AN ENANTIOSELECTIVE SYNTHESIS OF (+)-CROTANECINE

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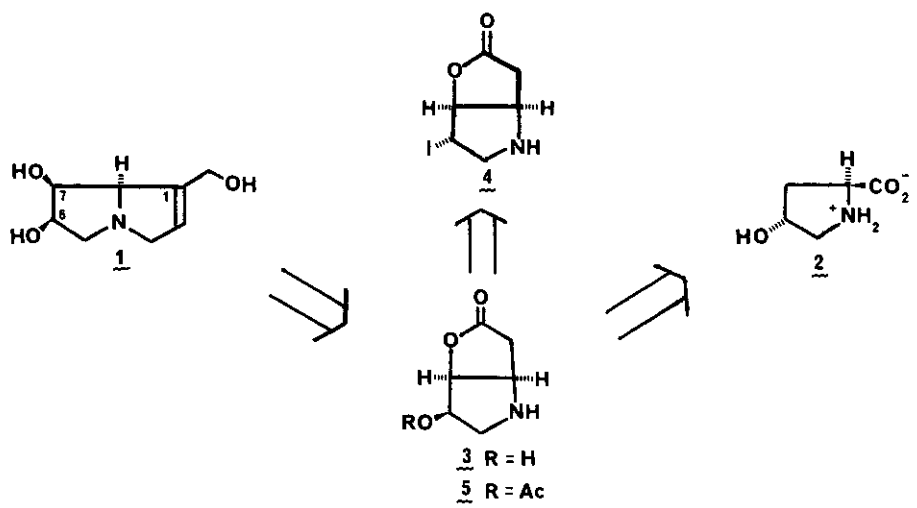
Abstract - (2S,4R)-4-Hydroxyproline was elaborated into (+)-crotanecine via (1S,5R,8R)-8-hydroxy-2-oxa-6-azabicyclo[3.3.0]octan-3-one.

We report an enantioselective first synthesis of crotanecine: a pyrrolizidine-triol originally isolated from the alkaloids of some Crotalaria species by Atal, Culvenor and co-workers[1], and shown by them to have the structure 1.

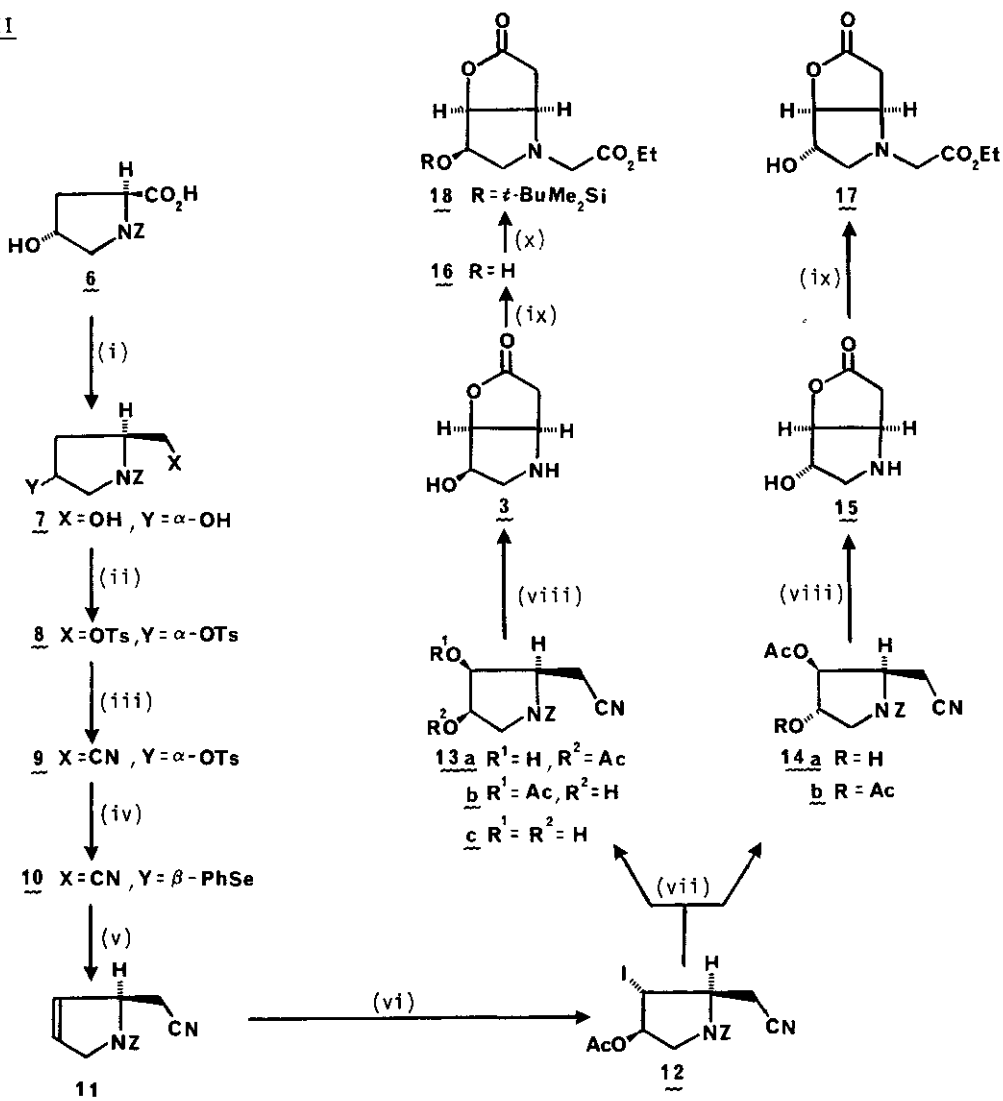
Crotanecine may be viewed as a 6β-hydroxy derivative of retronecine and it seemed to us that our route[2] to this latter necine might be adapted to provide 1, i.e. that (2S,4R)-4-hydroxyproline (2) might be elaborated into the hydroxy-lactone (3) and thence into 1 (Scheme I). Thus we hoped that 4, for which we had established[3] an efficient synthesis from 2, might be transformed into 5 by an S_N2 displacement of iodide by acetate. However, although we explored a variety of conditions involving silver acetate in acetic acid, we were unable to establish a satisfactory procedure for this reaction: at ambient temperature the displacement was extremely slow, and attempts to accelerate this by heat resulted in the formation of complex mixtures of products. Presumably the required endo-approach of the nucleophile was too sterically hindered.

Scheme I



We therefore decided to construct the cis-diol system before making the bicyclic lactone. After considerable experimentation, we achieved this as follows (Scheme II). A borane reduction of N-benzyloxycarbonyl-(2S,4R)-4-hydroxyproline (6) gave the diol 7[4]. The ditosylate 8 of this underwent selective displacement by cyanide to afford the tosyloxy-nitrile 9, and another displacement reaction then produced the phenylseleno-nitrile 10. Oxidative elimination of the phenylseleno group from 10 was, as anticipated[5], highly regioselective and cleanly gave the pyrroline-nitrile 11 (66% from 6).

Scheme II

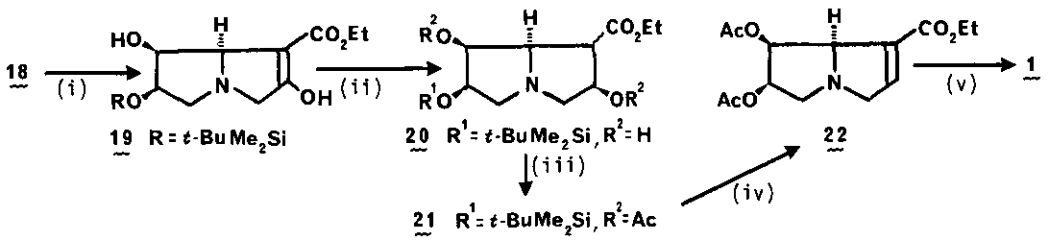


(i) $BH_3.Me_2S$/THF/0°C; (ii) TsCl/Py/0°C; (iii) NaCN/DMF/95°C; (iv) PhSeNa/THF-MeOH/65°C; (v) H_2O_2/5°C; Δ(R.T.); (vi) NIS/AcOH/60°; (vii) AcOH-H_2O (4:1)-AgOAc/95°C; (viii) MeOH-HCl/R.T.; (ix) $BrCH_2CO_2Et$-Na_2CO_3/EtOH/75°C; (x) t-$BuMe_2SiCl$/imidazole/55°C.

Excellent regioselectivity was also observed in the next reaction, in which 11 was treated with N-iodosuccinimide in acetic acid[6] to yield the iodo-acetate 12. When this compound was subjected to solvolysis in wet acetic acid containing silver acetate[7] the products were largely the cis-diol monoacetates (13a,13b) accompanied by smaller amounts of the diol itself (13c), and the corresponding trans-diol derivatives (14a,14b). This mixture could be separated by column-chromatography but we found it more convenient to treat it with methanol containing hydrogen chloride; thus converting it, after an aqueous workup, into a mixture of the hydrochlorides of the two hydroxy-lactones 3 and 15 (ca. 95:5). The pure hydrochloride of 3 could be obtained from this mixture by crystallisation but it again proved to be expeditious to delay this separation: until after N-alkylation of the lactones with ethyl bromoacetate to give 16 and 17. Flash chromatography[8] of this mixture then gave pure 16 (63% overall from 11). The relative stereochemistry of 16, originally deduced from ^{1}H-nmr data[9], was confirmed by an X-ray crystallographic structure determination carried out on its hydrobromide salt[10].

Initial experiments revealed that the Dieckmann condensation of 16 gave very polar products that were difficult to isolate. Accordingly 16 was converted into the silylated derivative 18, and then treated with potassium ethoxide in toluene. The hydrochloric acid-soluble crude products of this reaction were then immediately reduced with sodium cyanoborohydride, at pH 4. It proved best to acetylate the products from this reaction without further purification, and then subject them to a treatment with tetra-n-butylaminonium fluoride in THF to which was subsequently added acetic anhydride. From the products of this sequence of reactions (Scheme III: 18→19→20→21→22) we then isolated by flash chromatography 22 (13% from 16): elimination of the 2-acetoxy function apparently accompanied the desilylation.

Scheme III



(i) $KOEt/PhCH_3/0°\rightarrow R.T.$; (ii) $NaBH_3CN/H_2O$/pH 4/R.T.; (iii) Ac_2O/DMF/65°C; (iv) Bu_4NF/THF/R.T.; Ac_2O/R.T.; (v) Dibal/THF/-78°C→R.T.

Finally diisobutylaluminium hydride reduction of 22 gave 1 (76%, 4% from 6), mp 190-193°C (hot stage), $[\alpha]_D$ + 44 ± 4° (c 0.0048, EtOH) whose ir and ^{1}H-nmr spectra were superimposable upon those of natural crotanecine (Lit. mp 192°C[11], 202-203.5°C[1]; $[\alpha]_D$ + 39.2° (c 1.3, EtOH)[11].

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

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2. H. Rüeger and M. Benn, Heterocycles, 1983, 20, 1331.
3. H. Rüeger and M. Benn, Heterocycles, 1982, 19, 23.
4. This and all subsequent compounds with the exception of those in the set 19-21 were fully characterised by spectroscopic methods, usually supplemented by combustion analyses. Compounds 20 and 21 were observed by ^{1}H-nmr spectroscopy during explorations of the individual steps 18→20, and 20→21. None of the intermediates crystallised, but 3.HCl had mp 178-179°C, $[\alpha]_D$ + 20° (c 0.009, EtOH) and 4.HBr had mp 186-187°C.
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9. In particular the values for 16, $J_{3,4}$ = 5.2 Hz; and in 17, $J_{3,4}$ = 1.3 Hz.
10. This structure determination was carried out in the X-ray Crystallographic Service Laboratory of our Department by Dr. John Richardson. As with our other experiments, details are available on request.
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