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Complementary asymmetric routes to fused tricyclic (*R*)-2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines and (*R*)-1,2,3,4,5,5a,6,7-octahydro-[1,4]diazepino[1,2-*a*]quinolines

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ABSTRACT

Two distinct enantioselective approaches to (*R*)-2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines and (*R*)-1,2,3,4,5,5a,6,7-octahydro-[1,4]diazepino[1,2-*a*]quinolines, low MW tricyclic organic scaffolds with a high degree of molecular complexity, are described. The key transformation in route 1 is the lateral lithiation of an *N*-Boc-*o*-toluidine and dianion trap with (*S*)-*tert*-butyldimethyl(oxiran-2-ylmethoxy)silane. An intramolecular S_N2 cyclization then forms the optically pure tetrahydroquinoline core. Route 2 involves the coupling of (*R*)-2-(4-benzyl-1-(Boc)piperazin-2-yl)acetaldehyde or (*R*)-2-(4-benzyl-1-(Boc)-1,4-diazepan-2-yl)acetaldehyde with an aryllithium and a subsequent intramolecular S_NAr reaction to form the tricycle. Both synthetic routes were valuable for preparing and identifying ligands targeting GPCRs expressed in the central nervous system (CNS).

Structurally complex small molecules are attractive drug discovery leads as evidence suggests they can bind their targets with higher specificity[1] and may have superior ADMET properties[1b,c,2] versus less complex structures. In 2009 Lovering et al. reported sp^3 carbon fraction [Fsp^3, where Fsp^3 = (number of sp^3 hybridized carbons/total carbon count)] and the presence or absence of stereocenters as two simple metrics of molecular complexity that, taken individually, correlated positively with clinical success.[2a,3] Consequently, these simple 2D molecular descriptors have found application in drug discovery programs.[4] Unfortunately, early drug leads are often rich in unsaturation[5] which is due, in part, to the widespread use of high-throughput sp^2–sp^2 coupling reactions employed by medicinal chemists.[6] While advancements in both natural product synthesis and diversity-oriented synthesis (DOS)[7] facilitate the availability of more diverse and structurally complex molecules for drug discovery, there still exists a demand for new chemical structures with increased saturation, as well as new synthetic methodologies to prepare them.

As part of an internal drug discovery program to identify orally bioavailable non prodrug ligands targeting GPCRs expressed in the CNS, the tetrahydroquinoline based tricyclic scaffolds **1** and **2** (Fig. 1) were recognized as key structural components of a number of early leads. These chemical entities, which exhibit high molecular complexity by both containing a chiral center and having sp^3 fractions equal to 0.50 and 0.54, respectively,[8] are excellent starting points for lead optimization. In this regard, synthetic access to enantiopure tricyclic compounds **1** and **2** was warranted.

Despite a number of literature references to substructure **1**,[9] an enantioselective route to the fused tricyclic core has not been reported.[10] Compound **2** represents an entirely novel structure with no synthetic routes reported. It was envisioned that enantioselective synthetic routes could be co-developed for both structures (**1** and **2**) as they share a common chiral tetrahydroquinoline core. The details of the design and implementation of two complementary asymmetric routes to both (*R*)-2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines (**1**) and (*R*)-1,2,3,4,5,5a,6,7-octahydro-[1,4]diazepino[1,2-*a*]quinolines (**2**) are described herein.

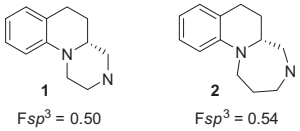

Figure 1. Tricyclic scaffolds (*R*)-2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline (**1**) and (*R*)-1,2,3,4,5,5a,6,7-octahydro-[1,4]diazepino[1,2-*a*]quinoline (**2**).

A previous report[11] from these laboratories detailed the asymmetric synthesis of the tricyclic indoline (*R*)-methyl 2-(7-hydroxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (**3**)

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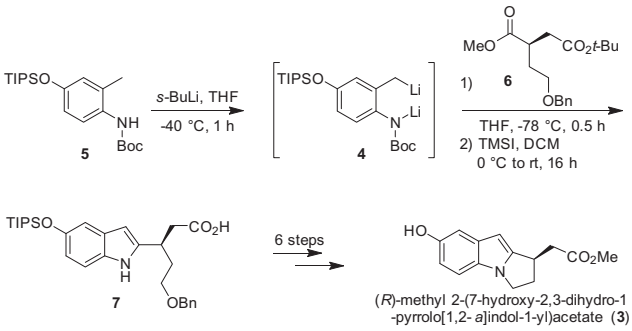
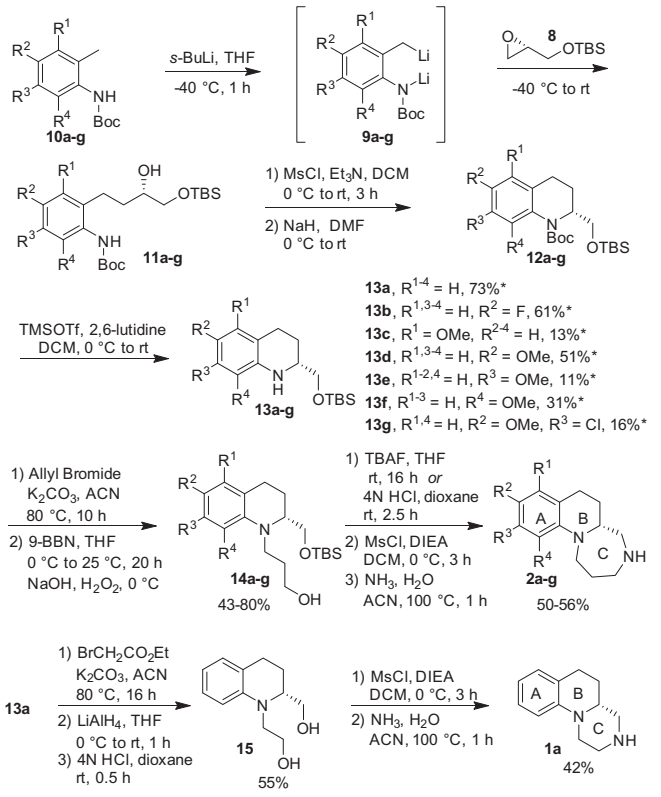
which showcased a modified version of Smith's[12] modular 2-substituted indole synthesis (Scheme 1). The key reaction involved trapping the dianion (**4**) generated from an *N*-Boc-*o*-toluidine (**5**) with an acyclic ester (**6**) containing a tertiary asymmetric carbon atom at the α-position. In the following step, an acid-mediated intramolecular ring closure formed the chiral indole (**7**). We sought to further exploit this lateral lithiation methodology toward the stereoselective synthesis of the tetrahydroquinoline core of tricycles **1** and **2** by employing commercially available (*S*)-*tert*-butyldimethyl(oxiran-2-ylmethoxy)silane (**8**) as the electrophilic trap.[13] As shown in Scheme 2, dianions (**9a–g**) generated from various substituted-*N*-Boc-*o*-toluidines (**10a–g**) were trapped with epoxide **8** to give secondary alcohols **11a–g**. Alcohol mesylation followed by deprotonation of the aniline nitrogen with sodium hydride effected intramolecular ring closure with stereochemical inversion to yield the optically pure bis-protected bicycles **12a–g**. Selective removal of the *N*-Boc groups using TMSOTf in the presence of 2,6-lutidine gave (*R*)-2-(((*tert*-butyldimethylsilyl)oxy) methyl)-1,2,3,4-tetrahydroquinolines **13a–g**. Overall yields for the four step sequence varied from 11% (**13e**) to 73% (**13a**). This was primarily due to the efficiency of the dilithiation step where the reactivity of epoxide **8** with dianions **9a–g** varied depending on the R^{1-4} substituents.



Scheme 1. Previously reported synthesis of (*R*)-methyl 2-(7-hydroxy-2,3-dihydro-1*H*-yrrolo[1,2-*a*]indol-1-yl)acetate (**3**).

The unsubstituted nucleophile **9a**, and those having a single fluorine (**9b**) or methoxy substituent *ortho* (**9f**) or *para* (**9d**) to the nitrogen atom gave yields superior to those with substitutions at the *meta* position (**9c**, **9e**, **9g**). The higher yielding substrates **9a–b**, **9d**, **9f** ultimately produced gram to multi-gram quantities of the corresponding tetrahydroquinolines (**13a–b**, **13d**, **13f**) and despite the modest yields with substrates **9c**, **9e**, and **9g**, the chemistry was adequate for our purposes and provided >500 mg of the corresponding tetrahydroquinolines **13c**, **13e**, and **13g**. Further optimization would likely expand both the yields and substrate scope for this novel approach to enantiopure 2-substituted-1,2,3,4-tetrahydroquinolines.[14]

Efforts to establish the final C ring initially focused on preparing the 6,6,7-systems **2a–g**. From **13a–g** an allylation and hydroboration-oxidation sequence gave intermediates **14a–g**. Desilylation of the TBS ether was performed using TBAF or 4N HCl in dioxane. The resulting diols were reacted with MsCl and DIEA in DCM, and ultimately aminated using ammonium hydroxide in ACN at 100 °C in a sealed reaction vessel which produced compounds **2a–g** in 50 to 56% yields (3 steps). Closure of the C ring to form the 6,6,6-fused tricyclic system (**1a**) was also demonstrated by a similar sequence including N-alkylation of **13a** with ethyl bromoacetate followed by lithium aluminum hydride reduction and acid mediated TBS-deprotection to give diol **15**. Cyclization (of **15**) was performed as described previously (for **2a–g**) to give tricycle **1a** in 42% yield.



Scheme 2. First generation synthesis of tricyclic compounds **2a–g** and **1a**. *Isolated yields from **10a–g** (4 steps).

While the lateral lithiation route was useful for preparing numerous analogs of **1** and **2**, its utility was somewhat limited. In particular, the ability to prepare multiple compounds varying R^{1-4} proved tedious and labor intensive as the aromatic A-ring of the molecules (**1** and **2**) were derived from the *N*-Boc-*o*-toluidine starting materials. In addition, SAR investigations prompted further exploration of substituents at R^1 (of **1** and **2**), which proved more difficult to prepare via this method. Lastly, the dilithiation reaction was incompatible with *N*-Boc-*o*-toluidines containing bromine atoms, which serve as useful handles to prepare analogs via metal mediated couplings at a late synthetic stage. Consequently, a more convergent asymmetric route that addressed these issues was developed.

Our second generation approach to compounds **1** and **2** was based on chemistry developed by Bernotas,[9c] which we applied to the preparation of racemic analogs of the 6,6,6-tricycle, ***rac*-1** (Scheme 3). The key step is a one-pot double cyclization reaction that involves 1,4-addition of 1,2-diaminoethane to enone **16**, lactamization (**17**), and intramolecular nucleophilic aromatic substitution (S_NAr) to deliver tricyclic ketone **18**. In this protocol, the chiral tertiary carbon is generated as a result of non-stereoselective 1,4-addition (of 1,2-diaminoethane) which results in the formation of racemic cyclization precursor **17**. We reasoned that *o*-fluorophenone **19**, an optically pure variant of **17** which lacks an epimerizable proton at the tertiary carbon, would be an appropriate synthetic precursor to give tricyclic ketone **20** through a stereospecific intramolecular S_NAr reaction.[15] A simple deoxygenation would produce the desired enantiopure tricycles **1** and **2**.

A convergent route to benzyl-protected 6,6,6-tricyclics **21a–b** starting from easily accessible and differentially protected (*R*)-2-hydroxyethyl-piperazine **22**[16] is shown in Scheme 4. Swern oxidation of **22** gave aldehyde **23**, which was then arylated with