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Novel tricyclic diamines 1. Synthesis of 1,4-diazaisotwistane and 1,4-diazahomoisotwistane as constrained 3-aminoquinuclidine isosteres

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ABSTRACT

Synthesis of the novel tricyclic diamines 1,4-diazaisotwistane and 1,4-diazahomoisotwistane are described. These compact tricyclic cores have one tertiary and one secondary amine and may serve as ring-constrained isosteres of 3-aminoquinuclidine. Both tricycles were prepared by a similar strategy involving saturation of an appropriately substituted aromatic azaindole, functionalization and intramolecular alkylation.

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3-Aminoquinuclidine moieties are found in a number of pharmacologically active compounds. Two notable targets that have a number of examples containing 3-aminoquinuclidine moieties are α7 nicotinic acetylcholine receptor agonists (e.g. Encenicline[1] and MEM-3454,[2] Fig. 1) and the serotonergic $5HT_3$ antagonists (e.g. Azasetron[3] and Palonosetron,[4] Fig. 1).

During the course of a recent medicinal chemistry project,[5] we wanted to prepare conformationally locked variants of 3-aminoquinuclidine such as tricycle **1**, which had not previously been described. We refer to this novel tricycle as 1,4-diazaisotwistane in analogy to the corresponding all-carbon analog, isotwistane. (Isotwistane[6] is tricyclo[4.3.1.0^{3,7}]decane; for clarity, isotwistane numbering is also used for the diaza analog, see Fig. 2).

Restrosynthetically, we envisioned protected 1,4-diazaisotwistane **2** arising via an intramolecular ring closure from a fully-saturated and appropriately functionalized fused bicyclic precursor (**3**). We anticipated that **3** in turn could be prepared from the corresponding aromatic heterocycle (**4**) (Fig. 3).

In the forward sense, beginning with commercially available aldehyde **5** (Scheme 1),[7] Boc protection was followed by reduction of the aldehyde with sodium borohydride to afford hydroxymethylazaindole **4**. Initial attempts at fully saturating this azaindole by hydrogenation over Adam's catalyst[8] were complicated by a major side product, bicycle **7**, wherein the hydroxymethyl group was reduced to the corresponding methyl substituent. Presumably, this hydrogenolysis arose prior to ring saturation, while this was still a benzylic-like hydroxymethyl group. This complication could be avoided by first reducing the five-membered ring by hydrogenation over Pearlman's catalyst to afford hydroxymethylazaindoline **8**. Reduction of the pyridine ring in a subsequent hydrogenation with Adam's catalyst in EtOH/AcOH afforded the saturated bicycle **6** in an approximately 2:1 ratio of diastereomers, which were

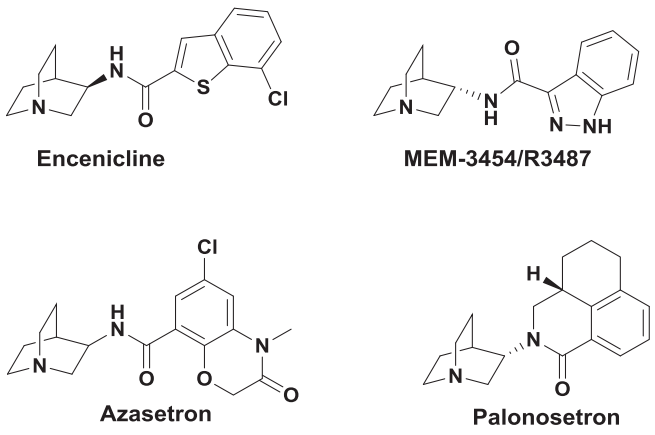

Fig. 1. Some examples of 3-aminoquinuclidine containing drugs.

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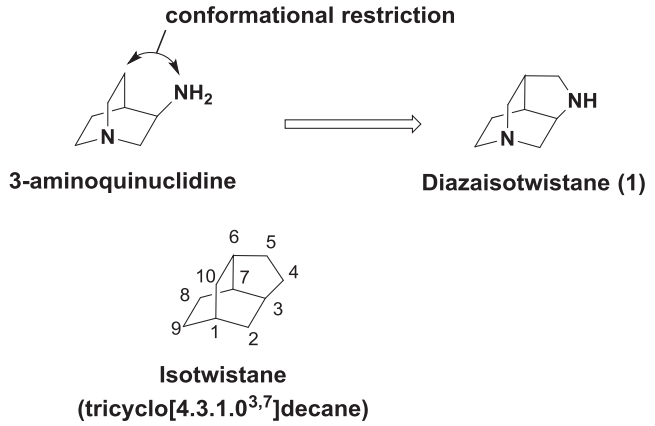


Fig. 2. Conformational restriction of 3-aminoquinuclidine.

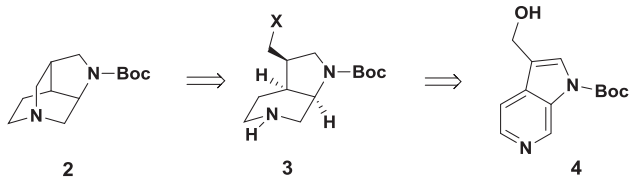


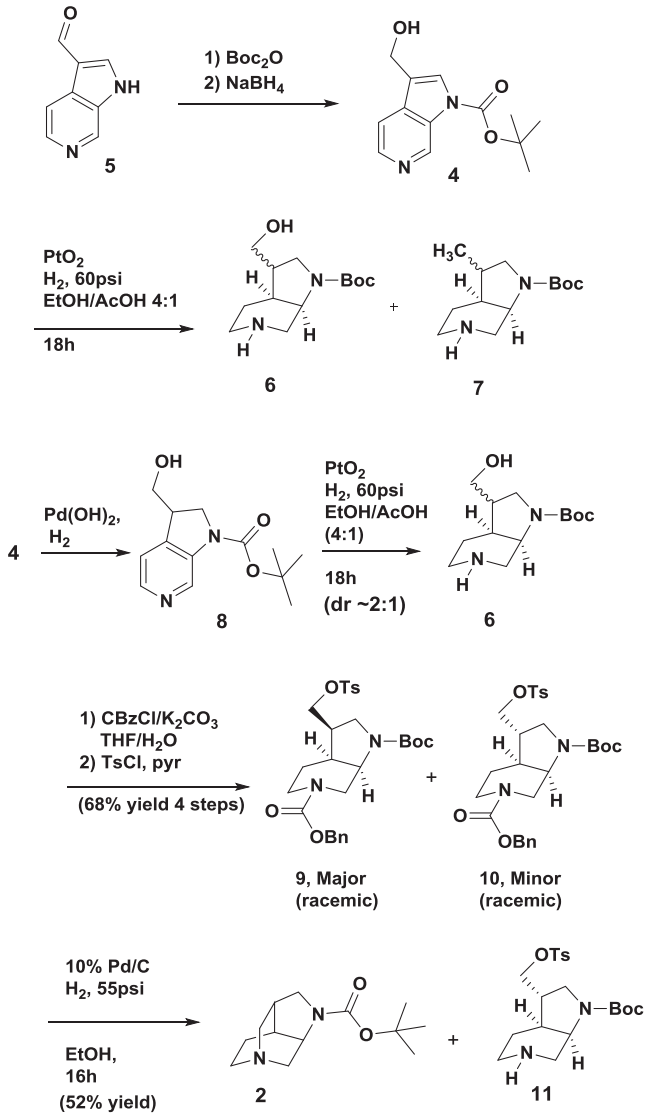
Fig. 3. Retrosynthesis.

carried on as a mixture. The secondary amine of saturated bicycle **6** was protected as its CBz derivative and the primary alcohol was converted to the corresponding tosylate to provide saturated bicycles **9** and **10**, as a racemic mixture of diastereomers. Hydrogenolysis of the Cbz group on the mixture of diastereomers **9** and **10** unveiled the secondary amine, which for the major, all-*cis*,[9] diastereomer, was set to undergo an intramolecular cyclization to afford the desired 1,4-diazaisotwistane **2**. The minor diastereomer was unable to undergo intramolecular cyclization in this case and could be separated as the piperidine tosylate **11** after the cyclization. Separation of these two products by silica gel chromatography was somewhat challenging and led to some loss in the isolated yield of the tricyclic product **2** (52% yield).

Gratifyingly, racemic Boc-protected 1,4-diazaisotwistane **2** crystallized from methanol (as a hemihydrate), and the structure was confirmed by X-ray crystallography (Fig. 4).

With access to the desired racemic 1,4-diazaisotwistane **2** accomplished, we next sought to access this material in an enantiopure state. Separation of the enantiomers of the racemic mixture of the 1,4-diazaisotwistane **2** by chiral chromatography (supercritical fluid chromatography, SFC) was quite challenging, but separation of the enantiomers of **9** prior to cyclization was facile and scalable (Scheme 2). The separated enantiomers of homochiral diastereomixture **9/10** could be cyclized exactly as the racemate, with the first eluting peak (**9/10a**) affording Boc-protected 1,4-diazaisotwistane **(3*S*)-2**, and the second eluting peak (**9/10b**) affording Boc-protected 1,4-diazaisotwistane **(3*R*)-2**.

Following the synthesis of the Boc-protected 1,4-diazaisotwistane **(3*R*)-2**, deprotection could be carried out under standard conditions by treatment with TFA to afford the trifluoroacetic acid salt as an oil (not shown). Alternatively, if *p*-TsOH was used in the deprotection step, the resultant salt, **(3*R*)-1** was a well-behaved crystalline solid, allowing for confirmation of absolute configuration by single-crystal X-ray analysis. Fig. 5 shows the X-ray structure of the 1,4-diazaisotwistane **(3*R*)-1**, with counterions removed for clarity. The opposite enantiomer **(3*S*)-1** could be prepared in the same manner starting from tosylate **9b**.



Scheme 1. Synthesis of diazaisotwistane core.

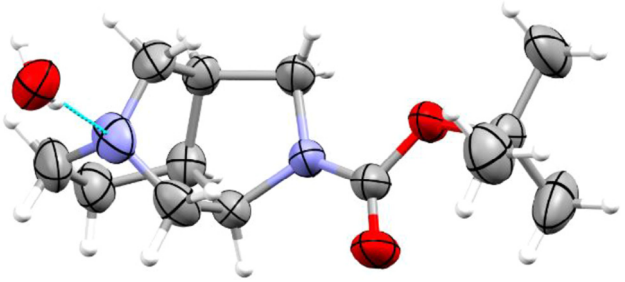


Fig. 4. ORTEP of Boc-1,4-diazaisotwistane hemihydrate (**2**).

Pleased that our synthetic strategy worked to prepare diazaisotwistane **1**, we anticipated that this approach could be applied to prepare additional novel tricycles. We felt that the homologous 1,4-diazahomoisotwistane (**12**, Fig. 6) would be similarly accessible starting with the homologous hydroxyethylazaindole **13**. It was thought that the slightly altered ring geometry in the homologated tricycle would make it a good comparitor to the 1,4-diazaisotwistane as a constrained 3-aminoquinuclidine isostere.

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