A Stereoselective Total Synthesis of Dasycarpidan Alkaloids: (±)-Dasycarpidone, (±)-Dasycarpidol and (±)-Nordasycarpidone

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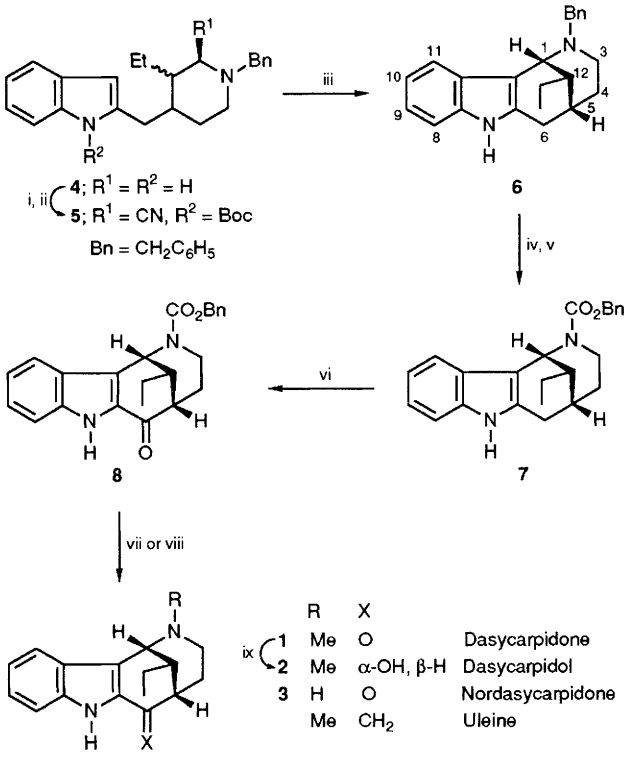
A stereoselective total synthesis of the dasycarpidan alkaloids dasycarpidone **1**, dasycarpidol **2** and nordasycarpidone **3** has been achieved from the tetracyclic intermediate **6**, the key step being the oxidation of the C-6 methylene group.

Several total syntheses[1–4] of the indole alkaloid dasycarpidone **1** and only one synthesis[4] of the alkaloid nordasycarpidone **3** have been accomplished since their structural elucidation in 1965.[5] However, the overall yields are low and, with only one exception,[4] the epimer at C-12 is the preponderant product. No synthesis of dasycarpidol **2**[5] has been described yet.

In this communication we report a stereoselective and efficient total synthesis of the above-mentioned alkaloids **1–3**. The control of the relative stereochemistry at C-12 was achieved[6] during the cyclization step to the tetracyclic derivative **6**: the piperidine *cis*-**4** was converted to a C-3 epimeric mixture of 2-cyanopiperidines **5**, whose cyclization by way of an iminium cation under equilibrating acidic conditions led to the dasycarpidan-type compound **6**, having the required relative stereochemistry at C-12, *i.e.* with the ethyl substituent equatorial with respect to the piperidine ring. It is worth mentioning that a similar iminium ion cyclization from a 2-acylindole analogue derivative has been reported to lead to the C-12 epimeric derivative as the major product and that attempts to induce epimerization at C-12 failed.[1]

The conversion of the key tetracyclic derivative **6** to the target natural products required two synthetic transformations: oxidation of the C-6 methylene group and removal (or exchange) of the nitrogen substituent. Although the oxidation of 2-alkylindoles to the corresponding 2-acylindoles is a known process,[7] attempts to convert the tetracyclic amine **6** to the corresponding 2-acylindole were unsuccessful. For this reason the basic nitrogen was protected as benzyl carbamate. This protection was not effected directly because it is known that gramine-type compounds undergo fragmentation when treated with acylating agents.[8] However, debenzylation of **6** followed by benzyloxycarbonylation of the resulting unstable secondary amine gave carbamate **7**† in 50% overall yield. As expected, oxidation of **7** with selenium dioxide[9] furnished the corresponding 2-acylindole **8** in acceptable yield, without any degree of epimerization at C-12. Removal of the benzyl carbamate protecting group of **8** by catalytic debenzylation, followed by *in situ* methylation of the resulting secondary amine, gave (±)-dasycarpidone **1**, ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_c 11.6 (Me), 24.8 (CH_2), 30.1 (C-4), 44.0

† All new compounds gave satisfactory analytical and spectral data. All yields are from material purified by flash chromatography.



Scheme 1 *Reagents and conditions*: i, $(Boc)_2O$, 50% aq. NaOH, Bu_4NHSO_4, toluene, room temp.; ii, 3-chloroperoxybenzoic acid, CH_2Cl_2, 0 °C, 1 h; then trifluoroacetic anhydride, −15 °C, 1 h; then aq. KCN, NaOAc, pH 4–5, 30 min; iii, AcOH–H_2O–dioxane (3:1:1), 90 °C, 14 h, 28% from **4**; iv, H_2, $Pd(OH)_2$, MeOH; v, $ClCO_2CH_2C_6H_5$, K_2CO_3, CH_2Cl_2 (two steps, 50%); vi, SeO_2, dioxane, 80 °C, 40 h (43%); vii, H_2, Pd-C, MeOH, aq. HCHO (**1**:76%); viii, $BF_3{\cdot}Et_2O$, Me_2S, CH_2Cl_2, room temp. (**3**:73%); ix, $NaBH_4$, MeOH, 6 h, room temp., **2** 61%, and its C-6 epimer 24%

(NMe), 46.0 (C-3), 46.3 (C-5), 49.6 (C-12), 56.2 (C-1), 112.7 (C-8), 119.9 (C-11b), 121.1 (C-10), 122.0 (C-11), 126.9 (C-9), 127.8 (C-11a), 132.9 (C-6a), 138.1 (C-7a), 193.5 (C-6), which showed it to be identical with a sample provided by Professor J. A. Joule (University of Manchester). The relative configuration at C-12 was evident from the chemical shift of C-4 as compared with δ 29.4 for the deethyl analogue.[10]

Reduction of **1** with sodium borohydride led stereoselectively to (±)-dasycarpidol **2**, which exhibited δ_C (50.3 MHz, $CDCl_3$) 11.8 (Me), 23.2 (CH_2), 25.3 (C-4), 35.4 (C-5), 44.2 (NMe), 46.1 (C-3), 47.3 (C-12), 56.0 (C-1), 65.1 (C-6), 105.0 (C-11b), 111.0 (C-8), 119.4 (C-11), 119.7 (C-10), 121.8 (C-9), 128.7 (C-11a), 136.4 (C-6a), 137.1 (C-7a). The coupling constant (*J* 5.7 Hz) of the doublet at δ 5.07 corresponding to H-6 in the ^1H NMR spectrum clearly indicated the formation of the natural *cis* H-5/H-6 stereoisomer.‡

Finally, cleavage of the benzyl carbamate group of **8** with boron trifluoride–ether and dimethyl sulphide gave (±)-nordasycarpidone **3**, which exhibited δ_C (50.3 MHz, $CDCl_3$) 11.5 (Me), 25.0 (CH_2), 30.2 (C-4), 37.2 (C-3), 47.4 (C-12), 49.0 (C-1 and C-5), 113.0 (C-8), 120.8 (C-10), 121.0 (C-11), 123.8 (C-11a), 125.1 (C-11b), 127.0 (C-9), 132.9 (C-6a), 139.0 (C-7a), 193.9 (C-6). Given that dasycarpidone had been previously converted to uleine,[1] this synthesis also represents a stereoselective formal total synthesis of the latter alkaloid.

We are grateful to Professor J. A. Joule for a sample of (±)-dasycarpidone. Financial support from the DGICYT, Spain (project PB88-0316) is gratefully acknowledged. Thanks are also due to the Departament d'Ensenyament (Generalitat de Catalunya) for a fellowship to one of us (J. G.).

Received, 26th July 1991; Com. 1/03857E

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‡ The epimer at C-6 was also isolated as a minor product. The ^1H NMR spectrum of this compound shows a singlet at δ 4.66 for H-6.