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Stereoselective Transformation of Indole Diazabicyclo[3.2.2]nonedione to Azepinoindole

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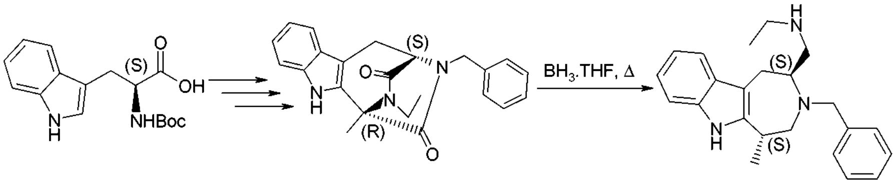
ABSTRACT



The synthesis of an indole diazabicyclo[3.2.2]nonedione derivative was achieved in a few steps starting from L-tryptophan. Reduction with borane–THF complex leads to fragmentation of the bicycle and the stereoselective formation of an azepinoindole derivative was observed.

We would like to report in this letter a novel and efficient route to access 2*S*,5*S* disubstituted azepinoindoles from L-tryptophan. The key transformation of the reaction sequence is the stereoselective fragmentation of an indole diazabicyclo[3.2.2]nonedione with borane−THF complex.

In the eighties, Ottenheijm and co-workers reported the synthesis of an indole diazabicyclo[3.2.2]nonedione derivative starting from indole-3-pyruvic acid.[1] The key step was the intramolecular Pictet−Spengler reaction between a α-ketoamide and an amide group. In 1996, using the same strategy, Mortier and co-workers reported the synthesis of a similar compound starting from an arylidene piperazidione derivative.[2] In both cases, achiral starting materials were used and led to racemic diastereomeric mixtures of bicyclic compounds. The same key step was used by Czarnocki in the diastereoselective synthesis of 1-benzyltetrahydroisoquinoline.[3]

L-Tryptophan **1** was used as starting material for the synthesis of chiral indole diazabicyclo[3.2.2]nonedione skeletons. Amide bond formation was carried out under standard conditions to give the ethyl amide derivative **2** quantitatively. After Boc deprotection, the nitrogen was *N*-benzylated in a two-step procedure. Acylation of the acyclic precursor **3** with pyruvyl chloride[4] gave the intermediate α-ketoamide derivative, which was not isolated and was exposed directly to TFA to afford the bicycle **4** in good yield via a Pictect−Spengler-type cyclization (Scheme 1).

Compound **4** was submitted for in-house water-solubility measurements where it was classified in a medium range (value around 0.05 g/L) but with no measurable pK_a. To improve solubility, it was decided to reduce the amide groups to tertiary amines. The reduction methodology was chosen carefully in order to be compatible with solid-phase supports in view of exploratory work. The selected reaction protocol used a borane−THF complex reduction followed by a mild oxidative workup procedure (iodine, triethylamine, and

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(1) (a) Ottenheijim, H. C. J.; Plate, R.; Noordik, J. H.; Hersheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147. (b) Plate, R.; Nivard, R. J. F.; Ottenheijim, H. C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2473.

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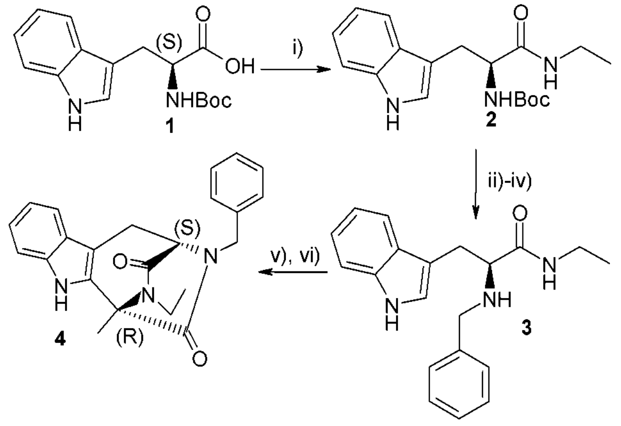
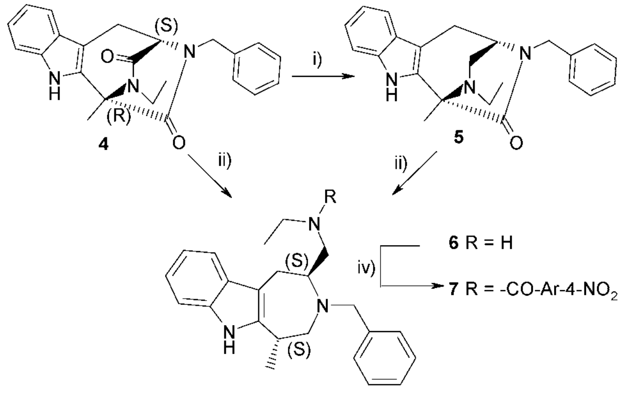
10.1021/ol0271990 CCC: $22.00

Scheme 1[a]



[a] Reaction conditions: (i) $EtNH_2$·HCl, TEA, HOBt, DCC, THF, rt, 16 h (100%); (ii) 4 N HCl/MeOH, rt, 6 h; (iii) Na_2CO_3, PhCHO, TMOF, MeOH, rt, 16 h; (iv) $NaBH_4$, MeOH, rt, 1 h (70%, 3 steps); (v) MeCOCOCl, TEA, DCM, 0 °C, 1 h then aqueous workup; (vi) 20% TFA/DCM, rt, 2 h (80%, 2 steps).

Scheme 2[a]



[a] Reaction conditions: (i) (a) BH_3·THF (10 equiv), THF, rt, 16 h, (b) MeOH, TEA, I_2, THF, rt, 2 h (95%); (ii) (a) BH_3·THF (10 equiv), THF, 80 °C, 24 h, (b) MeOH, TEA, I_2, THF, rt, 2 h (60%); (iii) 4-NO_2ArCOCl, TEA, DCM, rt, 2 h (80%).

methanol).[5] In the first reduction experiment, **4** was treated in THF with 10 equiv of BH_3·THF at 50 °C for 6 h. No more starting material was observed and two new products were detected by HPLC. The completely reduced material was not detected by LC/MS. The first product had a mass + 14 (corresponding to a monoreduced derivative) and the second product had a mass + 2 (rupture of a C−C bond). The two derivatives were isolated by flash chromatography on silica gel, analyzed, and characterized. They were assigned to the structures **5** and **6**. Conditions for selective formation of **5** and **6** were optimized. When the reduction was carried out at rt, **5** was obtained selectively whereas at higher temperature (80 °C) **6** was the major product. In addition, we observed that **5** represents an intermediate in the formation of **6**. In fact, when **5** was reacted with borane−THF complex, **6** was obtained (Scheme 2).

The first amide bond reduction took place from the less hindered face of the molecule to give **5**. The amide group at the lower face of the molecule is shielded by the *N*-ethyl, *N*-benzyl, and *exo*-methyl groups whereas only the *N*-ethyl and *N*-benzyl groups surround the amide group of the upper face. The second amide reduction was more demanding from an energetic point of view and required higher reaction temperature; however, no formation of the expected diazabicyclononene was observed. From NMR analysis, it was not possible to assign the relative configuration of the two stereocenters (cis or trans) of **6**. Different derivatives were synthesized to obtain suitable crystals for X-ray analysis. Finally, the structure was solved for the nitrobenzoate derivative **7**.[6] The 3-D structure showed relative trans configuration between the two substituents (Figure 1).

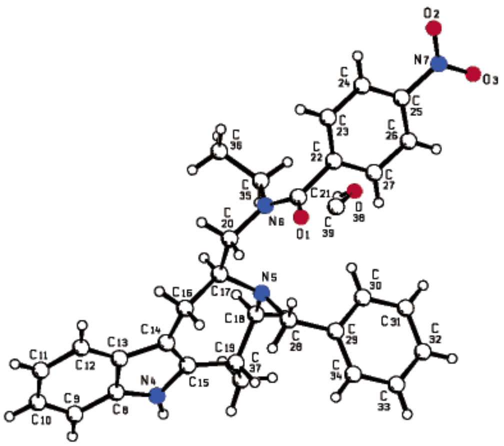


Figure 1. X-ray of **7**·MeOH.

The water-solubility of the azepinoindole was measured in-house and showed at pH 6.8 low solubility (<0.001 g/L) for R = H, and good solubility (>0.1 g/L) was observed for R = Ac with measurable pK_a at 9.8 and 4.2.

To propose a reaction mechanism, a couple of transformations were carried out. When **4** was treated with a 1 M solution of $LiAlH_4$ in THF at 60 °C for 3 h, the tetrahydro compound **8** was obtained in 60% yield and no fragmentation was observed. When **8** was treated with borane−THF complex at 80 °C, the fragmentation product **6** was obtained. Therefore, the observed fragmentation does not require the presence of an amide group (Scheme 3).

To investigate the role of the indole system, compound **4** was reduced with sodium cyanoborohydride in TFA.[7] Two diastereoisomers (only major shown) were obtained in a 6/1

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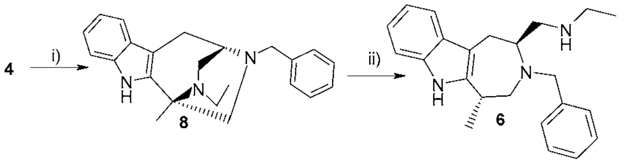
(5) Hall, D. G.; Laplante, C.; Manku, S.; Nagendran, J. *J. Org. Chem.* **1999**, *64*, 698.

(6) CCDC 189473 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crstallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax (+44) 1223-336-033; e-mail deposit@ccdc.cam.ac.uk).

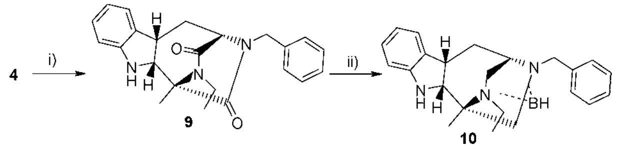
Scheme 3[a]



[a] Reaction conditions: (i) 1 M $LiAlH_4$/THF, 60 °C, 3 h (60%), (ii) (a) BH_3·THF (20 equiv), THF, 75 °C, 24 h, (b) MeOH, TEA, I_2, THF, rt, 2 h (80%).

ratio in favor of diastereoisomer **9** bearing the two hydrogens in the same side of the *N*-ethyl amide (less hindered face). The amide bond reduction was carried out under identical reaction conditions as for conversion of **4** to **6**. No fragmentation was observed and the reduced material **10** was quantitatively obtained as a borohydride complex (Scheme 4).

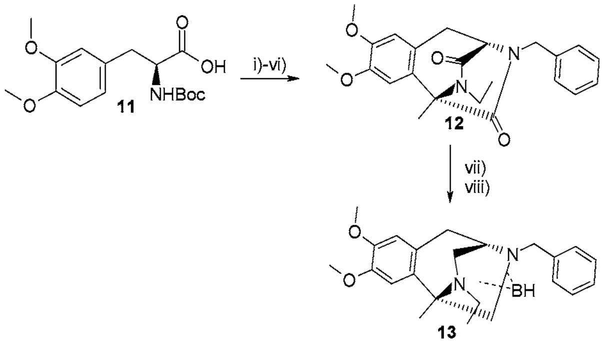
Scheme 4[a]



[a] Reaction conditions: (i) TFA, $NaBH_3CN$ (6 equiv), rt, 30 min (70%), (ii) (a) BH_3·THF (10 equiv), THF, 80 °C, 24 h, (b) MeOH, TEA, I_2, THF, rt, 2 h (90%).

To explore the scope and limitation of this novel fragmentation, tryptophan was replaced by 3,4-dimethoxy L-DOPA. The same reaction sequence was carried out to obtain the [3.2.2] bicycle. When **12** was subjected to the borane reduction step, bireduced compound **13** was obtained with one boron complexed to the adduct. No fragmentation was observed (Scheme 5).

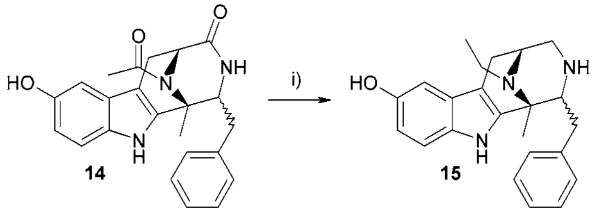
Scheme 5[a]



[a] Reaction conditions: (i) $EtNH_2$·HCl, TEA, HOBt, DCC, THF, rt, 16 h (82%); (ii) 4 N HCl/MeOH, rt, 6 h; (iii) Na_2CO_3, PhCHO, TMOF, MeOH, rt, 16 h; (iv) $NaBH_4$, MeOH, rt, 1 h (70%, 3 steps); (v) MeCOCOCl, TEA, DCM, 0 °C, 1 h; (vi) 10% TFA/DCM, 50 °C, 16 h (84%, 2 steps); (vii) BH_3·THF (10 equiv), THF, 70 °C, 16 h; (viii) MeOH, TEA, I_2, THF, rt, 2h (60%, 2 steps).

The series of experiments demonstrates that the indole ring and the presence of boron are essential for the fragmentation, therefore a possible mechanism for the stereoselective formation of **6** was postulated (Scheme 7). The final product of the reduction (tetrahydro derivative **5a**) was obtained as a borane complex. This intermediate could probably undergo, under heating, a boron-assisted retro-Michael addition or an aza-type fragmentation.[8] Computer modeling shows a torsion angle of 58.6° for C=C−C(Me)−N allowing a possible overlap of the π orbital of C=C and the C−N bonds which helps to facilitate the fragmentation. In addition, when similar conditions of amide bond reduction were used for an indole diazabicyclo[3.3.1]nonenone,[9] no fragmentation was observed (Scheme 6). Modeling of **14** gave a torsion angle of 10° for the C=C−C(Me)−N, which allowed no possible overlap of the orbitals.

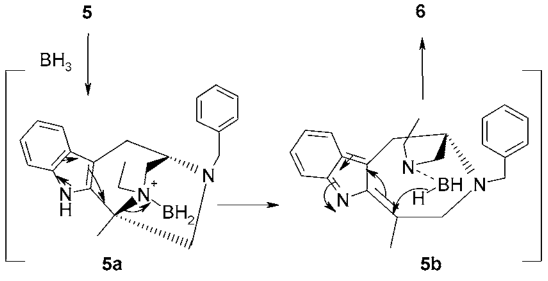
Scheme 6[a]



[a] Reaction conditions: (i) (a) BH_3·THF (20 equiv), THF, 75 °C, 24 h, (b) MeOH, TEA, I_2, THF, rt, 2 h (65%).

In the second step, one hydride from a molecule of BH_3 (in excess in the reaction mixture) complexed to the secondary nitrogen **5b** is transferred to the Michael acceptor from the top face to afford **6** (Scheme 7).

Scheme 7. Proposed Mechanism for the Transformation of **5** to **6**



In conclusion, we have shown an efficient synthesis of chiral indole [3.2.2] bicycles that can be used as starting material to obtain azepinoindole derivatives stereoselectively.

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Supporting Information Available: Detailed descriptions of experimental procedures for the synthesis of **4**, **5**, **6**, **8**, **9**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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