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AN ENANTIOSELECTIVE SYNTHESIS OF (+)-CROTANECINE BY AN INTRAMOLECULAR AZIDE 1,3-DIPOLAR CYCLOADDITION

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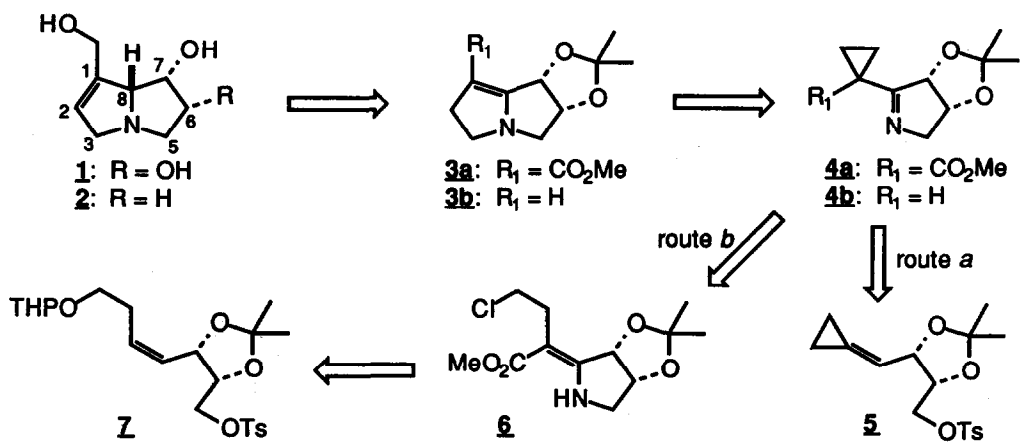
Abstract: An efficient, enantioselective synthesis of (+)-crotanecine (1) has been accomplished by an intramolecular azide [2+3] dipolar cycloaddition starting from 2,3-*O*-isopropylidene-D-erythrose (8).

As a part of our research objectives directed at development of a general synthetic methodology for functionalized indolizidine and pyrrolizidine alkaloids,[1] we have recently reported a practical, stereoselective synthesis of (-)-swainsonine by an intramolecular azide [2+3] dipolar cycloaddition (IAC).[2] As outlined in Scheme I, it appeared to us that a tandem use of the IAC reaction and a cyclopropylimine rearrangement[3] would provide an efficient route to pyrrolizidine alkaloids. Herein we wish to communicate an efficient, stereospecific synthesis of (+)-crotanecine (1).[4] Alkaloids containing the pyrrolizidine nucleus such as 1 and 2 have attracted considerable interest because of their diverse biological activity.[5]

Scheme I

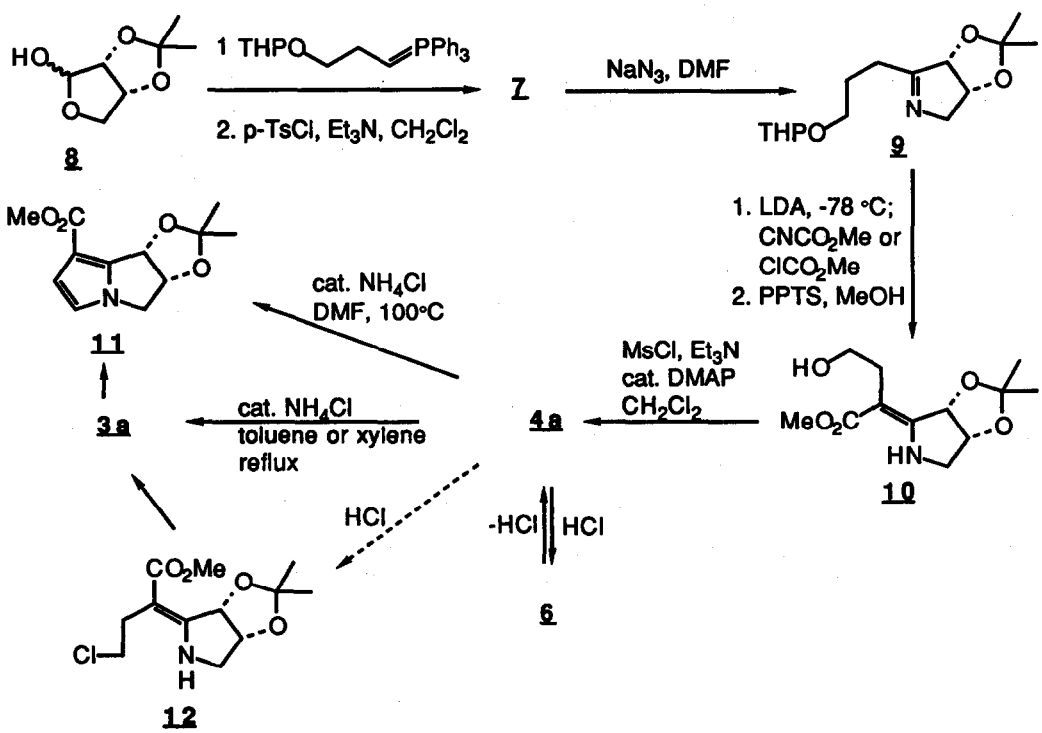


Route *a* would provide a conceptually appealing and operationally simple one-pot synthesis of the tricyclic enamine 3b from the cyclopropyl tosylate 5. The latter should be readily available from the Wittig reaction of cyclopropyltriphenylphosphonium bromide with 2,3-*O*-isopropylidene-D-erythrose (8).[6] Concern about potential difficulty of installing the hydroxymethyl or carbomethoxy group at the C-1 (pyrrolizidine numbering) position of enamine 3b,[7] however, led us to undertake route *b*, wherein it could be put into place at an earlier stage (*vide infra*).

As outlined in Scheme II, the requisite starting material **7** was prepared by the Wittig reaction of **8** with (3-tetrahydropyranyloxypropyl)triphenylphosphonium bromide [$KN(SiMe_3)_2$, THF, -78 → 0 °C] and subsequent treatment with p-toluenesulfonyl chloride.[8] Displacement of the tosyl group in **7** with sodium azide and the concomitant IAC reaction gave the imine **9** in 65% overall yield from **8**.[9] The carbomethoxylation was then accomplished in 57% yield by sequential treatment of imine **9** at -78 °C with LDA and Mander's reagent[10], or more conveniently, methyl chloroformate. Subsequent deprotection of the tetrahydropyranyl group with PPTS in methanol gave a single alcohol **10** [mp 83~85 °C; $[\alpha]_D^{20}$ = -113.39° (*c* 0.54, $CHCl_3$)] in 73% yield. The chemical shift of the proton on nitrogen at δ 7.95 is diagnostic for the expected geometry of the vinylogous carbamate double bond. The cyclopropyl imine **4a**, $[\alpha]_D^{20}$ = -6.20° (*c* 1.87, $CHCl_3$), was then readily prepared in 91% yield by the usual Crossland mesylation procedure.[11]

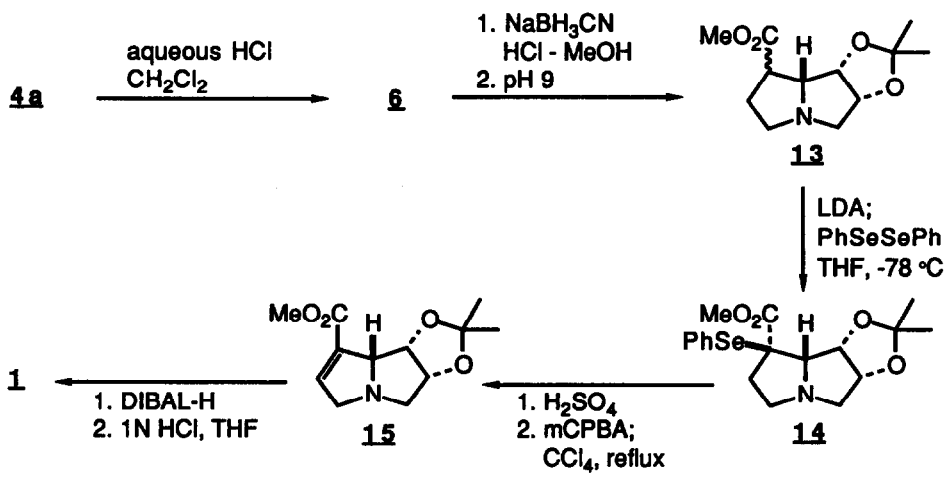
Despite several attempts (cat. NH_4Cl, refluxing toluene or xylene) an acid-catalyzed cyclopropylimine rearrangement of **4a** failed to afford any significant amount of the desired product **3a**. The use of DMF as a solvent, on the other hand, gave pyrrole **11** [mp 95~98 °C; IR ($CHCl_3$) 1699 cm^{-1}; $[\alpha]_D^{20}$ = -122.2° (*c* 0.135, $CHCl_3$)] in 35% yield (based on 74% conversion), along with a trace amount of **3a**. We believe that the difficulty with which **4a** undergoes the acid-catalyzed rearrangement can be attributed to the unfavorable double bond geometry of the intermediate **6** [^1H NMR($CDCl_3$) δ 8.01 (HN)] *vis-a-vis* the requisite **12**.[3c] Enamide **6** [mp 82~84 °C; $[\alpha]_D^{20}$ = -116.79° (*c* 0.40, $CHCl_3$)] could be easily prepared by treating **4a** with aqueous HCl in CH_2Cl_2. We note in passing that our result is in marked contrast to the successful rearrangement of a similar cyclopropyl imine previously reported by Pinnick.[12]

Scheme II



Finally, cyclization to the pyrrolizidine skeleton was effected by initial reduction of the double bond in enamide **6**. Thus, treatment with $NaBH_3CN$ in acidic methanol followed by basic workup gave a diastereomeric mixture of amino esters **13** having the 8*R* configuration. Assignment of the stereochemistry of the ring-junction (C-8) methine proton was based on the expected hydride delivery from the *convex* face and was subsequently confirmed by the eventual conversion to **1**. Subsequent reaction with diphenyl diselenide proceeded uneventfully to give α-selenoester **14**, $[\alpha]_D^{20}$ = -69.82° (*c* 1.11, $CHCl_3$), in 56% isolated yield. Conversion of the latter to the dehydropyrrolizidine derivative **15**, $[\alpha]_D^{20}$ = +52.10° (*c* 0.19, $CHCl_3$), was achieved in 47% (95% based on recovered **14**) yield by the procedure reported by Vedejs for retronecine (**2**): protonation of the amine nitrogen, followed by the usual selenium oxidation (mCPBA) and thermal elimination.[13] The synthesis was then completed by DIBAL-H reduction and subsequent acidic hydrolysis to afford crotanecine (**1**) in 76% overall yield: the ^1H NMR spectrum (in CD_3OD) of synthetic **1** was identical with that of natural material.[14] Its optical rotation and the melting point also were found to be comparable to the literature values {$[\alpha]_D$ = +34.5° (*c* 0.055, EtOH); mp 188~190 °C} [lit. mp 202~203.5 °C[4a]; 192 °C[4b]; $[\alpha]_D^{20}$ = +39.2° (*c* 1.3, EtOH)[4b]].

Scheme III



In summary, a short and enantioselective synthesis of crotonecine (**1**) has been achieved by the intramolecular azide dipolar cycloaddition.[15] Further synthetic applications of the strategy delineated above to other indolizidine and pyrrolizidine alkaloids will be reported in due course.

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8. All new compounds are fully characterized by IR spectra, ^1H and ^{13}C NMR spectra, mass spectra, HRMS, and optical rotations:
(a) **15**: IR 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.32 (s, 3H), 3.03 (dd, J = 14.2, 3.3 Hz, 1H), 3.22 (d, J = 14.2 Hz, 1H), 3.77 (s, 3H), 4.03 (m, 2H), 4.34 (br s, 1H), 4.75 (m, 2H), 6.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 23.9, 26.1, 51.6, 55.9, 62.2, 74.0, 81.8, 84.2, 112.2, 132.6, 140.3, 163.9. (b) **1**: ^1H NMR [300 MHz, CD_3OD (ref. 3.30)] δ 2.60 (dd, J = 10.2, 8.8 Hz, 1H), 3.23 (dd, J = 6.7, 8.8 Hz, 1H), 3.38~3.43 (m, 1H), 3.86 (m, J_{AB} = 14.8 Hz, 1H), 4.04 (t, J = 3.8 Hz, 1H), 4.15~4.20 (m, 4H), 5.71 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) 59.3, 59.9, 64.2, 72.4, 74.8, 76.2, 125.5, 140.2.

9. For related IAC reactions in natural products synthesis, see (a) ref. 2 and references cited therein. (b) Taber, D. F.; Deker, P. B.; Fales, H. M.; Jones, T. H.; Lloyd, H. A. *J. Org. Chem.* **1988**, *53*, 2968. (c) Heidt, P. C.; Bergmeier, S. C.; Pearson, W. H. *Tetrahedron Lett.* following paper.

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14. Kindly furnished by Professor Michael H. Benn, Department of Chemistry, University of Calgary, Canada.

15. Retronecine (**2**) should also be readily available from ester **13** by the γ-lactone formation and subsequent deoxygenation of the superfluous C-6 hydroxyl group. Alternatively, it could be prepared by the route described starting from the commercially available (*R*)-malic acid. This will be the subject of a forthcoming full paper: Bennett, R. B. III; Choi, J.-R.; Cha, J. K. unpublished results.

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