# Efficient Access to the 'Ziegler Intermediate' in the Total Synthesis of Forskolin

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Lactone **3**, easily prepared from hydroxy-β-ionone, is transformed into the Ziegler intermediate in forskolin synthesis by a straightforward strategy involving two new rearrangements.

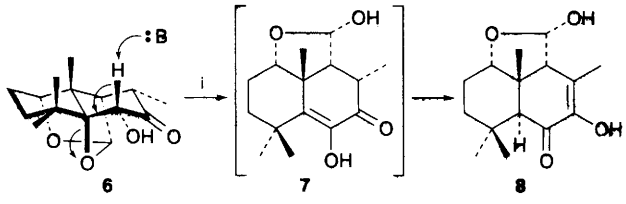
We have focused our attention for several years on the development of synthetic approaches towards the preparation of key intermediates in the synthesis of the highly oxygenated diterpene forskolin **1**. At this time three different routes have successfully synthesised this molecule,[1] two of them proceeding through the intermediate **2**. This key intermediate was first synthesised by Ziegler *et al.* and several formal syntheses of forskolin have been achieved by different preparations of this compound.[2]

In previous work we have described an efficient preparation of the tricyclic lactone **3** in racemic[3] and optically pure forms.[4] Here, we describe a new, short and simple methodology to obtain the Ziegler key intermediate involving this material.

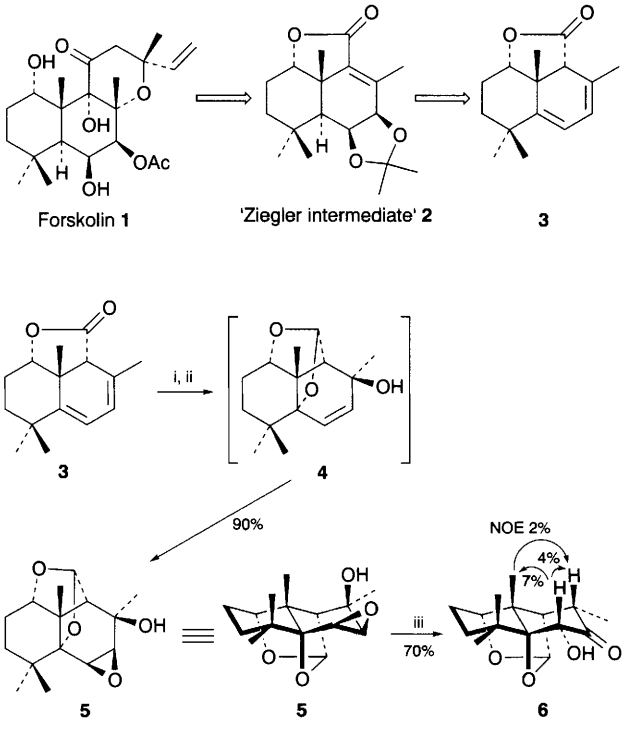
The DIBAL-H reduction of lactone **3**, followed by prolonged exposure of the obtained lactol to an excess (3 equiv.) of MCPBA resulted in the tricyclic epoxide–alcohol **5** *via* intermediate **4** in 90% overall yield. Compound **4** can be isolated when 1 equiv. of MCPBA is used. A compound similar to compound **4** (opposite configuration at C-8) was obtained by Cha *et al.*[5] in the epoxidation of the lactol with *tert*-butylhydroperoxide in the presence of $VO(acac)_2$. In an attempt to open the epoxide ring by aqueous acidic treatment ($HClO_4$ in THF), **5** was transformed into the hydroxy-ketone **6** by an unexpected rearrangement. The $^1H$ NMR spectrum of the resulting material had a methyl doublet at $\delta$ = 1.22 (*J* 6.9 Hz). The $^{13}C$ NMR spectrum showed the presence of a keto group. Exhaustive homo- and hetero-nuclear 2D NMR studies confirmed the proposed structure **6**.† The stereochemistry at the 6-OH and 8-Me in **6** was assigned on the basis of nuclear Overhauser effects between 6-H and 8-H, 6-H and the angular 10-Me and between 8-H and 10-Me. We think that this reaction occurs through the conversion of the epoxide ring of **5** into an intermediate diol,[6] which, by protonation of the tertiary 8-OH followed by hydride migration from position 7 to position 8, leads to compounds **6**.

Treatment of **6** with base (DBU) led to diosphenol **8** in 82% yield *via* a second reaction in which the abstraction of hydrogen 6-H triggers the fragmentation of the tetrahydrofuran ring resulting in intermediate diosphenol **7**, which, in turn, is transformed into the more stable diosphenol **8**. A hydrogen atom has been introduced at the ring junction resulting in a stereochemistry which was later proved correct. Only one lactol was obtained with a coupling constant of 5.2 Hz between 10-H and 11-H.

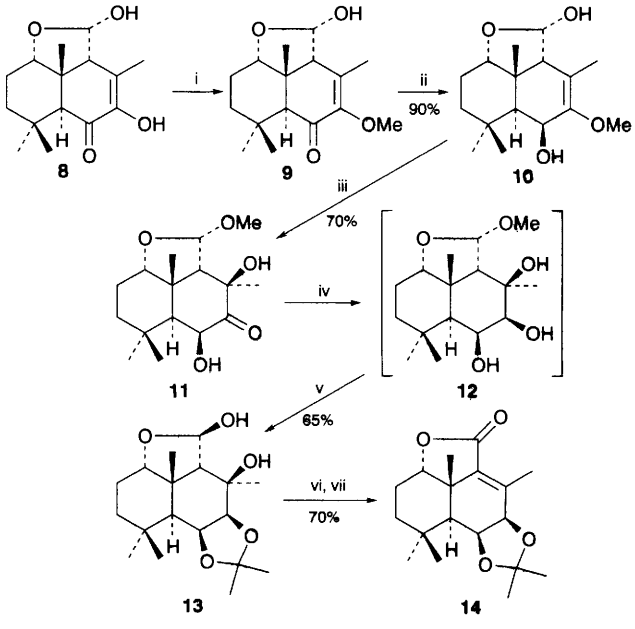
Methylation of the OH groups of **8** (MeI, NaH, 3 equiv. in THF) to give **9**, followed by reduction (DIBAL-H, 1.5 equiv. in THF, 0 °C–room temp., 2 h) led to compound **10**.‡ The ketodiol **11** was obtained by epoxidation of **10** with aqueous MCPBA in ethanol (in the presence of 0.5 equiv. of $Na_2CO_3$). Reduction ($NaBH_4$ in ethanol, 0 °C) to give **12** then protection of the diol




**Scheme 2** *Reagents and conditions*: i, DBU (3 equiv.), benzene, 80 °C, 2 h




**Scheme 1** *Reagents and conditions*: i, DIBAL-H, THF, 0 °C; ii, MCPBA (3 equiv.), $CH_2Cl_2$, 48 h; iii, $HClO_4$ (1.3 equiv.), THF, 2.5 h at 50 °C then 20 h at room temp.




**Scheme 3** *Reagents and conditions*: i, MeI, NaH (3 equiv.), THF, room temp., 12 h; ii, DIBAL-H (1.5 equiv.), THF, 0 °C–room temp., 2 h; iii, MCPBA (1 equiv.), $Na_2CO_3$ (0.5 equiv.), EtOH/$H_2O$ (1/6), 0 °C–room temp., 2 h; iv, $NaBH_4$ (1 equiv.), EtOH, 0 °C, 1 h; v, *p*-toluenesulfonic acid, 2,2-dimethoxypropane, room temp., 18 h; vi, Jones reagent (1.5 equiv.), acetone, room temp., 1 h; vii, $SOCl_2$ (12 equiv.), pyridine, 0 °C, 1 h

led to **13** in which epimerization of the 11-OMe had occurred. Jones oxidation ($CrO_3$, $H_2SO_4$, 1.5 equiv., in acetone, 0 °C, 1 h), and dehydration ($SOCl_2$, pyridine, 0 °C, 1 h) produced the desired Ziegler intermediate **14** in 15% overall yield from lactone **3** (not optimised). The $^1H$ and $^{13}C$ spectra of this sample were identical to those of a sample prepared by a completely different method[7] and to the data already published.[1]

In conclusion this strategy which involves simple, stereocontrolled reactions and inexpensive reagents and allows an easy and straightforward preparation of an important intermediate in the forskolin synthesis.

*Received, 3rd April 1995; Com. 5/02115D*

## Footnote

† *NMR data* for compound **6**: $\delta_H$ (400 MHz, $CDCl_3$) 5.08 (1 H, s, 11-H), 4.48 (1 H, dd, *J* 1.1, 4.1 Hz, 6-H), 4.01 (1 H, d, *J* 3.0, 1-H), 3.65 (1 H, d, *J* 4.12 Hz, OH), 2.61 (1 H, m, 8-H), 2.22 (1 H, d, *J* 4.3 Hz, 9-H), 1.95 (1 H, m, 3-H), 1.75 (2 H, m, 2-H), 1.45 (3 H, s, 10-Me), 1.22 (3 H, d, *J* 6.9 Hz, 8-Me), 1.20 (3 H, s, 4-Me), 1.12 (3 H, s, 4-Me) and 1.00 (1 H, m, 3-H); $\delta_C$ (100 MHz, $CDCl_3$) 208.6 (C-7), 100.5 (C-11), 87.7 (C-5), 82.3 (C-1), 78.2 (C-6), 60.3 (C-9), 47.5 (C-10), 39.0 (C-8), 35.8 (C-4), 31.9 (C-3), 28.8 (4-Me), 22.0 (4-Me), 21.6 (C-2), 14.4 (10-Me) and 12.8 (8-Me).

‡ For compound **10**: $\delta_H$ (400 MHz, $CDCl_3$) 4.61 (1 H, d, *J* 5 Hz, 11-H), 4.47 (1 H, brs, 6-H), 3.85 (1 H, t, *J* 2.5 Hz, 1-H), 3.60 (3 H, s, OMe), 3.37 (3 H, s, OMe), 2.07 (1 H, d, *J* 5 Hz, 9-H), 1.79 (2 H, m, 2-H), 1.64 (3 H, s, Me), 1.37 (1 H, d, *J* 3.4 Hz, 5-H), 1.23 (3 H, s, Me), 1.17 (3 H, brs, Me), 1.10 (2 H, m, 3-H) and 0.98 (3 H, s, Me); $\delta_C$ (50 MHz, $CDCl_3$) 151.0 (C-8), 114.8 (C-7), 109.4 (C-11), 83.4 (C-1), 64.9 (C-6), 63.2 (C-9), 58.04 (OMe), 55.8 (OMe), 46.6 (C-5), 42.8 (C-10), 37.2 (C-3), 33.2 (C-4), 31.7 (Me), 22.9 (Me), 22.0 (C-2), 19.6 (Me) and 14.9 (8-Me).

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