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Total Synthesis of Forskolin - Part II#

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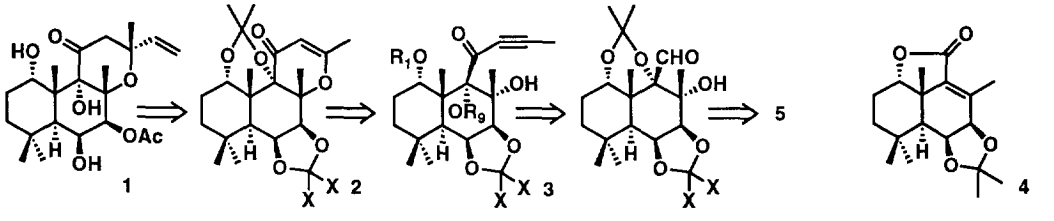
Abstract : The further elaboration of the key-intermediate **5** into forskolin **1** has been achieved via two different routes. Key features of this new total synthesis are: 1) the stereospecific formation of the 6β, 7β, 8α-triol via the BF_3-Et_2O assisted opening of the epoxy carbamate **8**; 2) use of the 8α, 11-di-*t*-butylsilylene ketal for the specific protection of the 6β, 7β-diol, from the tetrol $\mathbf{10_A}$; two new sequences for the formation of the dihydro-γ-pyrone ring in high overall yield from **23**; 4) the stereoselective divinyl cuprate conjugate α-addition on the dihydro-γ-pyrone **16** or **28**, in the presence of BF_3-Et_2O, with the stereochemistry required for forskolin synthesis.

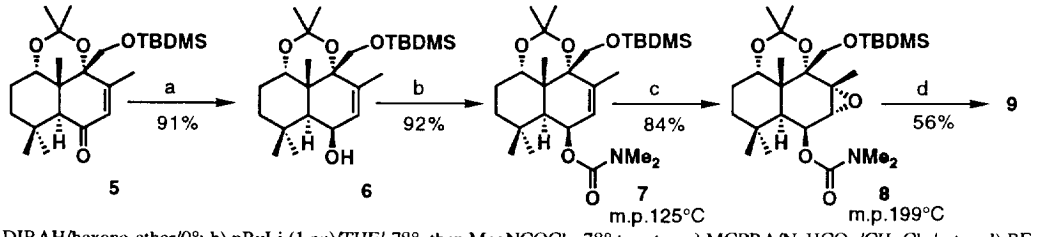
This note describes the further elaboration of the *trans*-fused enone **5** [1] into forskolin **1**. Our aim was to complete a synthesis significantly different from the syntheses of Ziegler [2], Ikegami [3] and Corey [4] which -incidentally- involved the same key intermediate **4**, since then the target of numerous formal syntheses of forskolin [5]. Therefore, our target was forskolin and our concern was to avoid **4** and try to find other solutions for the problems associated with the elaboration of the 6β, 7β and 8α, 9α diols and with the construction of the C-ring. We first achieved the reconstruction of forskolin from an intermediate such as **2** [6].



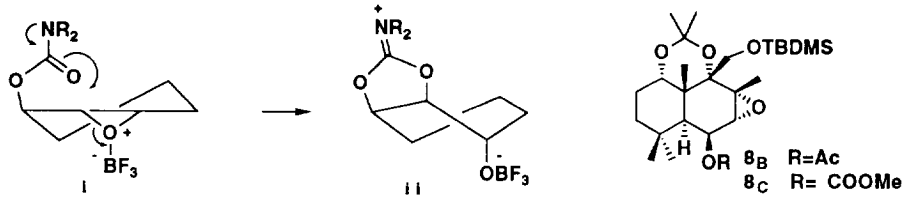
We also initially planned to introduce as early as possible the 1α and 9α OH and protect them as an acetonide in order to get an intermediate **3** (X, X=O or X=Me; R_1, R_9 = CMe_2) which might allow to avoid some problems already met by Ziegler and coworkers [2] for the dihydro-γ-pyrone formation with a precursor **3** having a free 9α-OH (R_1=TBDMS; R_9=H; X=Me).
Reduction of **5** with DIBAH afforded **6** in 91% yield, which gave very cleanly the 7β, 8β-epoxide (92%) in a hydroxyl group directed reaction with $Mo(CO)_6$/tBuOOH, as already reported for a related compound by Corey [4a]; reaction of **6** with MCPBA was less stereoselective, yielding the β (84%) and α (9%) epoxides. In contrast, epoxidation of the carbamate **7** (92% from **6**) in buffered conditions with MCPBA gave the α (**8**) and β epoxides, isolated in 84% and 6% yield. Hence, no stereodirecting effect of the 6β-carbamate was observed here, in contrast with some previous generalization [7] and the α-epoxide is the one expected due to steric and conformational effects. At this point, in order to develop a solution different from those already achieved on a 7β, 8β-epoxide [2, 4], we examined the intramolecular opening of the 7α, 8α-epoxide; thus, reaction of **8** in the

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

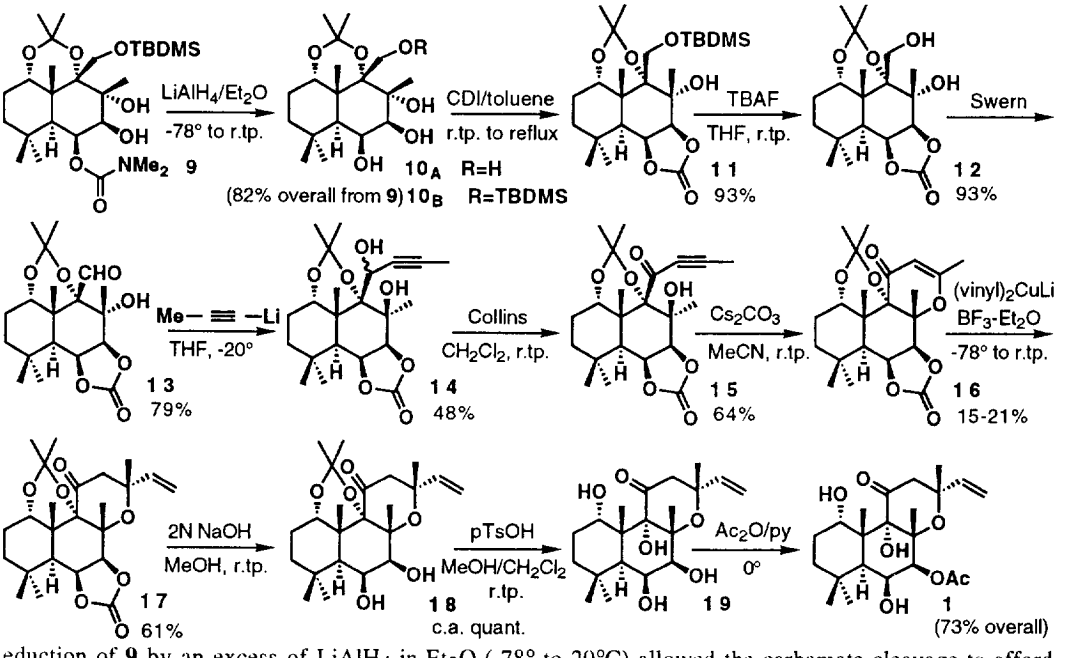
presence of BF_3-Et_2O gave the carbamate **9** (56%), the carbonate **11** (5%) and 14% starting material **8** was recovered. It is worth pointing out that this assisted opening involves a preboat transition state **i**, which should lead to an intermediate iminium ion **ii** and to the carbonate **11** after hydrolysis; the anomalous formation of **9** might reflect an early transition state; noteworthy, similar attempted intramolecular openings of $\mathbf{8_B}$ or $\mathbf{8_C}$ in the presence of BF_3-Et_2O failed completely, the starting material being then recovered in good yield.



a) DIBAH/hexane-ether/0°; b) nBuLi (1 eq)/THF/-78°, then Me_2NCOCl, -78° to r. tp.; c) MCPBA/$NaHCO_3$/CH_2Cl_2/r. tp.; d) BF_3-Et_2O (1.5 eq), Et_2O, 0° to r. tp., and neutralization with Et_3N (2.3 eq) followed by aqueous borax.



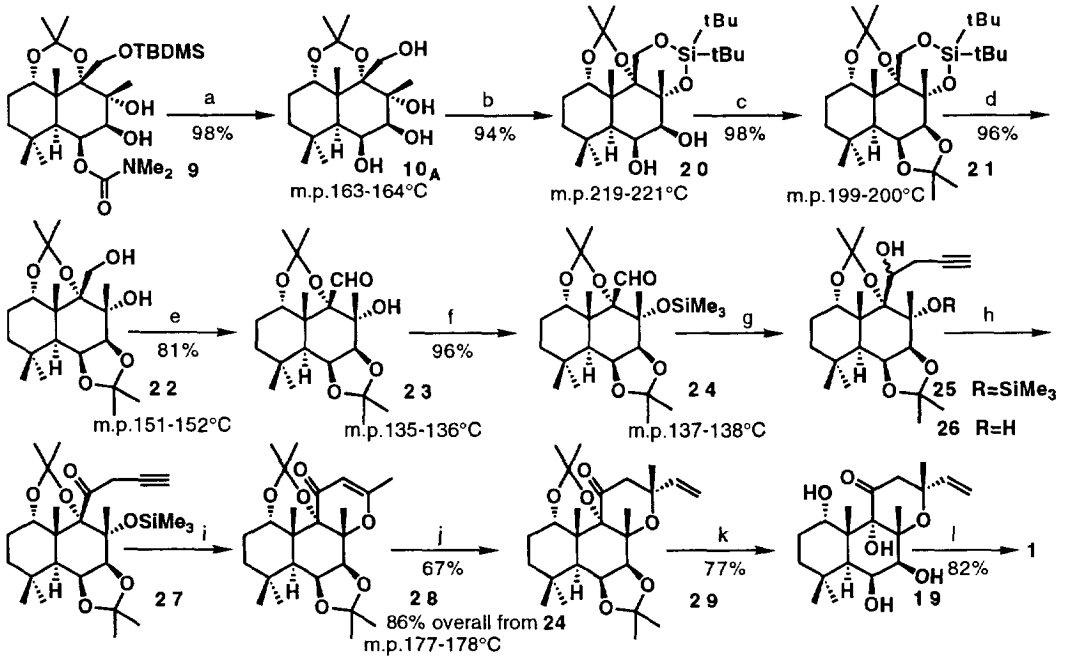
First completed synthesis of forskolin [8] :



Reduction of **9** by an excess of $LiAlH_4$ in Et_2O (-78° to 20°C) allowed the carbamate cleavage to afford however a mixture of $\mathbf{10_A}$ (77%) and $\mathbf{10_B}$ (17%); a highly selective silylation of $\mathbf{10_A}$ gave $\mathbf{10_B}$ in 85% yield (TBDMSCl/DMAP/pyridine/r.tp.), thus giving a good access to $\mathbf{10_B}$ (82% overall from **9**). Selective 7β-alkoxy imidazolide formation was secured , at 20°C with carbonyldiimidazole in toluene, and after clean completion (followed by TLC), heating the reaction mixture to reflux gave the carbonate **11** in good yield (93%). Further clean desilylation gave **12** (93%) and Swern oxidation afforded the aldehyde **13** (79%) with

some recovered **12** (13%). Propynyl lithium addition to the aldehyde **13** proved to be quite a difficult reaction, due to the two quite unreactive partners and also to a very easy retroaldol process. Other organometallic reagents were useless with **13** ; retroaldolisation occurred even with a preformed propynyl lithium / $CeCl_3$ reagent which, as we checked before use, did not enolize $PhCH_2COCH_2Ph$ [9], but led almost quantitatively to **13** (43%) and the corresponding 8-epimer (57%). On the other hand, to avoid the retroaldolisation, protection of the 8α-OH of **13** as a trimethylsilyl ether (Me_3SiOTf/N-methylimidazole, CH_2Cl_2, r. tp., 96%) gave a quite unreactive aldehyde and only cleavage of the 6β, 7β-carbonate occurred then with propynyl lithium. *However, after many experiments, we could get the desired dihydro-γ-pyrone* ***16*** *via a sequence* **13 -> 16**, *involving in fact as shown afterwards two successive epimerisations at the 8 position in a completely unexpected way, due again to retroaldol reactions.* Thus, condensation of **13** at -20°C with an excess of propynyl lithium (prepared in situ from propyne and BuLi in THF at -78°C) gave **14** (48%) as a mixture of 2 diastereoisomers besides other retroaldol products; **14** (as 2 diast.) was oxidized into the alkynyl ketone **15** (64%) with CrO_3-py_2. *The required dihydro-γ-pyrone* **16** *was obtained* from **15** (Cs_2CO_3 / CH_3CN / r. tp.), *but only in 15-21% yield, and identified with the same compound prepared from forskolin*; other compounds were an isomeric dihydro-γ-pyrone (epimer at C-8, 15-28%) and a product of *5-exo-dig* cyclization (39-50%) . Surprisingly also, a product of *5-exo-dig* cyclization was formed from **15** in an almost quantitative yield with $Hg(TFA)_2$ / NEt_3 in CH_2Cl_2 (-78°C to r. tp.). Clearly more work remains to be done concerning the geometric factors which control the *5-exo-dig* with respect to the *6-endo-dig* closure. Conjugate addition of divinyl cuprate in the presence of BF_3-Et_2O, as we already showed for a related compound [6], gave stereoselectively **17** in 61% yield. Forskolin was finally obtained in 73% overall yield from **17**.

Forskolin synthesis: modified scheme and improvements [10]



a) NaOH/MeOH, reflux; b) $(tBu)_2Si(OTf)_2$/DMAP/pyridine, r.tp.; c) 2-methoxy propene, PPTS/CH_2Cl_2, r.tp.; d) TBAF/THF, r.tp.; e) DMSO/$(COCl)_2$/NEt_3, CH_2Cl_2, -78° to r.tp.; f) TMSOTf/N-methylimidazole, CH_2Cl_2, r.tp.; g) propargylMgBr, Et_2O, -30°; for **25** -> **26**: TBAF/THF, r.tp.; h) **25** -> **27**: Collins, CH_2Cl_2, r.tp., 94% overall from **24**; i) TBAF/AcOH/THF, r.tp., 92%; j) divinylcuprate, BF_3-Et_2O, THF, -78° to r.tp.; k) see text; l) Ac_2O/pyridine, 0°.

In order to try to favour the dihydro-γ -pyrone formation, and to get a solution different from those already developped in the previous syntheses [2-4], we chose a propargylic ketone or an allenic ketone as a precursor. Due to the problems we got in our first approach with the cleavage of the 6β, 7β-carbonate by organometallic reagents for the conversion of **13** into **14**, and also to the experience we had already with protecting groups in forskolin derivatives or synthetic intermediates, we chose to establish the 6β, 7β-acetonide as early as possible

to get a key intermediate such as **23** or **24** in order to be able to use more reactive Grignard reagents, although the hydrolysis of such an acetonide was already known to be quite difficult [2-4, 6, 11]. Our preliminary experiments showed it was not possible to directly protect the 6β, 7β-diol with enough selectivity from the triol $\mathbf{10_B}$. An efficient selective protection of the 8α-OH and 11-OH of $\mathbf{10_A}$ (98% yield from **9**) was required in order to further establish the 6β, 7β-acetonide; an excellent solution to this difficult problem was found with the di-*t*-butyl dialkoxysilylene derivative **20** (94% from $\mathbf{10_A}$). Formation of the 6β, 7β-acetonide was then straightforward in slightly acidic conditions to afford **21** in 98% yield; deprotection of the silylene ketal with TBAF in THF, at room temperature, gave **22** (96%) which was oxidized with Swern reagent into the aldehyde **23** (isolated in 81% yield). In order to avoid retroaldolisation which would occur by reacting **23** with organometallic reagents, as we already discussed, protection of the tertiary 8α-OH as a trimethylsilyl ether was achieved efficiently in mild conditions (TMSOTf/N-methyl imidazole/CH_2Cl_2/r. tp.) to yield **24** (96%). Further condensation with an excess allenic Grignard reagent, prepared in situ from propargyl bromide [12], in Et_2O at -30°C, gave **25** in an almost quantitative yield as a c.a. 1/1 mixture of two diastereoisomers, which was deprotected (TBAF/THF/r. tp.) to afford the diols **26**, epimeric at C-11, which were isolated after chromatography in 43% and 45% overall yield from **24**. Oxidation of the mixture of diastereoisomers with an excess of Collins reagent and further reaction on silicagel in CH_2Cl_2, at room temperature, afforded the required dihydro-γ-pyrone **28** in 69% isolated yield (overall from the mixture of epimeric diols **26**). A more efficient access to **28** was developped via a Collins oxidation of the mixture of the alcohols **25** to get **27** (94% overall from **24**) and further desilylation of **27** in buffered conditions (TBAF (1.1 eq) / AcOH (1.15 eq), THF, r. tp.) directly gave **28** in 92% yield. Hence it is worth pointing out the efficiency of these two sequences involving a quite easy mild ring closure which gave only **28**, compared with the problems previously met by us with the alkynyl ketone **15**, or with a related compound **3** by Ziegler and coworkers [2c]. Those cyclizations most likely occur via a *6-endo-dig* pathway on the intermediate allenic ketone. *The structure of* **28** *was established unambiguously with an authentic sample derived from forskolin* [6] *and by further conversion into forskolin.* Conjugate addition of divinyl cuprate (prepared in situ from vinyl tri-*n*-butyltin / nBuLi, and CuI), in the presence of BF_3-Et_2O, as we already described [6], in Et_2O at -78°C, gave stereoselectively -with now improved conditions - the desired α–adduct **29** isolated in 67% yield and the C-13 epimer (16%). Noteworthy, the formation of **29** involves a preboat transition state compared with a prechair transition state for the β-adduct. Hydrolysis of **29** to get **19** proved to be, as expected [2d, 3, 4a, 6, 11], quite a difficult problem; however, after much work, we found suitable and reliable conditions leading to a slow, but very clean, efficient hydrolysis to afford **19** in 77% yield (0.025M **29**, pTsOH 20 eq, THF-H_2O 1/1, 20°C, 12 days). A highly selective acylation of the 7β-OH, as already known [13], gave forskolin in 82% yield.

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