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Synthesis of Novel Polycyclic Indolyldiamines

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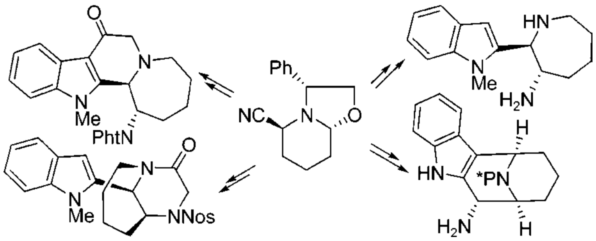
ABSTRACT



A rapid and stereoselective access to novel polycyclic indolyldiamines is described. The key step involves simple chemoselective transformations of a common bicyclic aminal intermediate, easily available on a large scale from an enantiomerically pure cyano oxazolopiperidine precursor.

The design and synthesis of structurally diverse, optically pure diamines continues to be an area of intense research in medicinal and coordination chemistry, as well as in asymmetric catalysis.[1] In medicinal chemistry particularly, introduction of heteroaromatic motifs on ethylenediamines increases their pharmaceutical value.[2] Considering the growing interest in bioactive indole derivatives, we decided to investigate the introduction of this nucleus on conformationally restricted diamines.

In the context of our synthetic studies on constrained diamine systems, we recently reported a simple route to enantiopure mono- or disubstituted 3-aminoazepanes **3** or **5**, respectively, starting from 2-cyano-6-oxazolopiperidine **1**.[3] The key step involved reductive or alkylative ring-enlargement of bridged bicyclic intermediates in a totally regio- and diastereoselective manner (Figure 1). Although various indole derivatives from natural or synthetic sources are known to exhibit interesting biological activities, very few examples that include an azepane core have been

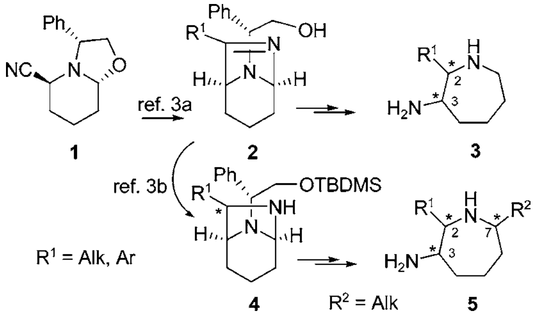


Figure 1. General strategy for the synthesis of polysubstituted azepanes.

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(1) For a recent review, see: (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2581. For selected leading references, see: (b) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640. (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (d) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (e) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.

(2) (a) Michalson, E. T.; Szmuszkovicz, J. *Prog. Drug Res.* **1989**, *33*, 135. (b) Wong, E.; Giandomenico, C. M. *Chem. Rev.* **1999**, *99*, 2451.

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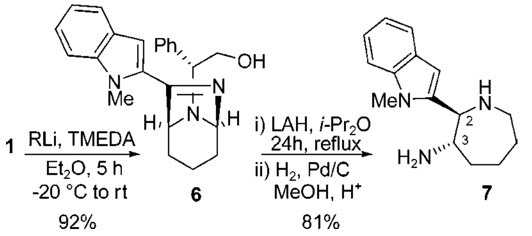
described.[4] Reports of bioactive carba analogues of eudistomines[5] prompted us to test the reactivity of bicyclic indole derivatives **2** or **4** toward the synthesis of new polycyclic scaffolds.

We first focused on the preparation of 2-substituted 3-aminoazepane **3** in the *N*-methyl indole series. The imino bicyclic compound **6** can be prepared in multigram quantities using Et_2O−TMEDA as the solvent system. High and reproducible yields were obtained following an optimized sonication procedure. Standard reductive conditions were then applied to achieve diastereoselective access to the 3-aminoazepane core.

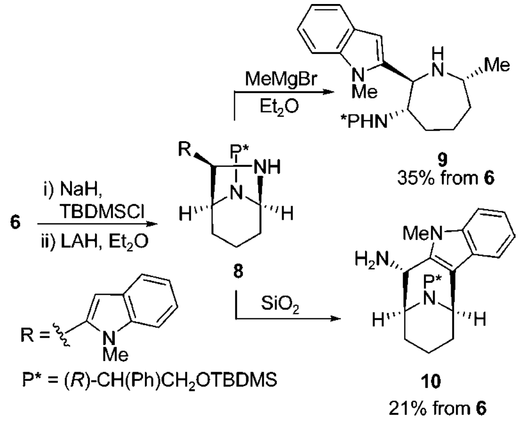
Although ring enlargement in the phenyl or furyl series proceeded at room temperature,[3b] harsher reaction conditions (an excess of reagent in refluxing isopropyl ether) were needed to achieve ring enlargement in the indole series (Scheme 1). Thus, unprotected 2-substituted 3-aminoazepane derivative **7** was obtained in 74% overall yield from **1** after hydrogenolysis of the chiral appendage. The trans relative configuration was assigned by comparison with previously reported structures ($J_{2,3}$ = 9.6 Hz).[3]

Scheme 1. Reductive Ring Enlargement in the Indole Series



Intra- or intermolecular nucleophilic attack was then evaluated on the bicyclic aminal system **8**. The indole nucleus was expected to compete with an external nucleophile in reactions involving reactive iminium species.[6] Side chain O-protection was first performed to avoid any competitive morpholine formation (Scheme 2).[7,8] Subsequent imine reduction was conducted using LAH under mild conditions, leading to compound **8** in a diastereomerically pure form.[9]

Scheme 2. Chemoselective Activation of Bicyclic Aminal **8**



Methylmagnesium bromide was used as the external nucleophilic reagent for the alkylative ring-enlargement process. Best results were obtained using a slight excess (3.5 equiv) of Grignard reagent in refluxing Et_2O, leading to compound **9** in 51% yield as a single diastereomer. Its 2,7-trans relative configuration could be assigned by comparison to previous spectroscopic data in the phenyl series.[3b]

Compound **10**, resulting from the intramolecular nucleophilic attack of indole C3, was never detected in the ring enlargement reaction mixture, indicating a fully chemoselective seven-membered iminium ion formation. However, this bridged heterocycle was isolated when aminal **8** was purified by chromatography on silica gel and could also be obtained in modest but reproducible yield by adding SiO_2 directly to a solution of aminal **8**.

As a nonprotected indole moiety could be of interest in the search for bioactive products, we applied our initial alkylation step using *N*-phenylsulfonylindole (Scheme 3).

Lithiated sulfonylindole proved to be unreactive with compound **1** in Et_2O but, in THF, led to a new bridged tetracycle **11** characterized by an *exo* imine function (carbon peak at 165.3 ppm) and a deshielded H-6 proton signal (δ = 5.52 ppm). Interestingly, a desulfonylation of the indole moiety occurred during this synthetic transformation.[10] The same compound could be obtained using the carboxylated indole as a nucleophilic species under the standard conditions reported by Katritzky and co-workers.[11] The formation of the tetracycle **11** can be easily explained by an intramolecular attack of the transient N-lithiated indole species on the

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(3) (a) Cutri, S.; Bonin, M.; Micouin, L.; Froelich, O.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **2000**, *41*, 1179. (b) Cutri, S.; Bonin, M.; Micouin, L.; Chiaroni, A.; Husson, H.-P. *J. Org. Chem.* **2003**, *68*, 2645.

(4) (a) Ennis, M. D.; Hoffman, R. L.; Ghazal, N. B.; Olson, R. M.; Knauer, C. S.; Chio, C. L.; Hyslop, D. K.; Campbell, J. E.; Fitzgerald, L. W.; Nichols, N. F.; Svensson, K. A.; McCall, R. B.; Haber, C. L.; Kagey, M. L.; Dinh, D. M. *Bioorg. Med. Chem. Lett.* **2003**, 2369. (b) Frédérich, M.; Jacquier, M.-J.; Thépenier, P.; De Mol, P.; Philippe, G.; Delaude, C.; Angenot, L.; Zèches-Hanrot, M. *J. Nat. Prod.* **2002**, *65*, 1382. (c) Bennasar, M.-L.; Jimenez, J.-M.; Vidal, B.; Sufi, A.; Bosch, J. *J. Org. Chem.* **1999**, *64*, 9605.

(5) Isolation eudistomins: (a) Rinehart, K. L., Jr.; Kobayashi, J.; Harbour, G. C.; Hughes, R. G., Jr.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 1524. Biological activities: (b) Van Maerseveen, J. H.; Hermkens, P. H. H.; De Clercq, E.; Balzarini, J.; Scheeren, H. W.; Kruse, C. G. *J. Med. Chem.* **1992**, *35*, 3223. Synthesis and analogues: (c) Van Maerseveen, J. H.; Scheeren, H. W.; De Clercq, E.; Balzarini, J.; Kruse, C. G. *Bioorg. Med. Chem.* **1997**, *5*, 955. (d) Liu, J.-J.; Hino, T.; Tsuruoka, A.; Nakagawa, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3487. (e) Yamashita, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2003**, *5*, 738. (f) Kurihara, T.; Sakamoto, Y.; Kimura, T.; Ohishi, H.; Harusawa, S.; Yoneda, R.; Suzutani, T.; Azuma, M. *Chem. Pharm. Bull.* **1996**, *44*, 900.

(6) For a recent review on the synthesis of heterocycles based on iminium ion cyclizations, see: Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311.

(7) Froelich, O.; Desos, P.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem.* **1996**, *61*, 6700.

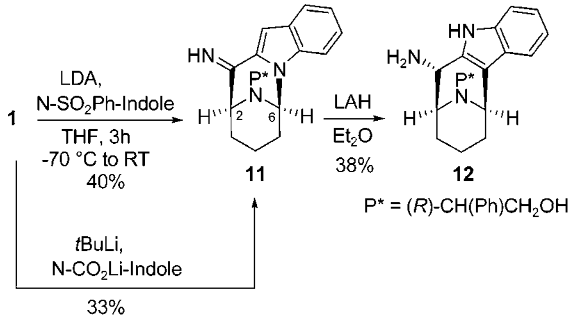
(8) Compound **8** could be characterized by NMR, but all attempts of chromatographic purifications led to its rearrangement or degradation.

(9) Absolute configuration of the newly created center was determined unambiguously by chemical correlation with the corresponding O-silylated piperidine.[3b]

(10) Sundberg, R. J.; Broome, R.; PowersWalters, C.; Schnur, D. *J. Heterocycl. Chem.* **1981**, *18*, 807.

(11) Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, *26*, 5935.

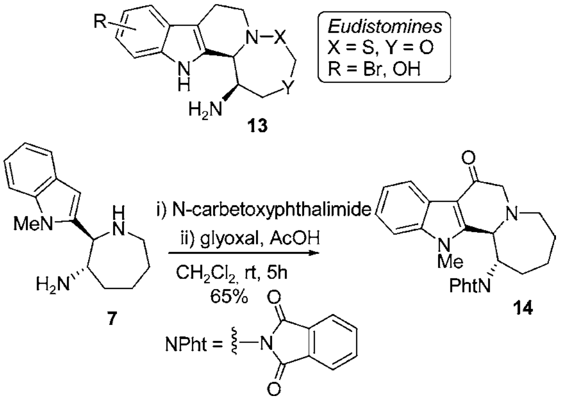
Scheme 3. Rearrangements of Indolic Aminals



transient iminium ion delivered by the oxazolidine ring. Although this compound proved to be quite stable, even under chromatographic purification conditions, an N to C rearrangement occurred during its reduction by LAH, leading to **12** as a single diastereomer.[12] The same relative configuration was assigned to compounds **10** and **12** on the basis of the consistency of their ^{1}H and ^{13}C NMR chemical shifts.

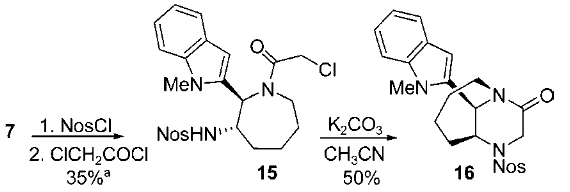
In the course of this general reactivity study, we investigated the use of derivative **7** as a starting material for the synthesis of carba analogues of eudistomines **13** (Scheme 4). Previous structure−activity relationships had shown significant antiviral and antitumoral activities of tetracyclic indole derivatives of this type.[5] We planned to obtain this target tetracyclic core by building the C ring using a bis-electrophile. Although this synthetic pathway is well documented,[13] it has mainly been applied to unprotected indole precursors. As expected, despite its major nucleophilicity on C3, the indole N-methylated substrate was difficult to cyclize in comparison to unprotected derivatives, since the anion cannot be formed. Finally, protection of the exocyclic amino group as a phthalimide and subsequent reaction using glyoxal as the bridging agent[14] led to the formation of the eudistomine analogue **14**.

Scheme 4. Preparation of Tetracyclic Azepanes



Interestingly, when the *o*-nosyl protective group and the chloroacetamide precursor were used in the presence of K$_2$CO$_3$ as the scavenger (Scheme 5),[15] compound **15** yielded the bridged piperazinone **16**.

Scheme 5. Cyclization to Piperazinones



^{a} Yield was 70% on the basis of recovered unreacted material.

In summary, we have established a rapid and stereoselective access to several new indolyldiamine polycyclic systems. These scaffolds can be obtained using simple chemoselective transformations of a common bicyclic aminal intermediate and could be of interest in a diversity-oriented search for new bioactive substances.

Acknowledgment. We thank the Ligue Nationale contre le Cancer and MRT (Picasso action) for financial support.

Supporting Information Available: Experimental procedures and characterization for compounds **6**, **7**, **9**−**12**, and **14**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] For a similar desulfonylation reaction, followed by an N to C rearrangement, see: (a) Rubiralta, M.; Diez, A.; Vila, C. *Tetrahedron* **1990**, *46*, 4443. (b) Rubiralta, M.; Diez, A.; Bosch, J.; Solans, X. *J. Org. Chem.* **1989**, *54*, 5591.

[13] For selected examples, see: (a) Melnyck, P.; Legrand, B.; Gasche, J.; Ducrot, P.; Thal, C. *Tetrahedron* **1995**, *51*, 1941. (b) Suzuki, H.; Iwata, C.; Sakurai, K.; Tokumoto, K.; Takahashi, H.; Hanada, M.; Yokoyama, Y.; Murakami, Y. *Tetrahedron* **1997**, *53*, 1593. (c) Suzuki, H.; Yokoyama, Y.; Miyagi, C.; Murakami, Y. *Chem. Pharm. Bull.* **1991**, *39*, 2170.

[14] For an example of the use of glyoxal as a bridging agent, see: Alexakis, A.; Tranchier, J.-P.; Lensen, N.; Mangeney, P. *J. Am. Chem. Soc.* **1995**, *117*, 10767 and references therein.

[15] (a) Dinsmore, C. J.; Beshore, D. C. *Org. Prep. Proced. Int.* **2002**, *34*, 367. (b) Dinsmore, C. J.; Bergman, J. M.; Bogusky, M. J.; Culberson, J. C.; Hamilton, K. A.; Graham, S. L. *Org. Lett.* **2001**, *3*, 865.