N-Substituted Pyrrolidin-3-ones as Heterocyclic Building Blocks. Enantioselective Synthesis of 8-Epi- and 1,8,8a-Triepi-castanospermine

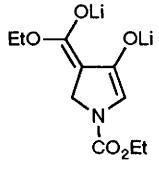
Timothy Gallagher,*[a] Melvyn Giles,[a] R. Sankara Subramanian[a] and Michael S. Hadley[b]

[a] *School of Chemistry, Bath University, Bath BA2 7AY, UK*
[b] *SmithKline Beecham Pharmaceuticals, The Pinnacles, Harlow CM19 5AD, UK*

Regioselective aldol reaction of dianion **1** with aldehyde **5** provides the basis of a new approach to the construction of polyhydroxy indolizidines and the application of this methodology to the synthesis of 8-epicastanospermine **11** and 1,8,8a-triepicastanospermine **12** is described.

We have recently described the generation of the β-ketoester dianion **1** which serves as a functional equivalent of the C-2 enolate **2** of *N*-ethoxycarbonylpyrrolidin-3-one.[1] Although enolate **2** is not easily accessible by conventional enolization techniques[2] this methodology provides an efficient means of constructing 2-substituted 3-hydroxypyrrolidines. This heterocyclic fragment is also present as an integral component of a number of important synthetic targets and in this communication we describe the application of **1** to the synthesis of polyhydroxy indolizidines related to castanospermine **3**.[3] This alkaloid, which is a potent glycosidase inhibitor, has attracted interest as a potential antiviral agent and a number of synthetic studies directed towards castanospermine and its derivatives have been described.[4]

Our general synthetic strategy is based on recognising the relationship of the 1,3-diol function (at C-1 and C-8) of castanospermine to an aldol adduct formally derived from the C-2 enolate **2** and an appropriately substituted aldehyde. The



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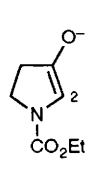

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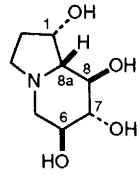

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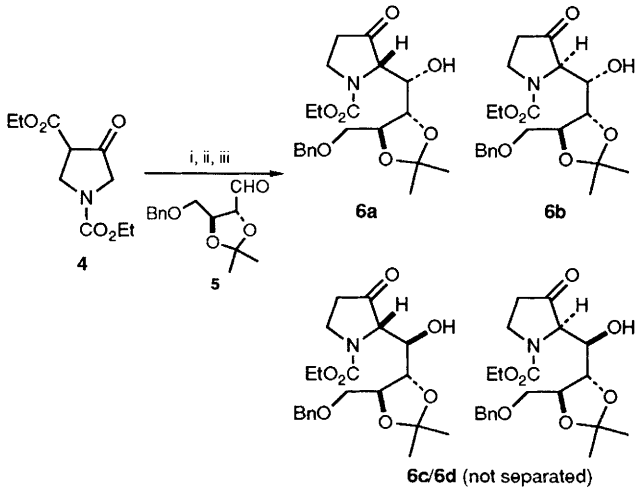
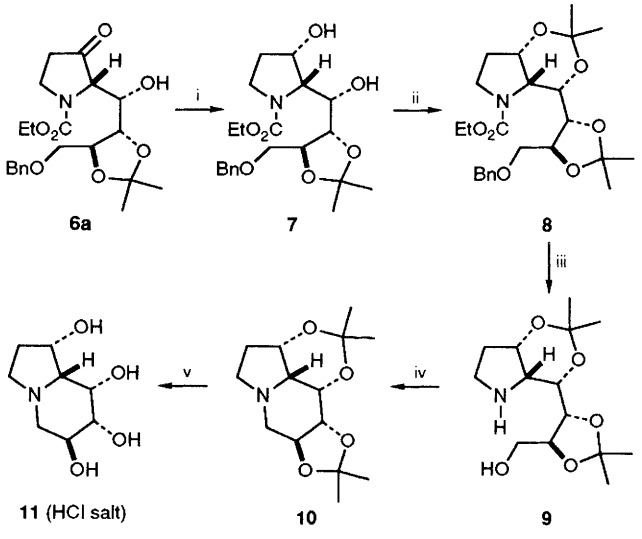
aldol sequence was implemented as shown in Scheme 1.† Double deprotonation of β-ketoester **4** followed by regioselective condensation of the resulting dianion with aldehyde **5**[5] [prepared in four steps from (*R*,*R*)-diethyl tartrate] gave,

† All new compounds gave satisfactory spectral data (IR, ^{1}H and ^{13}C NMR) and were further characterised by elemental analysis and/or high resolution mass measurement; all yields refer to isolated material, homogeneous by TLC. For convenience, the numbering system used throughout the text corresponds to castanospermine.

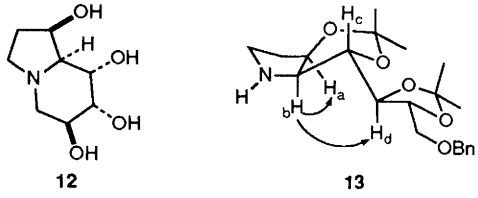


Scheme 1 *Reagents and conditions*: i, Lithium diisopropylamide (LDA), 2 equiv., dimethylpropylene urea (DMPU) [*N*,*N*-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one], THF, −78 to −50 °C; ii, **5**; iii, NaCl, DMSO, H_2O, 130 °C (48% overall)



Scheme 2 *Reagents and conditions*: i, $NaBH_4$, MeOH, 80% ii, $(MeO)_2CMe_2$, *p*-$MeC_6H_4SO_3H$, 77%; iii, KOH propane-1,2-diol, 140 °C, then H_2, Pd/C (61%); iv, PPh_3, CBr_4, $EtNPr^i_2$; v, 2 mol dm^{-3} HCl, then ion exchange chromatography (Dowex 50) (60% from **9**)

after ester cleavage–decarboxylation, the four possible diastereoisomers **6a–d** as a 3 : 3 : 1 : 1 mixture (based on HPLC) in 48% yield.‡ The two major aldol adducts **6a** and **6b** were obtained in pure form by flash chromatography, although stereochemical assignments could not be carried out until a later stage (see below). The stereochemical course of this aldol reaction corresponds to a non-chelation-controlled Felkin–Ahn[6] addition of dianion **1** to aldehyde **5**; similar *anti*-selective nucleophilic additions to **5** have been reported by Mukaiyama.[5] Although **6a** and **6b** do not have the correct stereochemistry required for castanospermine itself, both isomers were carried through to the corresponding polyhydroxy indolizidines. This was done primarily to establish the viability of the overall strategy and is illustrated in detail in Scheme 2 for aldol adduct **6a**.



Reduction of **6a** using $NaBH_4$ (or Bu^i_2AlH) proceeded from the less hindered face of the pyrrolidine ring to give exclusively the *syn*-1,3-diol **7**. This diol function was protected as the corresponding acetonide **8** and then cleavage of the carbamate moiety and hydrogenolysis of the primary benzyl ether gave the crystalline amino alcohol **9**. The structure of **9** was established by X-ray crystallographic analysis[7] and this served to confirm both the stereochemical course of the aldol reaction (Scheme 1) and the subsequent reduction of **6a**. The indolizidine skeleton was then completed by intramolecular *N*-alkylation to give **10** and, finally, cleavage of acetonide protecting groups under acidic conditions gave 8-epicastanospermine **11**, which was isolated as the corresponding hydrochloride salt {m.p. 243–245 °C (methanol); $[\alpha]_D^{19}$ +58.4 (*c* 0.55, H_2O)}.

The sequence shown in Scheme 2 proceeded in 20% overall yield and the other major aldol adduct **6b** was converted to 1,8,8a-triepicastanospermine **12** {m.p. 168–169.5 °C (ethanol); $[\alpha]_D^{22}$ −30.3 (*c* 0.15, H_2O)} in 12% overall yield using essentially the same reaction conditions. Stereochemical assignments in this latter case were less straightforward as none of the intermediates was suitable for crystallographic analysis. However, the 1,8a-*syn*,8,8a-*anti* relationship was readily established by a series of nuclear Overhauser experiments on the rigid bis(acetonide) **13**. Irradiation of H_b resulted in enhancement of the signals due to both H_a and H_d but not of that corresponding to H_c. Furthermore, irradiation of H_c produced no enhancement of either H_a or H_b. Observation of a large coupling ($^3J_{b,c}$ 8.7 Hz) provided additional evidence for a *trans*-relationship between H_b and H_c, with the 1,3-dioxane ring adopting predominantly a twist boat conformation.

In summary, the pyrrolidinone unit **1** forms the basis of an efficient entry to polyhydroxy indolizidines and synthetic access to novel stereoisomers, such as **12**, is of value in this area.§ Although castanospermine itself is commercially available, this molecule still represents an important synthetic challenge within the context of the chemistry described above. To achieve this goal will require a more detailed understanding of the aldol reactivity of dianion **1** and this, and a number of other stereochemical issues, are now being examined.

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‡ HPLC analysis (using Lichrosorb Diol with hexane–propan-2-ol) was carried out after ester cleavage–decarboxylation. As a result, this may not reflect the selectivity exhibited by dianion **1** towards aldehyde **5** but analysis of the crude aldol product was complicated by the presence of both diastereoisomers and enol contributions. Broadening of the ^{1}H NMR spectrum, due to carbamate resonance, precluded direct stereochemical assignment of **6a–d**. Distribution of **6a–d** was sensitive to the solvent used [tetrahydrofuran (THF), Et_2O or 1,2-dimethoxyethane] although isomer **6a** was always a major component.

§ 8-Epicastanospermine **11** has been reported by Ganem[4c] and 6,7-diepicastanospermine (the enantiomer of **12**) has been described by Sih.[4k] 8-Epicastanospermine inhibited β-glycosidase (almond) but was significantly less active than castanospermine itself; 1,8,8a-triepicastanospermine **12** was virtually inactive in this assay. Similar trends were observed for the inhibition of amyloglycosidase (*Aspergillus niger*).

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