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SYNTHESIS OF 14,15-DEHYDROFORSKOLIN VIA DIMETHYL DIAZOMETHYLPHOSPHONATE ANION REACTION WITH AN ALDEHYDE

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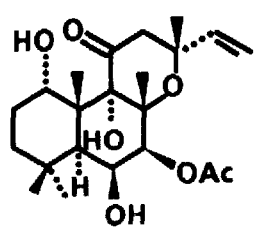
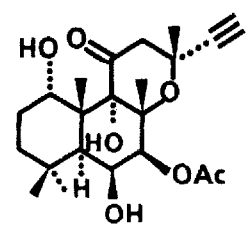
Abstract : 14,15-Dehydroforskolin is prepared by the reaction of the dimethyl diazomethylphosphonate anion with 13 α-carboxaldehydes obtained from forskolin. Isolation of a by-product gives the first evidence of the reactivity of the primary phosphonate adduct, by intramolecular quenching, before its evolution into carbenoid or carbene intermediates.

Forskolin 1 is a unique tool for studying both the biochemistry and regulation of adenylate cyclase, or the physiological functions of cyclic AMP (1,2). The synthesis of forskolin analogs should provide new approaches to discuss interactions of forskolin with adenylate cyclase, and also possibly to get more selective physiological responses. Therefore, a number of forskolin derivatives have been tested for adenylate cyclase activation (3-5), for their positive inotropic and blood pressure lowering properties (5-7). The 1α and 9α hydroxyl functions and the 13α vinyl group have been shown to be relatively critical for biological activity and are supposed to be at the site of interaction of forskolin with the enzyme (1,3). In order to get more insight concerning that hypothesis, we developed some methodology to modify the 13 position (8) and herein report the first synthesis of 14,15-dehydroforskolin 2 starting from forskolin.



1



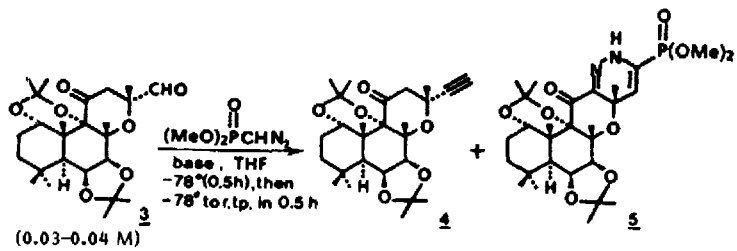
2

We first tried the base-induced reaction of dimethyl diazomethylphosphonate (9) with the aldehyde 3, directly available in 81 % overall yield from forskolin (8), since such a reaction has been shown to give the corresponding homologous alkynes with simple aldehydes (10,11).

$$RCHO \longrightarrow RC \equiv CH$$

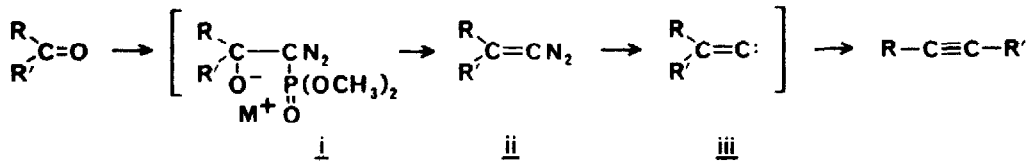
The bis-acetonide 3 was used in order to avoid the partial hydrolysis and 7β to 6β acyl migration occurring in basic conditions with forskolin derivatives (8,12).

The acetylenic product 4 was thus obtained in good yield with either nBuLi (70 %) or tBuOK (81 %) as a base for generating the anion, at -78°C in THF (10,11). However, interestingly, the compound 5 could be isolated in 12-15 % yield by using nBuLi whereas no such by-product was observed with tBuOK.



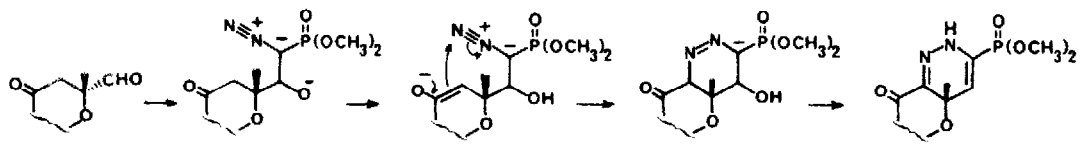
$(MeO)_2\overset{O}{\overset{\|}{P}}CHN_2$ / tBuOK ($^1/_1$) (2 eq.)	81 %	—
$(MeO)_2\overset{O}{\overset{\|}{P}}CHN_2$ / nBuLi ($^1/_1$) (1,5-2,0 eq.)	70 %	12-15 % + 6-9 % recovered 3

Concerning the formation of alkyne, GILBERT and coworkers have brought some convincing evidence of the intervention of an unstable diazoethene ii, formed from the primary adduct i, and decomposing at low temperature into an alkylidene carbene iii yielding the alkyne (11,13).



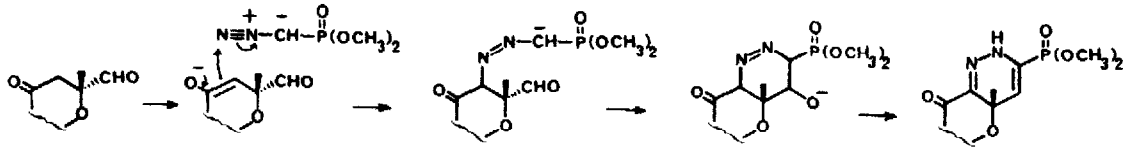
The generation of such carbene or carbenoid intermediates is also shown in other reactions of diazophosphonate anions with carbonyl compounds (13,14). The primary adduct i appears to be only a transient species and has never been quenched or detected by low temperature ^{13}C or ^{31}P NMR (11). To our knowledge, the isolation of 5 is the first evidence of some lifetime and reactivity of the primary adduct i in such condensations, since 5 may be formed according to scheme I by an intramolecular quenching.

Scheme I



The exact mechanism of formation of 5 remains quite intriguing, particularly because elimination of the phosphate group was not observed in the intermediate adducts. On the other hand, compound 5 most likely is not produced via a primary nucleophilic addition of the 11,12-enolate to the terminal nitrogen of the diazophosphonate (scheme II), since we checked that no such adduct is formed in the condensation of the preformed lithium 11,12-enolate of the 1α,9α:6β,7β-bisacetonide of 7β-deacetyl forskolin (LDA/THF/-78°C) with dimethyl diazomethylphosphonate (98 % starting material recovered) (15).

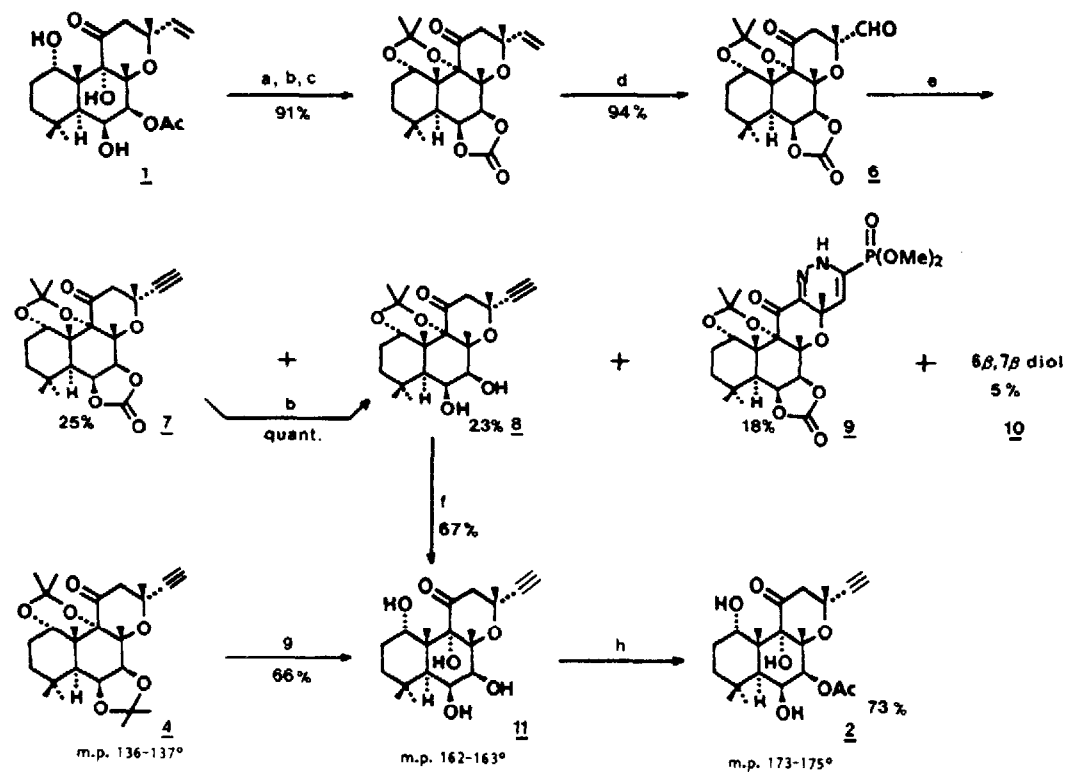
Scheme II



The primary open-chain adduct i may be more stabilized with the lithium than with the potassium salt, as is the case with betaines in the Wittig reaction (17), and also possibly due to chelation in forskolin derivatives.

14,15-Dehydroforskolin 2 was first prepared according to scheme III, starting from the aldehyde 6 obtained in 85 % overall yield from forskolin (18). The 6β, 7β-carbonate was used in that sequence in order to avoid the relatively harsh acidic conditions necessary for the 6β,7β-acetonide hydrolysis in forskolin derivatives (8, 19, 20).

Scheme III



a) 2-methoxy propene, pTsOH, CH_2Cl_2 ; b) NaOH, H_2O-CH_3OH ; c) carbonyldiimidazole, toluene ; d) O_3, CH_2Cl_2-CH_3OH, pyridine, -78°; e) $(MeO)_2POCHN_2$, nBuLi, THF, -78° to r.tp. ; f) aq. HCl/THF, r.tp. ; g) aq. HCl/THF, $H_2NCONHNH_2$-HCl, r.tp. ; h) Ac_2O-pyridine, 0°.

However, in addition to partial hydrolysis, the 6β,7β-carbonate 6 gave significantly more side-reaction products (9 and 10) than the 6β,7β-acetonide 3 in the same conditions. Thus, best access to 2 was achieved via the tBuOK induced diazophosphonate condensation with the aldehyde 3, since we could obtain 11 in 66 % yield by acidic hydrolysis of 4 in modified Corey conditions (20) (scheme III).

14,15-Dehydroforskolin 2 has been shown to be a potent activator of adenylate cyclase.

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18. NMR ($CDCl_3$, 250 MHz and 400 MHz) (δ/TMS ; J (Hz)).
    2 : CH_3 : 1.03 (s) ; 1.25 (s) ; 1.39 (s) ; 1.59 (s) ; 1.65 (s) ; Ac : 2.17 (s) ; ≡CH : 2.46 (s) ; H-1 : 4.75 (t after exchange, J = 2.5) ; H-5 : 2.24 (d, J = 2.5) ; H-6 : 4.50 (dd after exchange, J = 2.5, 4) ; H-7 : 5.41 (d, J = 4) ; CH_2-12 : 2.73, 3.31 (d, J = 18.5) ; OH : 1.74 (s) ; 2.67 (d, J = 3.5) ; 6.64 (s).
    4 : CH_3 : 1.07 (s) ; 1.19 (s) ; 1.31 (s) ; 1.33 (s) ; 1.36 (s) ; 1.44 (s) ; 1.48 (s) ; 1.52 (s) ; 1.59 (s) ; C≡CH : 2.40 (s) ; H-1 : 4.48 (m) ; H-5 : 2.65 (d, J = 4.5) ; H-6 : 4.66 (dd, J = 4.5, 6.5) ; H-7 : 4.36 (d, J = 6.5) ; CH_2-12 : 2.81, 3.21 (d, J = 20).
    5 : CH_3 : 1.05 (s) ; 1.07 (s) ; 1.12 (s) ; 1.21 (s) ; 1.24 (s) ; 1.40 (s) ; 1.47 (s) ; 1.57 (s) ; 1.60 (s) ; P-OCH_3 : 3.78 (d, J = 11.5) ; H-1 : 4.35 (m) ; H-5 : 2.57 (d, J = 4) ; H-6 : 4.68 (dd, J = 4,6) ; =CH : 5.78 (dd ; d after exchange, J P-H = 12); N-H : 8.55 (dd, J = 2,5).
    9 : CH_3 : 1.05 (s) ; 1.10 (s) ; 1.13 (s) ; 1.22 (s) ; 1.25 (s) ; 1.49 (s) ; 1.67 (s) ; P-OCH_3 : 3.79 (d, J = 11.5) ; H-1 : 4.38 (m) ; H-5 : 2.57 (d, J = 3.5) ; H-6 : 5.12 (dd ; J = 7, 3.5) ; H-7 : 4.78 (d, J = 7) ; =CH : 5.79 (dd, J = 12, 2.5 ; d after D_2O, J = 12) ; N-H : 8.69 (broad dd).
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