The Intramolecular Nitrile Oxide Cycloaddition Route to Forskolin

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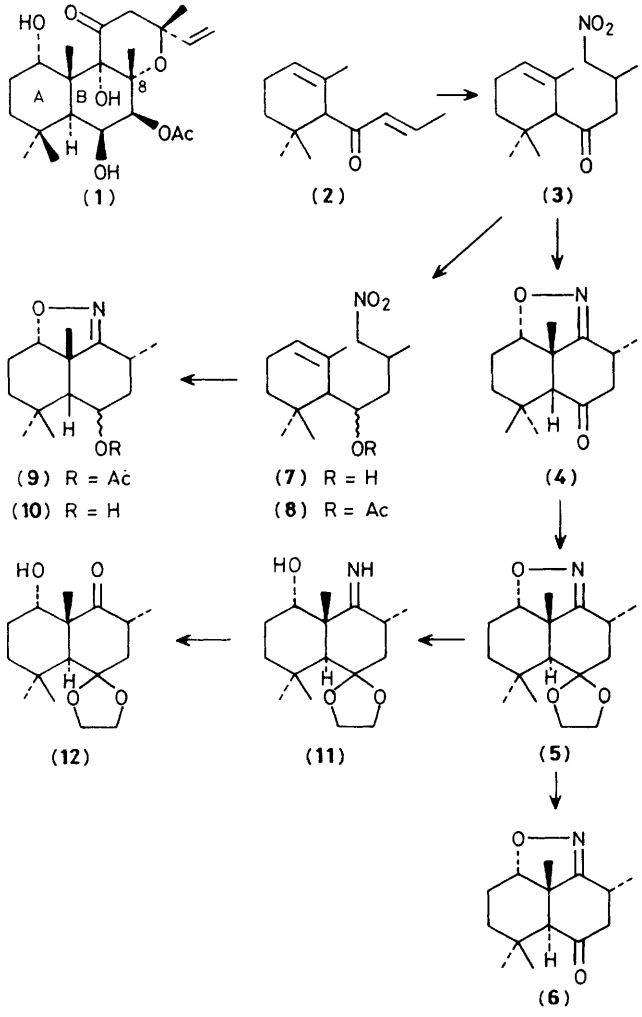
A strategy for the construction of the AB ring system of forskolin based on [3 + 2] nitrile oxide intramolecular cycloaddition is reported.

Forskolin (**1**), the major diterpenoid isolated from the Indian plant *Coleus forskohlii*,[1] is a challenging synthetic target owing to its unusual structure with the presence of eight asymmetric centres, the high degree of functionalization and, last but not least, the important biological properties.[2] Recently three conceptually similar approaches to a functionalized AB ring system of (**1**), based on the use of an intramolecular Diels–Alder reaction have been reported,[3–5] prompting us to describe our preliminary results in this area. Our strategy involves the utilization of intramolecular nitrile oxide cycloaddition, a reaction employed in the synthesis of natural products only comparatively recently,[6] but continuously growing in both popularity and practicability.[7]

Commerically available α-damascone (**2**) underwent tetramethylguanidine-catalysed nitromethane addition to afford a 95% yield of the Michael adduct (**3**).† Treatment of (**3**) under Mukaiyama conditions[8] for generating a nitrile oxide furnished a 20% yield of (**4**) [m.p. 95—97 °C (from light petroleum)], in which some of the required stereochemistry has been introduced. However, the *cis*-ring junction is clearly not required in the final molecule, but epimerization to the *trans*-decalin could be envisaged by taking advantage of the suitably located carbonyl group. The stereochemistry of the methyl group at C-8 is controlled by a sterically less congested transition state, which minimizes methyl–methyl interaction.[7] It poses no problem since further elaboration will require the formation of a double bond between this centre and C-7.

Acetalization of (**4**) under standard conditions proceeded with concomitant epimerization to give (**5**) [m.p. 73—74 °C (from n-pentane)] in 55% yield. Removal of the acetal moiety by the usual aqueous acid treatment led quantitatively to the *trans*-fused ketone (**6**) [m.p. 117—118 °C (from Et_2O–light petroleum, 1 : 1)]. Alteration of the molecule to produce a more favourable geometry for the cycloaddition step was



† All new compounds gave satisfactory spectral and analytical data. Yields are not optimized.

achieved by reducing (**3**) to the alcohol (**7**) (AlH_3; Et_2O; 0 °C). The corresponding acetyl derivative (**8**), obtained quantitatively by a standard procedure (Ac_2O; pyridine; room temp.; 6 h), underwent intramolecular cycloaddition on the trisubstituted double bond (PhNCO; Et_3N; 80 °C; 48 h) to afford a 90% yield of (**9**) as a mixture of diastereoisomers. Saponification (K_2CO_3; MeOH–H_2O, 3 : 1; reflux; 4 h) gave the alcohol (**10**), which, without purification, was transformed by Moffatt oxidation into an inseparable mixture (1 : 1) of ketones (**4**) and (**6**), which was directly acetalized to produce (**5**) in a less straightforward but more convenient pathway.

Unmasking of the heterocyclic nucleus to reveal the β-hydroxy ketone by known hydrogenolytic methods[9] preserving the protective group (W-2 Raney nickel, acetic acid or boric acid) led surprisingly to the isolation of the stable β-hydroxy imine intermediate (**11**) (m.p. 99—100 °C‡) which, however, can be hydrolysed to the crucial intermediate (**12**) [m.p. 103—104 °C (from n-pentane)] by stirring for 12 h in the presence of SiO_2. In conclusion a highly functionalized AB ring system along the route to forskolin (**1**) has been synthesized, and its elaboration to the target compound is currently under active investigation.

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‡ To the best of our knowledge this is first example of isolation of the labile β-hydroxy imine intermediate during the transformation of Δ^2-isoxazolines to β-hydroxy ketones.

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