ChemComm

Short cuts toward forskolin synthesis: a pentacyclic approach†

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Received (in Cambridge, UK) 6th June 2000, Accepted 11th July 2000
First published as an Advance Article on the web 25th August 2000

A practical synthetic route for the preparation of forskolin intermediate 20 is described. Previously reported lactone 3 was converted to 20 through intermediate 16. The main feature of this work lies in the formation and the cleavage of a tetracyclic intermediate for the stereochemical control in the formation of the tricyclic core of forskolin.

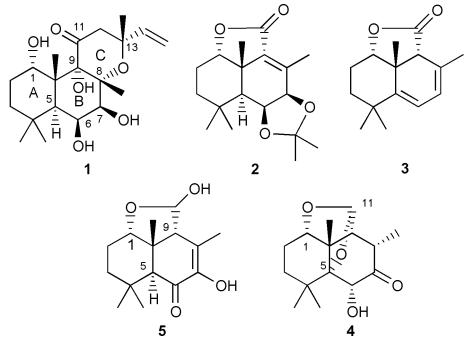
Forskolin **1**,[1] a labdane diterpene isolated from the roots of the Indian plant *Coleus forskolii*, has emerged as a highly attractive target for total[2] and partial[3] synthetic investigations. Besides the challenging structure of this natural product, its biological and therapeutic potential, mainly in the cardiovascular area,[4] has encouraged the efforts of numerous synthetic chemistry groups all over the world.

However, despite the diversity of the synthetic schemes used in the early steps of these studies, most of them have emphasized the so called 'Ziegler intermediate', **2** (Scheme 1), as the most versatile synthon for further synthetic strategies aimed at the formation of the tetrahydropyran ring of the target molecule.[5]

In preceding work, we designed several synthetic approaches toward the fully functionalized decalinic system of forskolin (A/B bicycle). Our approaches were mainly based either on the use of pericyclic reactions[6] or on the transformation of lactone **3**,[7] available in enantiomeric pure form.[8] This later methodology led to a highly efficient synthesis of the 'Ziegler intermediate'.[9]

The main original feature of this synthesis relies on the stereochemical control of the ring junction of the bicycle A/B through the formation, in the earlier steps of the synthetic scheme, of an intramolecular ketal **4** of the carbonyl group at C-11. This ketal links C-11 to C-1 and C-5 through an oxygen atom (Scheme 1). A base induced rearrangement of the tetracyclic system of **4** with fragmentation of the tetrahydrofuran ring produced the α-hydroxyketone **5** with complete stereocontrol of the asymetric centers C-1, C-5, C-9 and C-10 under thermodynamic conditions.

In order to design a more straightforward route to forskolin, we have investigated the possibility of formation of the tetrahydropyran ring C of **1** in an early stage of the synthesis, through introduction of the three missing carbon atoms as an allyl residue at the beginning of the synthetic sequence.



Scheme 1

Lactone **3** was first submitted to the previously described regioselective epoxidation procedure (MCPBA, CH_2Cl_2, 92%) to produce known epoxide **6**.[9a] Then the Grignard addition of allylmagnesium bromide stereoselectively produced hemiketal **7**, having the three required carbons. Hemiketal **7** was in turn converted into tetracyclic ketal **8** upon treatment with silica gel under sonication (Scheme 2, 86% from **6**) using our previously reported strategy.[9]

Epoxidation of both double bonds was then performed in a one-pot procedure using an excess of peracid; diepoxide **9a**,**b** was obtained in 76% yield (MCPBA, 4 eq., CH_2Cl_2, rt) as a mixture (1:1) of epimers at C-13. Then, reduction of **9** by lithium aluminium hydride led in high yield to the reductive opening of the more reactive 13,14-epoxide, while the basicity of the reaction conditions allowed a Payne-like rearrangement of the 8-hydroxy-6,7-epoxide and gave 6α-alcohol **10a**,**b**.

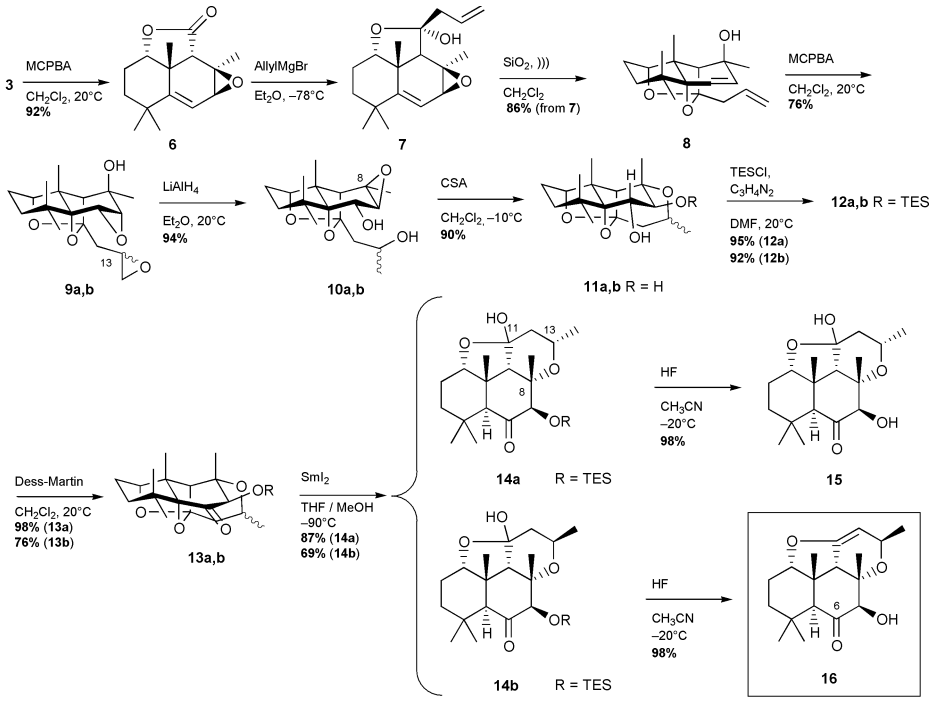
The key step in this sequence of reactions was the acid catalyzed formation of the tetrahydropyran ring C of the target molecule (camphorsulfonic acid, CH_2Cl_2, −10 °C, 90%), which resulted in a stereoselective inversion of the configuration at C-8 (Scheme 2), leading to the pentacyclic diols **11a**† and **11b** which can be separated by careful chromatography. The following steps were thus performed on both epimers separately. The two equatorial hydroxy groups at C-6 and C-7 were easily differentiated according to their steric hindrance: etherification with one eq. of chlorotriethylsilane (imidazole, DMF, 95%) yielded the formation of the mono-silyl ether at C-7 **12a** and **12b**. Then, **13a** and **13b** were synthesized through oxidation with Dess–Martin's periodinane (CH_2Cl_2, rt). Thereafter, extensive experimental investigations using various reaction conditions allowed the emergence of samarium(II) iodide as the best reducing agent to perform the desired cleavage of the C–O bond at C-5, thus leading to the formation of hemiketals **14a** and **14b** in 70% yield [5 eq. SmI_2, THF–MeOH (50:1) 13 mM, −90 °C, hydrolysis and extraction performed at pH 7.4, phosphate buffer].

At this stage of the synthesis, the synthetic aim was to reduce the carbonyl group at C-6 and to cleave the C-11 carbonyl ketal in order to complete the functional elaboration of ring C of forskolin.

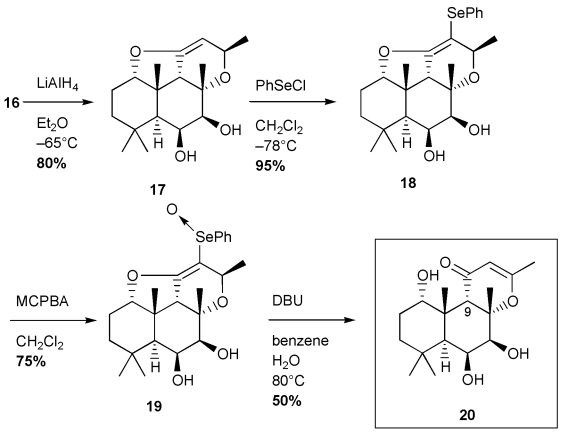
Treatment with hydrofluoric acid in acetonitrile of isomer **14a** cleanly gave the expected free alcohol **15** while isomer **14b**, under similar conditions, produced enol ether **16** in quantitative yield.

Taking advantage of this unexpected dehydration, we completed this approach by reduction of the carbonyl at C-6 ($LiAlH_4$, Et_2O, −65 °C, 85%) to give **17** with the correct diol configurations (Scheme 3). Thereafter, treatment of enol ether **17** with phenylselanyl chloride at low temperature resulted in addition of the phenylselenenyl group at C-12,[10] without cleaving the enol ether. This reaction was assumed to proceed through a two step procedure, consisting of the electrophilic addition of the phenylselanyl moiety, followed by hydrochloric acid elimination. Then, oxidation of the selenium and elimination of the resulting selenoxide under basic conditions led to the formation of the desired dehydro-γ-pyrone **20**.[11] Compound **20** is also the result of a two step reaction, involving hydroxide

DOI: 10.1039/b004515m



Scheme 2



Scheme 3

addition to the activated enol followed by phenylselenenic acid elimination.

In summary, we have developed a practical, stereoselective synthetic route to analogs of 9-deoxyforskolin and forskolin **1**, taking account of the previous reports dedicated to the introduction of the vinyl group at C-13 as a cuprate,[2c] and of the hydroxy group at C-9.[12]

Notes and references

† CCDC 182/1719. See http://www.rsc.org/suppdata/cc/b0/b004515m/ for crystallographic files in .cif format.

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11 (400 MHz, $CDCl_3$) δ_H(ppm): 5.08 (br s, H-12), 4.46 (br s, H-7), 4.12 (br t, 4 Hz, H-1β), 3.53 (d, 4 Hz, H-6), 2.50 (s, H-9), 2.03 (m, 2H, H-2), 1.61 (s, 3H), 1.46 (s, 3H), 1.33 (s, 3H), 1.19 (s, 3H), 1.05 (s, 3H). CIMS, (NH_3): 342 (M + NH_4^+), 325 (MH^+).

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