7.
    I. R. ($CHCl_3$): C=O 1674cm^{-1}; U. V. (EtOH): ε_{228} = 11900; ε_{325} = 60
    MS (FAB): *m/z* 423 (MH^+), 407 (M^+ - CH_3), 365 (M^+ - tBu), 307 (M^+ - TBDMS).

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