Pergamon

Tetrahedron Letters 40 (1999) 9293–9295

TETRAHEDRON LETTERS

Highly stereoselective synthesis of *exo* and *endo* indolotropanes

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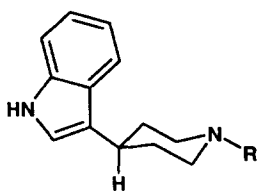
Received 31 August 1999; accepted 13 October 1999

Abstract

Highly stereoselective routes to *exo* and *endo* indolotropanes have been developed. This provides a facile route to these bicyclic analogues of the pharmaceutically active indolopiperidine motif.

Keywords: indoles; bicyclic heterocyclic compounds.

The indolopiperidine ring system **1** is well known in pharmaceutical research as a template for ligands at numerous G-protein coupled receptors (GPCR's) e.g. 5-hydroxytrypamine (5-HT) receptor subtypes and dopamine receptors.[1] In marked contrast, the related indolotropane analogues **2** and **3** are extremely poorly documented.[2] However, these tropane derivatives are of substantial interest for two reasons: the increased steric bulk around the basic nitrogen, and secondly, the conformationally locked piperidine ring, which 'freezes' the indole substituent in either the equatorial (*exo* isomer) or axial (*endo* isomer) orientation. Both of these features may impart useful affinity/selectivity advantages to the specific ligand under investigation.



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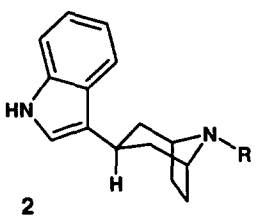

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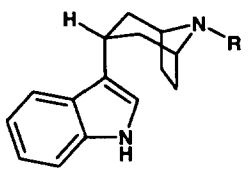

3

In the course of our work on selective ligands for specific GPCR's we became interested in a stereoselective route to these indolotropanes **2** and **3**. Initially, we followed the standard literature methodology illustrated in Scheme 1. Thus, condensation of indole with Boc-nortropinone[3] afforded the olefinic product **4**, which was then hydrogenated over palladium on charcoal to afford a 60:40 mixture of *exo*:*endo* isomers, respectively, which could not be separated by column chromatography. Examination

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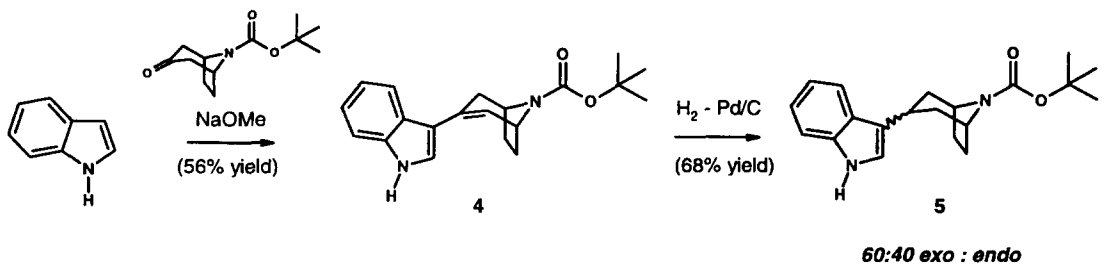
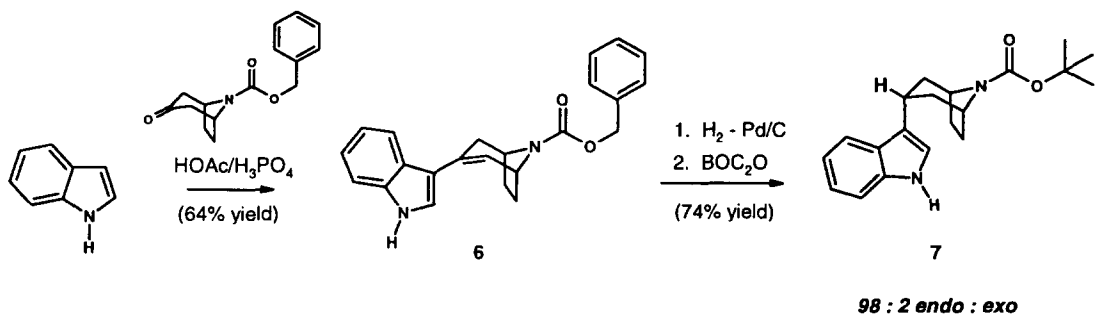
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01949-8

of molecular models suggests that both faces of the tetrahydropyridine ring in **4** are sterically hindered to a similar extent, thus giving rise to essentially a non-selective reduction process.



Scheme 1. Non selective route to indolotropanes

In marked contrast, the corresponding benzyloxycarbonyl protected intermediate **6**, prepared by a related method, underwent hydrogenation to afford a single isomer characterised as its *N*-Boc derivative. Analysis by NMR and HPLC indicated 98% isomeric purity as the *endo* isomer **7**. It is postulated that in this reduction process there is a rapid cleavage of the benzyloxycarbonyl group, followed by a slower hydrogenation of the double bond which now takes place from the less hindered *exo* face of the ring system to afford stereoselectively the *endo* isomer (Scheme 2).[4]

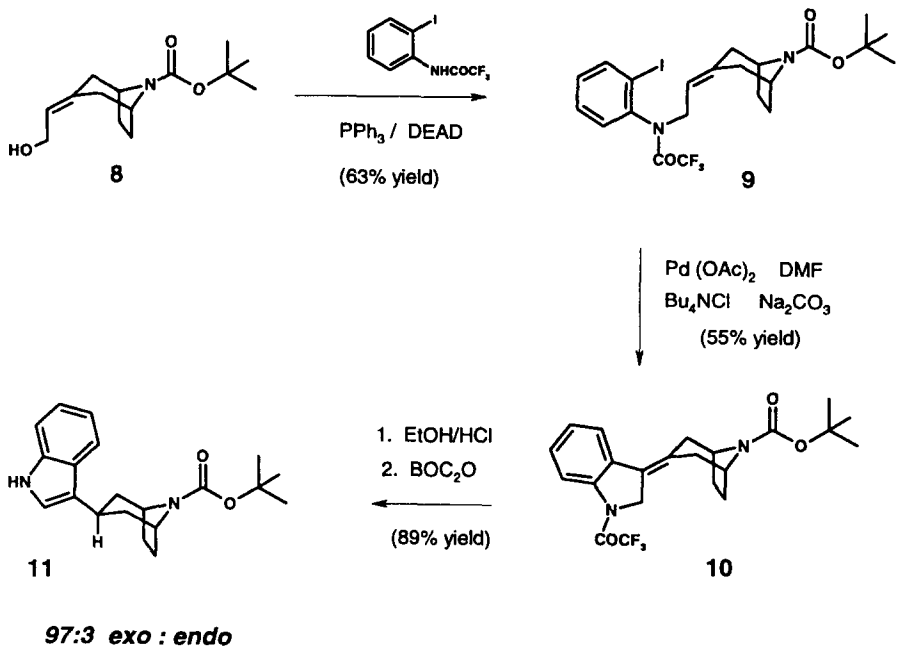


Scheme 2. Stereoselective route to *endo* indolotropanes

We now turned our attention to the use of the Heck indole synthesis for the preparation of the thermodynamically more stable *exo* indolotropane ring system.

Although the Heck route has been well documented for the synthesis of simple indoles, we are aware of only one paper[5] which uses this methodology for the synthesis of an indole containing a highly functionalised side chain at C-3. Mitsunobu alkylation of *N*-trifluoroacetyl-2-iodoaniline with the alcohol **8**[6] afforded the Heck precursor **9**, cyclisation of which at room temperature, using Larock's conditions,[7] furnished the indoline **10** in 55% yield. Surprisingly, in contrast to literature precedence,[8] the newly formed double bond remained exocyclic to the indoline ring and did not migrate under the reactions conditions to form an indole. However, treatment of **10** with ethanolic HCl brought about removal of both protecting groups and concomitant migration of the double bond to afford the desired *exo* indolotropane characterised as its *N*-Boc derivative **11**. Analysis by NMR and HPLC indicated 97% isomeric purity as the *exo* isomer (Scheme 3).[4]

Having achieved a stereoselective synthesis of the indolotropanes **7** and **11**, the *N*-Boc protecting group was removed using standard conditions (EtOH/HCl), and a variety of side chains were introduced by alkylation or reductive alkylation techniques. The structure and receptor binding profile of these compounds will be the subject of a future publication.



Scheme 3. Stereoselective route to *exo* indolotropanes

Acknowledgements

I am grateful to Simon Readshaw for NMR studies on **7** and **11**.

References

1. A search of Chemical Abstracts gave ~2000 references to substituted indolopiperidines mainly in the patent literature. For some examples, see: WO 9418196, WO 9316073, DE 2338283 and DE 2503816.
2. Only one literature reference could be found for this class of compound: Repke, D. B.; Artis, D. R.; Nelson, J. T.; Wong, E. H. F. *J. Org. Chem.* **1994**, *59*, 2164–2171.
3. Boc-nortropinone is commercially available from Fluka, or can be easily prepared from *N*-benzyltropinone by catalytic hydrogenation followed by reaction with Boc anhydride.
4. The stereochemistry of the *exo* and *endo* isomers was assigned by NOE studies and by examination of the characteristic coupling constants for the C-3′ proton.
5. Macor, J. E.; Ogilvie, R. J.; Wythes, M. J. *Tetrahedron Lett.* **1996**, *37*, 4289–4293.
6. The alcohol **8** was prepared from Boc-nortropinone by Wittig–Horner reaction with triethyl phosphonacetate (60%), followed by selective reduction at –40°C with DIBALH (~100%).
7. Larock, R. E.; Leuck, D. J.; Harrison, L. W. *Tetrahedron Lett.* **1988**, *29*, 6399–6402.
8. There are examples of the Heck indole synthesis carried out in the presence of silver salts, where the newly formed double bond does not migrate to form an indole. See, for example: Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1941–1942.