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A Simple Access to a Forskolin Precursor.

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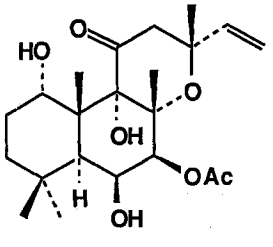
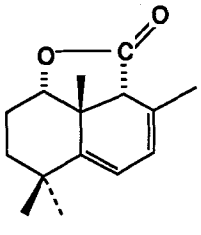
Summary : Key intermediates in a forskolin synthesis have been prepared in two steps from hydroxy-β-ionone by electrocyclisation.

Forskolin 1, a labdane diterpene isolated from *Coleus forskolii*, [1] is currently a target of great interest for many organic chemists due to its potential biological activities [2] and to the synthetic challenge it represents. In the various routes already explored for its total synthesis, lactone 2, prepared either through Diels-Alder reaction or by base-catalysed cyclisation, has often been used as a key intermediate.[3]



Forskoline 1



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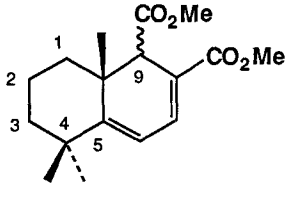

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This hexahydro-decalin structure is related to 8, an intermediate used in the synthesis of polygodial [4], an natural product with the drimane skeleton. Some years ago, we had developed an efficient and simple synthesis of polygodial, based on the stereochemical control of C-9 by thermodynamic or kinetic protonation of the enolate followed, by stereocontroled hydrogenation of the Δ^5 double bound.

In principle an electrocyclisation of the trienic hydroxy-ester 4 could lead to the desired product, assuming that trans-Δ^4 double bond in 4a could be isomerized into cis-Δ^4 in 4b . This problem has been studied in the dehydroxy series by Frater[5]. A recent publication by Venkataraman and Cha [6] dealing with such an approach prompt us to report our results which display some marked discrepancies with theirs.

Hydroxy-β-ionone 3 is an ideal precursor to prepare 4. The two missing carbons can be easily introduced by an Emmons-Wadsworth-Horner reaction using $(CH_3)_3SiCH_2CO_2Et$ (LDA 2-5 eq., THF, -78 °C to +20 °C in 4 hrs) to give 4 as a mixture of geometrical isomers (Δ^2 cis and trans, Δ^4 trans) . Various protected derivatives of 4 were then prepared according to standard procedures, in particular with BOM 4 a (benzyloxymethylene) or TBDMS 4b (dimethyl-t-butyl silyl) on the -OH group [7,8].

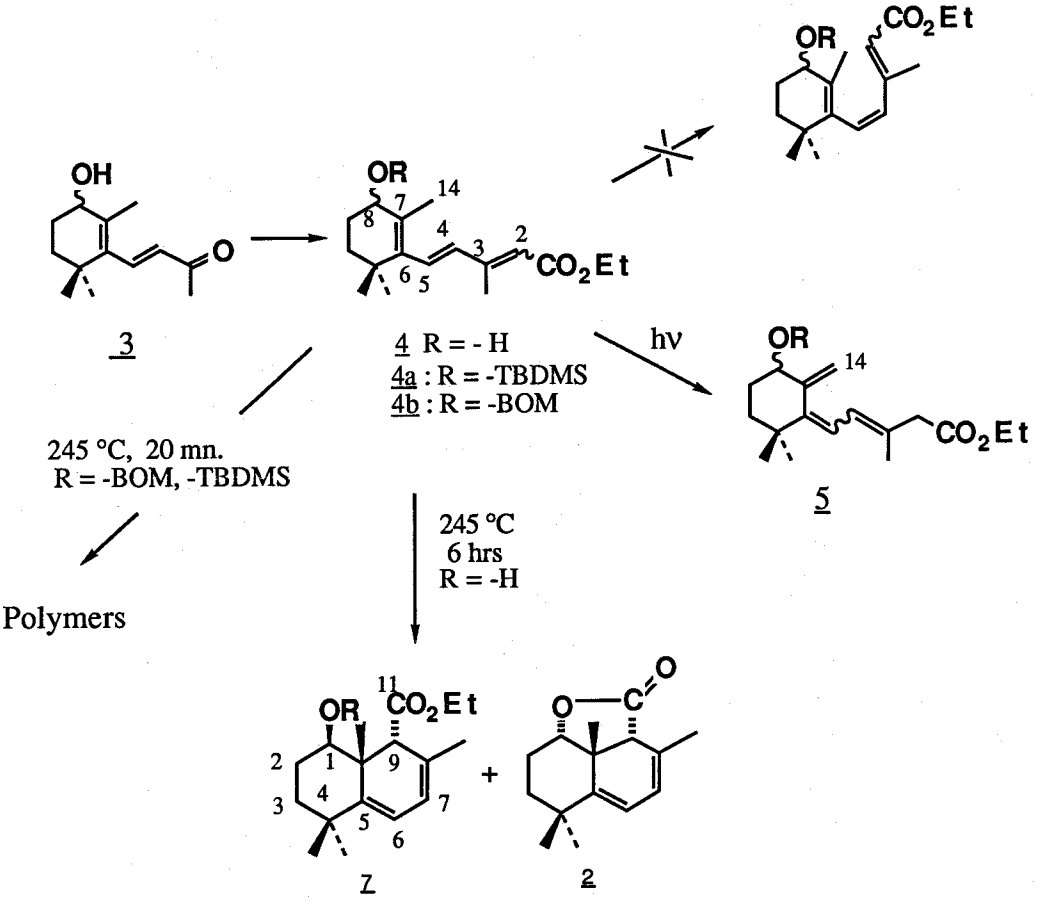
Photochemical isomerization of 4 (0.3 to 6 hrs) in the presence of various photosensibilisators (benzantrone-THF [5], acetophenone-benzene) was first attempted. Unfortunately a mixture of products was produced in which the presence 5 (two isomers, ^{1}H NMR : 4.7 and 5,3 ppm (t, J= 2,5 Hz) = H-14, H-14', 5.6-5.7 ppm =H-4, H-5, yield = 60 %) arising from what appears to be a 1-7 sigmatropy on cis Δ4 isomer of 4 could be shown by NMR.

Following the difficulties encountered in the photoisomerization, we next examined the possibility of direct thermal rearrangement of 4.

At 245 C° (1 hr., neat or in N,N-dimethylaniline) protected products 4a or 4b quickly disappeared from the reaction mixture . However, NMR analysis of the crude reaction mixture revealed a very complex pattern for the signals expected for H-9 as well as for those corresponding to the methylene proton of the methyl group. Clearly, the thermolysis of 4a or 4b produces a complicated mixture of products. After a tedious purification, only a small amount of lactone 2 could be isolated. Moreover, modification of the experimental conditions, and in particular increasing the dilution to minimize possible intermolecular reactions, did not result in any improvement. These observations are in sharp contrast to those of Venkataraman and Cha who claim clean isomerisation and electrocyclisation under similar conditions.

The formation of a small amount of lactone 2 following thermolysis seemed to indicate that the protecting group did not withstand the high temperature of the reaction, and from the outset, the protection of the allylic alcool seemed necessary to prevent dehydration under the harsh conditions used. However, this assumption turned out to be wrong. Thus, heating 4 in N,N-dimethylaniline for 6 hrs gave a clean 60/40 mixture consisting of lactone 2 and hydroxyester 7 in a combined yield of 65%. The structure of the latter was easily deduced from its NMR spectra[9].

The cis relationship between the -OH and the 12-methyl group is consistent with the quartet signal corresponding to axial H-1 at 3.65 ppm (J= 12 Hz, 5 Hz). Furthermore H-9 appears as a singlet as in lactone 2 and in compound 7. We had previously established that, in the drimane series, the signal for the H-9 proton is a singlet for the thermodynamically more stable compound where this proton is cis to the 12-methyl group. In the alternative trans arrangement, a long range coupling constant of 3 Hz between H-9 and H-7 is observed.



Although the underlying reasons for this clean cyclisation of the unprotected compound are not clear, this reaction gives an expedient access (two steps from readily available hydroxy-β-ionone) to bicyclic derivatives 2 and 7, both of which are interesting intermediates to forskolin and related molecules. Such applications are currently being examined.

References and notes.

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9. NMR. Data :

7: ^{1}H NMR (200 MHz, CDCl3) ppm : 5.8 (s, H-6, H-7); 4.15 (m, -0-$\underline{CH_2}CH_3$) ; 3.65 (q, H-1) ; 2.90 (s, H-9) ; 1.75 (s, CH_3) ; 1.2 (t, -0-CH2$\underline{CH_3}$) ; 1.1-1 (3 s, $\underline{CH_3}$).

7: ^{13}C NMR (50.3 MHz) ppm : 172.3 (C-11); 147.9 (C-5); 132.8 (C-8); 128.4 ,118.0 (C-6, C-7); 74.3 (C-1); 60.6 (-OCH_2); 56.2 (C-9); 44.5 (C-10); 34.7 (C-4); 37.7 - 14.4 (7 carbons).

2: ^{1}H NMR (200 MHz, CDCl3) ppm : 5.85 (m, H-6, H-7); 4.41 (t, H-1); 2.65 (s, H-9); 2.00 (s, CH_3); 1.25-1.10 (3 s, CH_3)

2: ^{13}C NMR (50.3 MHz) ppm : 176.3 (C-11); 141.6 (C-5); 127.6 (C-8); 120.7, 119.7 (C-6, C-7); 84.9 (C-1); 56.2 (C-9); 43.1 (C-4); 34.4 (C-10); 33.1 - 21.4 (6 carbons).

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