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A Synthetic Approach to the Tricyclic System of Forskolin from D-Galactose

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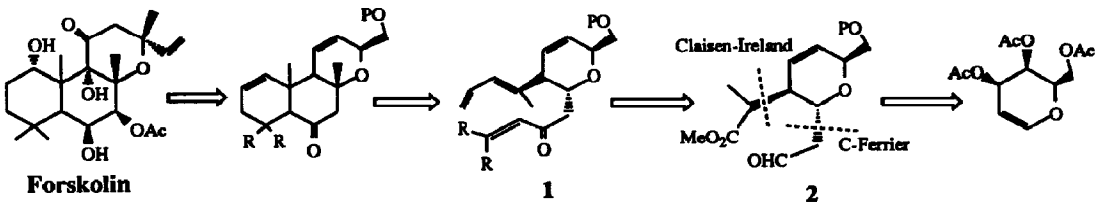
Abstract: *The synthesis of the tricyclic system of forskolin by an intramolecular Diels-Alder reaction is described, starting from tri-O-acetyl-D-galactal.*

Forskolin, a highly oxygenated labdane diterpene, exhibits a broad range of physiological activities through its ability to activate adenylate cyclase. The therapeutic potential of this natural product combined with its highly challenging structure have served to stimulate an important synthetic activity in a number of laboratories.[1,2]

In the majority of the previous synthetic approaches, an intramolecular Diels-Alder reaction was selected as the key step for the construction of an adequately functionalized AB ring system. In almost all cases, the elaboration of ring C was carried out in the final stages of the synthesis. In a new synthetic approach, we envisioned the construction of the ABC ring system of forskolin starting from the C ring by using a suitably functionalized tetrahydropyran subunit.

Our strategy, outlined in scheme 1, involves an intramolecular Diels-Alder cyclization of trienone **1** which should simultaneously assemble the A and B rings of the tricyclic skeleton of forskolin.



Scheme 1

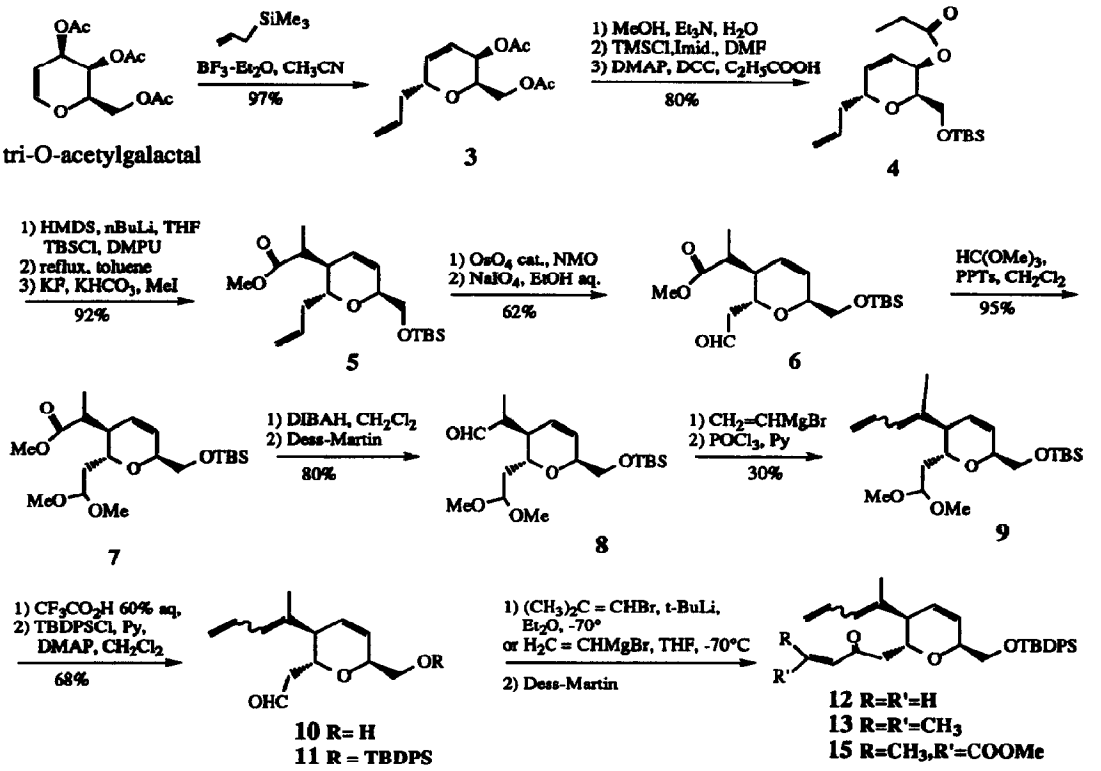
An added feature of our design lies in the use of the "chiron" approach, where intermediates could be constructed from optically active starting materials. The presence of the tetrahydropyran C ring obviously suggested the choice of carbohydrate derivatives as chiral building blocks.[3]

Over the last few years, carbohydrates have been extensively exploited in the synthesis of carbocyclic natural products.[4,5] Recently, we described a new methodology for mono and bifunctionalization of glycals based on the regioselective cleavage of a cyclobutane ring incorporated into the carbohydrate-like chiral building block.[6]

We now report the preparation of trienones such as 1 by stereoselective addition of carbon branches at C-1 and C-2 of D-galactal, and their reactivity under Diels-Alder reaction conditions.

The synthesis (scheme 2) was initiated by introduction of the allyl group at C-1 using the carbon-Ferrier rearrangement.[7] Thus, treatment of galactal triacetate[8] with allyltrimethylsilane in the presence of BF_3-Et_2O at -50°C cleanly afforded 3 as the sole α isomer in 97% yield. Hydrolysis of the acetates with Et_3N in aq. MeOH followed by protection of the primary hydroxyl group and esterification of the resulting allylic alcohol furnished 4 in good overall yield. At this stage, the carbon chain extention with the transfer of asymmetry at C-2 was achieved by Ireland's enolate-Claisen rearrangement.[9] To this end, allyl propionate 4 was treated with LHMDS-THF-DMPU followed by TBSCl to give the ketenesilyl acetal[10] which was heated in refluxing toluene.The crude rearrangement product was subjected to desilylation and methylation affording 5[11] as a mixture of methyl epimers (7:1 ratio, ^1H NMR)[12] in 92% overall yield after flash chromatography.

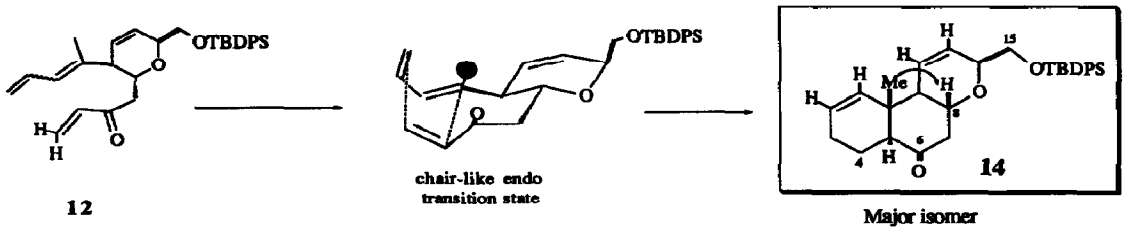
Chemoselective cleavage of the terminal double bond in compound 5 was achieved by hydroxylation (cat. OsO_4, NMO)[13] followed by diol cleavage with $NaIO_4$ to give 6 in 62% overall yield. After protection of the aldehyde as a dimethyl acetal ($HC(OMe)_3$, cat. PPTs, CH_2Cl_2, 95%), the ester 7 was converted into aldehyde 8 by reduction (excess DIBAH) followed oxidation of the resulting alcohol (Dess-Martin's periodinane[14]) in 80% yield. Attempts to achieve this transformation in one step using one equivalent of DIBAH led to a mixture of 8 and the primary alcohol, along with the starting ester.



Scheme 2

The elaboration of the diene part at C-2 was achieved by addition of vinylmagnesium bromide to aldehyde **8** in THF at -70°C followed by dehydration of the resulting mixture of stereoisomeric alcohols. While the Grignard reaction was smoothly effected (84%), the elimination proved troublesome. The best result was obtained with $POCl_3$-Py at 0°C affording the conjugated diene **9** as a mixture of E and Z isomers (2 : 1 ratio, ^1H NMR)) only in low yield (36%), although the starting material was consumed. Attempts to improve this yield using differents methods were unsuccessful.Treatment of **9** with aq. CF_3COOH in THF at room temperature furnished hydroxyaldehyde **10** which was converted to *tert*-butyldiphenylsilyl ether **11**. First attempts to prepare **11** by selective hydrolysis of the dimethyl acetal group under milder conditions (PPTS, PTSA, aq. oxalic acid ...) led only to the desilylated product, the aldehyde protective group was unaffected.

In order to test the feasibility of the IMDA reaction, the trienone **12** was first prepared. The addition of vinylmagnesium bromide to **11** gave rise to a mixture of diastereomeric alcohols which were readly oxidized with Dess-Martin's periodinane reagent[14] leading to the Diels-Alder precursor **12** in 45% overall yield. When **12** was heated in toluene in a sealed tube at 160°C for 20 hours, the expected cycloadduct was isolated as a mixture of isomers in a 6 :1 ratio (^1H NMR) in 65% yield. The stereochemistry of the major isomer **14**, having the angular methyl β (as in forskolin), was deduced by a combinaison of COSY and NOESY ^1H spectra at 400 MHz. In particular, the NOESY experiment revealed a cis relationship of the angular methyl group at C-10 with H-8 (terpenoid numbering). This product may result from "down side" facial approach of the dienophile which is dictated by the geometrical restriction in the IMDA transition state (scheme 3).[15,16]



Scheme 3

Lewis acid promoted Diels-Alder cyclization was then attempted. Fortunately, when **12** was treated with BF_3-Et_2O in CH_2Cl_2 at 0°C for 15 min, the desired isomer **14** was almost exclusively obtained in 50% yield.

It remained to determine whether trienone **13** could undergo the IMDA cyclization, bearing in mind that the presence of the gem-dimethyl group on the dienophile substructure would slow down the rate of cycloaddition.[17] The addition to **11** of 2-methylpropenyllithium, generated from *t*-BuLi and 1-bromo-2-methylpropene, and subsequent oxidation with the Dess-Martin reagent provided trienone **13**. Attempts to accomplish the cycloaddition under both thermal and Lewis-acid catalyzed conditions failed to give the desired product. Thus, when **13** was heated at 180°C for three days, the starting material was recovered unchanged. In the same manner, treatment of **13** with BF_3-Et_2O in CH_2Cl_2 was also ineffective, and the starting trienone was again unaltered. The greater steric demands imparted by the gem-dimethyl group on the transition state are sufficient to impede the cyclization. In order to overcome this difficulty, preparation of a trienone such as **15** with a doubly activated dienophile is now in progress.

In conclusion, a new approach to the chiral tricyclic system of forskolin which combines introduction of carbon chains at C-1 and C-2 of galactal with IMDA cyclization has been developed.

References and notes

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8 While this starting material is commercially available, its price is rather exorbitant. We therefore prepared it according to the described procedure: Kozikowski, A. P.; Jaemoon, L. *J. Org. Chem.* **1990**, *55*, 863-870.

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11 All new compounds are fully characterized by their spectroscopic and analytical data. **14:** $[\alpha]_D$ =-38 (c=7.8, $CHCl_3$). IR (CCl_4) ν_{max} : 1713 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ : 0.80 (s, 3H, Me-10) ; 1.07 (s, 9H, 3Me, OTDPS) ; 1.60-1.64 (m, 1H) ; 1.70-1.80 (m, 1H) ; 1.88-2.00 (m, 1H) ; 2.10-2.20 (m, 2H) ; 2.24 (dd, J = 13,0 Hz and 3.1 Hz, 1H, H-3) ; 2.58-2.70 (m, 2H, H-7 and H-5) ; 3.70-3.82 (m, 3H, H-8 and H-15) ; 4.33-4.42 (m, 1H, H-13) ; 5.73-5.78 (m, 2H, H-1 and H-2) ; 5.88-5.92 (m, 1H, H-12) ; 6.05 (dt, J = 10.3 Hz and 1.9 Hz, 1H, H-11);7.38-7.50 (m, 6H); 7.66-7.80 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$ δ : 19.1 (s, OTDPS) ; 22.0 (q, Me)-10) ; 23.6 (t, C-4) ; 24.7 (t, C-3) ; 26.8 (q, 3Me, OTDPS) ; 35.8 (s, C-10) ; 43.9 (d, C-9) ; 45.1 (t, C-7) ; 57.7 (d, C-5) ; 65.6 (t, C-15) ; 68.0 (d, C-8) ; 74.5 (d, C-13) ; 126.0 (d) ; 126.5 (d) ; 127.7 (d, 4CH ar.) ; 128.3 (d) ; 129.70 (d, ar.) ; 129.75 (d, ar.) ; 132.9 (d) ; 133.0 (s, ar.) ; 135.0 (s, ar.) ; 135.6 (d, 2CH ar.) ; 218.5 (s, C=O). Ms (CI,NH_3) m/z (%) 504 (23) $(M+NH_4)^+$, 410 (33), 409 (100).

12 The next steps were performed on this mixture, the asymmetry at this center being destroyed later in the synthesis.

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17 For an example of IMDA cyclization with a gem-dimethyl on the diene see: Bonnert, R. V.; Jenkins, P. *J. Chem. Soc. Perkin Trans. 1* **1989**, 413-418.

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