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## 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.<sup>2</sup> 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.<sup>7</sup>

methylguanidine-catalysed nitromethane addition to afford a 95% yield of the Michael adduct (3).† Treatment of (3) under Mukaiyama conditions8 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.<sup>7</sup> It poses no problem since further elaboration will require the formation of a double bond between this centre and C-7.

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<sub>2</sub>O-light petroleum, 1:1)]. Alteration of the molecule to produce a more favourable geometry for the cycloaddition step was

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NO<sub>2</sub> Commerically available  $\alpha$ -damascone (2) underwent tetra-(9) R = Ac (7) R = H(10) R = H(8) R = Ac HO NH Acetalization of (4) under standard conditions proceeded (12)(11)(6)

<sup>†</sup> All new compounds gave satisfactory spectral and analytical data. Yields are not optimized.

achieved by reducing (3) to the alcohol (7) (AlH<sub>3</sub>; Et<sub>2</sub>O; 0 °C). The corresponding acetyl derivative (8), obtained quantitatively by a standard procedure (Ac<sub>2</sub>O; pyridine; room temp.; 6 h), underwent intramolecular cycloaddition on the trisubstituted double bond (PhNCO; Et<sub>3</sub>N; 80 °C; 48 h) to afford a 90% yield of (9) as a mixture of diastereoisomers. Saponification (K<sub>2</sub>CO<sub>3</sub>; MeOH-H<sub>2</sub>O, 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<sup>9</sup> 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<sub>2</sub>. 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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<sup>‡</sup> To the best of our knowledge this is first example of isolation of the labile  $\beta$ -hydroxy imine intermediate during the transformation of  $\Delta^2$ -isoxazolines to  $\beta$ -hydroxy ketones.