Novel nitrile oxide cycloaddition approach towards papuamine: stereoselective synthesis of a potentially useful *trans*-hydrindane intermediate

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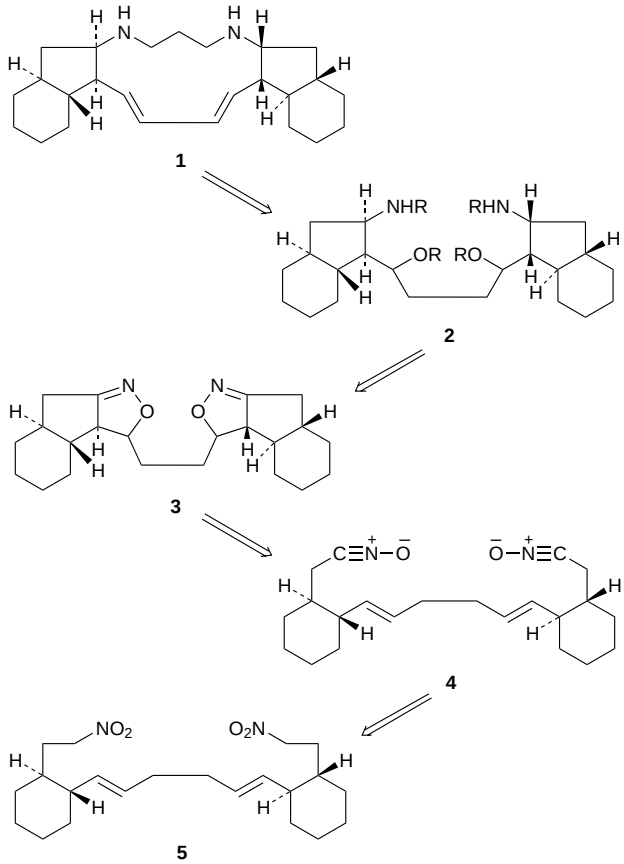
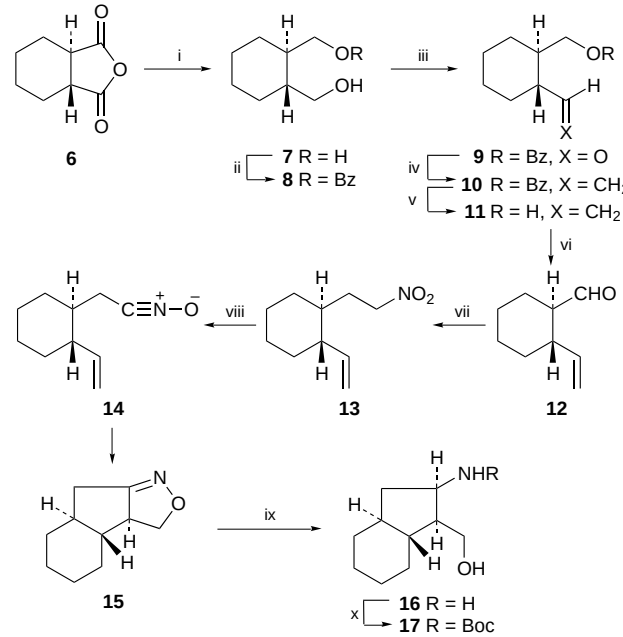
In a potentially useful approach to the marine alkaloid papuamine 1, a known *trans*-hydrindane intermediate 17 has been synthesised in racemic form using a model sequence of reactions involving a nitrile oxide cycloaddition as a key step.

Papuamine **1**, a unique C_2-symmetric pentacyclic alkaloid, was isolated from the marine sponge *Haliclona sp*.[1,2] The presence of two disubstituted *trans*-hydrindane units of identical chirality and a central diazadiene ring makes papuamine a challenging target for synthesis. A crucial task in such a synthesis is the stereoselective construction of the disubstituted *trans*-hydrindane unit incorporating four chiral centres. Three recent syntheses[3–5] of optically active papuamine have solved this problem either by reductive amination of suitably substituted *trans*-hydrindanone derivatives[3,4] or by utilising a highly stereoselective iminoene reaction.[5] We envisaged a novel and expedient strategy (Scheme 1) towards **1** involving the intramolecular cycloaddition of the bis-nitrile oxide **4** to give a bis-isoxazoline derivative **3**, which could be elaborated to the papuamine skeleton by reductive cleavage to **2** followed by the incorporation of a C_3-unit. The future success of this approach is critically dependent on the fidelity of the sequence **4** → **3** → **2**. We herein report an unusually simple but efficient synthesis of a racemic *trans*-hydrindane intermediate **17**, which is the racemate of an intermediate used[3] for papuamine, *via* the model sequence of conversions **14** → **15** → **17** involving a highly stereoselective, intramolecular, nitrile oxide cycloaddition and subsequent reduction of the isoxazoline ring (Scheme 2).



Scheme 1

The diol **7**, which was easily obtained from (±)-**6** by reduction with $LiAlH_4$, was monobenzoylated and the resulting alcohol **8**† was oxidised[6] with PCC to the aldehyde **9**. Wittig methylenation of **9** gave the olefinic ester **10**, which on deprotection furnished the alcohol **11**. Oxidation of **11** by PCC led to the aldehyde **12**, which was converted to the nitro compound **13** *via* a known protocol[7] involving reaction with nitromethane, acetylation and reduction with sodium borohydride without purification of any of the intermediate products. The conversion of **6** to **12** was effected *via* the above route in order to adapt this strategy for preparing enantiomerically pure intermediates required for the synthesis of optically active papuamine. The construction of the crucial *trans*-hydrindane skeleton was then achieved by the treatment of **13** with phenyl isocyanate leading to the formation of the nitrile oxide **14**, which underwent cycloaddition to furnish the isoxazoline **15**‡ as the exclusive product. The gross structure of **15** was



Scheme 2 *Reagents and conditions*: i, $LiAlH_4$, THF, 90%; ii, NaH (1 equiv.), then BzCl (1 equiv.), 82%; iii, PCC, neutral alumina, CH_2Cl_2, 96%; iv, $Ph_3PMe^+I^-$, BuLi, THF, 70%; v, NaOH, MeOH, H_2O, 96%; vi, PCC, neutral alumina, CH_2Cl_2, 92%; vii, CH_3NO_2, KF, then Ac_2O, then $NaBH_4$, EtOH (68% overall); viii, PhNCO, C_6H_6, 72%; ix, $LiAlH_4$, Et_2O, 88%; x, Boc_2O, EtOAc, 90%

established on the basis of ^1H and ^{13}C NMR spectral data. The stereochemistry of the newly formed chiral centre in the isoxazoline ring could not be determined unambiguously from the spectral data, although it could be tentatively assigned on the basis of the stereochemical outcome observed in the cycloaddition of analogous nitrile oxides.[8] The unambiguous assignment of the structure of **15** was provided by its reductive cleavage with $LiAlH_4$, resulting in the formation of the amino alcohol **16**, which was isolated as the Boc derivative **17**. A comparison of the IR, ^1H and ^{13}C NMR spectra of **17** with those of an intermediate reported[3] by Barrett *et al*. established the identity of the two derivatives. The high stereoselectivity observed in the reduction of the isoxazoline ring in **15** was in accord with the results obtained in similar reductions with $LiAlH_4$.[9]

The fact that the corresponding *N*-deprotected *O*-benzylated derivative of **17** was involved in the synthesis[3] of papuamine by Barrett *et al.* indicates the practical importance of the strategy. Moreover, since the work described above established the successful conversion of **13** to **16**, the synthesis of papuamine **1** from **5** appears to be a distinct possibility and is in progress.

We are indebted to Professor A. G. M. Barrett for providing the copies of the IR, ^1H and ^{13}C NMR spectra of **17**. A. S. gratefully acknowledges the award of a Research Associateship by CSIR, India. We are grateful to Dr A. Patra for the 300 MHz ^1H NMR spectrum of **17**. Thanks are due to Mr P. P. Ghosh Dastidar, Dr R. C. Yadav and Dr R. Mukhopadhyay for NMR and mass spectral analyses.

Footnotes

† All new compounds were liquids and were characterised by GC, IR, mass, and ^1H NMR spectral analyses; satisfactory ^{13}C NMR spectral data were recorded for **10**, **13**, **15** and **17**. The 300 MHz ^1H NMR and a 25 MHz ^{13}C NMR spectra of compound **17** were identical with those provided by Professor Barrett.

‡ *Selected spectral data* for **15**: ^1H ($CDCl_3$; 100 MHz): δ 2.48–2.84 (m, 1 H), 3.20–3.52 (m, 1 H), 3.80 (dd, *J* 8 and 12 Hz, 1 H) and 4.48 (dd, *J* 8 and 10 Hz, 1 H); ^{13}C ($CDCl_3$; 25 MHz): δ 25.8, 25.9, 27.7, 30.7, 31.4, 49.4, 49.9, 61.3 and 170.7.

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