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Synthesis of the Tangutorine Skeleton

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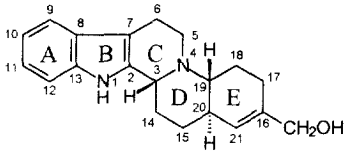
Abstract: The ring system of the novel indole alkaloid tangutorine (**1**) has been synthesized *via* the Fry reaction. The final key steps were an oxidation/reduction procedure or alternatively, an epimerization sequence. Conformational and stereochemical aspects of the skeleton are discussed.

Keywords: Indole alkaloid, α-amino nitrile, conformation, epimerization

Synthesis of the yohimbine skeleton[1] and its skeletal derivatives[2] has been of earlier interest in our laboratory. Recently, the biogenetically interesting indole alkaloid tangutorine (**1**)[3] was found in the leaves of *Nitraria tangutorum*.[4] Tangutorine incorporates a benz[*f*]indolo[2,3-*a*]quinolizidine unit, which is unique in the indole alkaloid series. In the original paper of Duan *et al.*[4] the stereochemistry of compound **1** was verified by crystal structure and NMR data. However, the structural formula presented for **1** contained an unfortunate drawing error: according to the ORTEP structure H-3 should be β and not α.



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Only two approaches to decahydro benz[*f*]indolo[2,3-*a*]quinolizidine have been reported in the literature and no stereochemical characterization has been presented.[5,6] We report an easy and selective route to the tangutorine skeleton *via* the Fry[7] reaction and discuss stereochemical and conformational aspects of the benz[*f*]indolo[2,3-*a*]quinolizidine structure.

The same synthetic approach that was used for the yohimbine skeleton[1] can be applied in constructing the dodecahydro benz[*f*]indolo[2,3-*a*]quinolizidine ring structure. Alkylation of 5,6,7,8-tetrahydroquinoline[8] with tryptophyl bromide gave salt **2** in 88% yield. When salt **2** was subjected to the Fry reaction conditions (KCN, 6N HCl, $NaBH_4$) followed by immediate acid-induced cyclization, three products were isolated: the unexpected α-amino nitrile **3** (10%) and compounds **4** (15%) and **5** (5%) (Scheme 1).[9]

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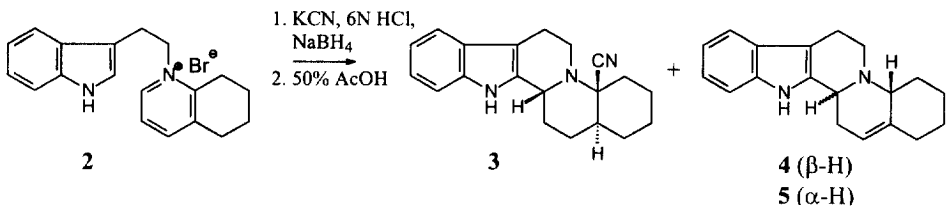
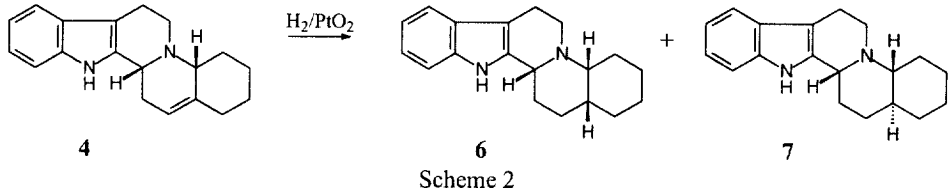


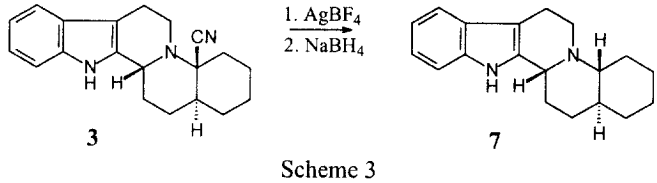
Scheme 1

Catalytic hydrogenation of compound **4** resulted in a mixture of compounds **6** and **7** (ratio 80:20, total yield 60%)(Scheme 2). As we expected from an examination of the molecular model of **4**, compound **6** turned out to be the predominant isomer. The poor stereoselectivity of the hydrogenation led us to examine the α-amino nitrile **3** more closely.



Scheme 2

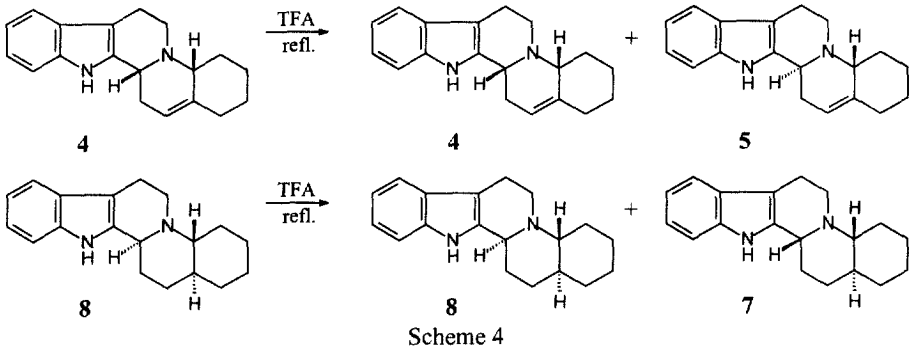
To our knowledge, only monocyanated products have been reported in the Fry reaction. However, α-amino nitrile **3** must be derived from a dicyano compound and thus presents an exception. If removal of the cyano group of compound **3** could be accomplished stereoselectively, an efficient route would be opened to the tangutorine skeleton. Indeed, this proved to be true: $AgBF_4$ treatment of **3** and reduction of the iminium species provided the tangutorine model **7** in 76% yield (Scheme 3).



Scheme 3

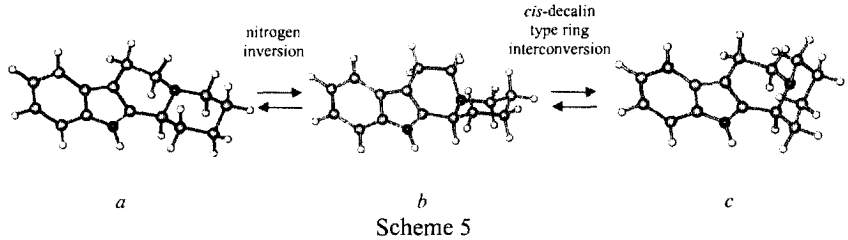
The stereochemistry of **7**[10] was easily verified by inspecting the coupling system of H-19 (δ 1.95 ppm, ddd, J = 3, 10 and 10.5 Hz), which results from D/E *trans* ring juncture. Furthermore, irradiation of H-3 resulted in an NOE at H-19, among others, verifying that H-3 and H-19 are *cis*, and thus establishing the structure of **7** presented in Scheme 3. Compound **7** could also be obtained by manipulating the stereochemistry at C-3 *via* an acid-catalysed epimerization reaction (Scheme 4).[11] When compound **4** was refluxed in TFA overnight, a

60:40 ratio[12] of **4** and **5** was obtained. Catalytic hydrogenation of compound **5** resulted mainly in **8** (56%), which could be epimerized to a mixture of compounds **7** and **8** (ratio[12] 60:40). Hence, the tangutorine skeleton **7** was available from compound **4** by an epimerization sequence. The epimerization provides additional proof of the stereochemistry of **8**,[13] supplementary to the NMR data.



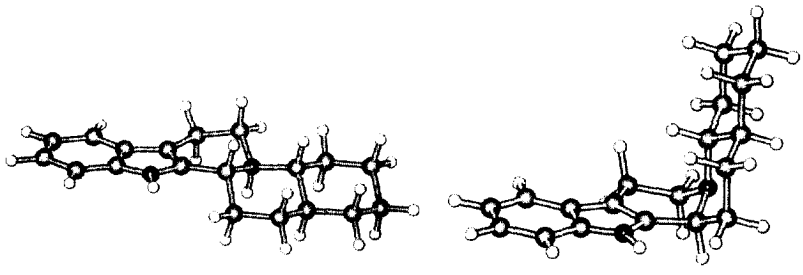
Scheme 4

The conformational behaviour of tangutorine (**1**) resembles that of the indolo[2,3-*a*]quinolizidine system, which can exist in three main conformations (conformations *a*, *b* and *c*) (Scheme 5).[14,15]



Scheme 5

The D/E *trans* ring juncture in compounds **7** and **8** forces the conformational equilibrium to its extremes. The tangutorine skeleton **7** is "locked" in conformation *a* and hence possesses a C/D *trans* ring juncture. Proof is provided by NMR studies: chemical shifts of C-6 (22.1 ppm) and H-3 (3.38 ppm) are characteristic for compounds that are completely in conformation *a*.[14] Compound **8**, on the other hand, is completely in conformation *c* possessing a C/D *cis* ring juncture. This can again be confirmed by NMR (C-6: 16.2 ppm and H-3: 4.76 ppm).[14] The NMR data of compound **7** resemble those reported for tangutorine (**1**),[4] confirming that **1** also exists completely in conformation *a*.



7 8

In summary, after the Fry reaction, the tangutorine skeleton **7** was synthesized by two approaches: the first involved an oxidation/reduction procedure of α-amino nitrile **3** and the second an epimerization sequence involving compounds **4** and **8**. The first approach provides **7** selectively, whereas the second always results in pairs of epimers. Practically for the first time these two synthetic pathways provide an easy and selective route to the tangutorine skeleton and hence can be utilized in the total synthesis of tangutorine (**1**).

References and Notes

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9. Yields of the Fry reaction and especially the cyclization are unoptimized.
10. Selected NMR data of compound **7**: ^{1}H NMR ($CDCl_3$): δ 3.38 (dd, 1H, J = 2 and 11.5 Hz, H-3), 1.95 (ddd, 1H, J = 3, 10 and 10.5 Hz, H-19); ^{13}C NMR: δ 67.1 (C-19), 60.6 (C-3), 41.5 (C-20), 22.1 (C-6).
11. For a review, see: Lounasmaa, M.; Berner, M.; Tolvanen, A. *Heterocycles* **1998**, *48*, 1275-1290.
12. Determined by ^{1}H NMR integration. Yields in epimerization reactions were nearly quantitative.
13. Selected NMR data of compound **8**: ^{1}H NMR ($CDCl_3$): δ 4.76 (br s, 1H, H-3), 2.64 (ddd, 1H, J = 3, 10.5 and 11 Hz, H-19); ^{13}C NMR: δ 58.6 (C-19), 57.1 (C-3), 40.0 (C-20), 16.2 (C-6).
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