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Stereoselective Synthesis of 3-Substituted Tetrahydropyrazinoisoquinolines via Intramolecular Cyclization of Enantiomerically Enriched Dihydro-2*H*-pyrazines

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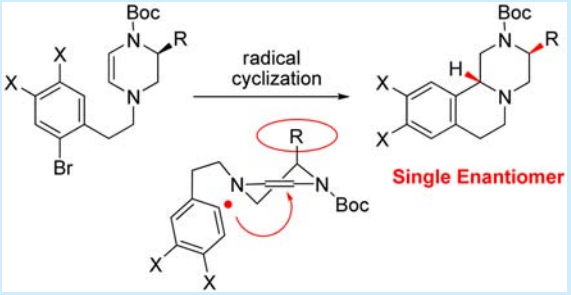
Supporting Information

ABSTRACT: The preparation of 3-substituted tetrahydropyrazinoisoquinolines using the tributyltin hydride mediated intramolecular radical cyclization of suitably protected 2-substituted 3,4-dihydropyrazines is reported. The compounds are obtained as single enantiomers, as the relative configuration of the new generated stereogenic center is driven by the stereochemistry of the 2-substituted carbon in the starting materials, which is in turn derived from naturally occurring amino acids.



The 2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]iso-quinoline-2-amine scaffold **1** (Figure 1) is found in a variety of natural products and pharmaceutically active ingredients. Alkaloids including such a moiety are known to act as α2-adrenoceptor antagonists,[1−3] opioid receptor antagonists,[4] and dipeptidyl peptidase IV (DPP-IV) inhibitors.[5] Moreover the class of alangium and ipecac alkaloids is known to have a potent eukaryotic cytotoxicity,[6,7] as in the case of emetine **2** or its synthetic derivative dihydroemetine,[8−10] which have been successfully used as anticancer and antiviral drugs[11−14] and for the treatment of protozoal infections.[11,14,15] Finally, the pyrazinoisoquinoline scaffold is present in the structure of Praziquantel **3**, which is the current drug of choice in the treatment of Schistosomiasis, a neglected tropical disease which affects more than 200 million people worldwide.[18−23]

From these considerations it is clearly apparent how the stereoselective modification of the 2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolines scaffold can be of great interest for the search for new drug candidates, and much effort has been devoted to this task.[24] For instance the Ugi multicomponent reaction,[25] the amidoalkylation and *N*-acyliminium ion cyclization of amido-acetals[26] and a radical cyclization[27] approach have been exploited to prepare highly diverse Praziquantel derivatives, even in a combinatorial way.

Analogs of Praziquantel of type **6** (Figure 2) have been reported, displaying some similarities with the original drug, but with decreased activity.[28] Inter alia, a series of novel pyrazino[2,1-*a*]isoquinolines **5** (Figure 2) have been prepared, resulting in a new structural type for the development of novel non-azole antifungal agents,[29] as well as some mimetics of

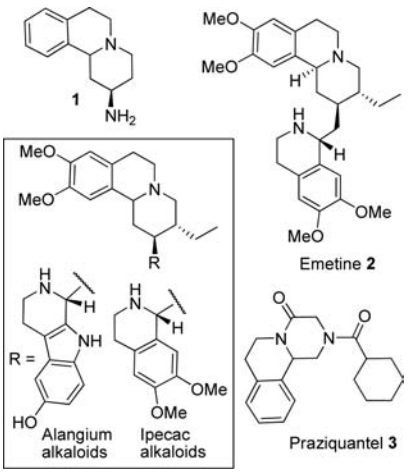


Figure 1. Biologically active molecules containing the 2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline scaffold.

emetines, in which the methine carbon C2 in the ABC-ring system is replaced by nitrogen.[30] The latter compounds showed less toxicity than emetine, but also lower antiamaebian and antitumoral activity (i.e., azaemetine **4**, Figure 2). Nevertheless, such derivatives are considered very attractive emetine mimetics, since they resemble their natural counterpart regarding the preferred conformation and charge distribution

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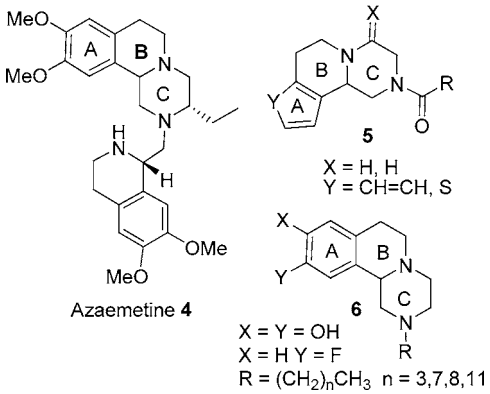


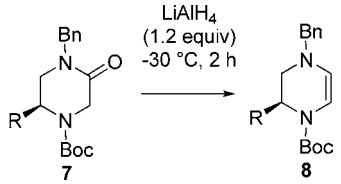
Figure 2. Pyrazino[2,1-*a*]isoquinoline scaffold in some biologically active compounds.

at physiological pH, and are also able to allow the attachment of different ring systems to the scaffold thus opening the way to the preparation of a broad variety of analogues.

Generally the pyrazino[2,1-*a*]isoquinoline moiety is efficiently prepared via acetylation of arylethylamines, cyclization, and reduction of the obtained ketopiperazine.[31] Nevertheless new synthetic approaches, able to lead to a more decorated scaffold, need to be investigated.

For instance, a multistep synthesis of enantiomerically enriched bioactive 2-aza-analogs of Ipecac and Alangium alkaloids has been recently reported[32] starting from a chiral amino acid and using a complete diastereoselective Speckamp cyclization[33] as a key step to obtain an oxo-piperazine which is eventually reduced. Here we describe our approach to the tetrahydropyrazinoisoquinoline skeleton which is based on the intramolecular radical cyclization of suitably protected 2-substituted 3,4-dihydropyrazines **8** (Scheme 1).

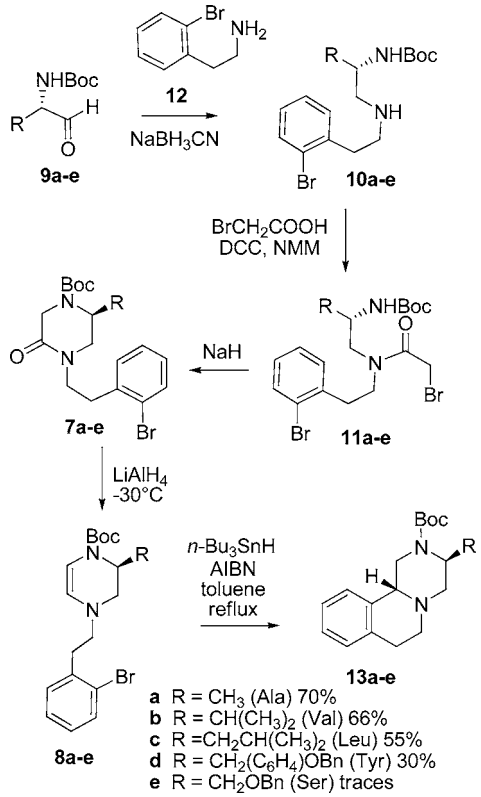
Scheme 1. Preparation of Chiral Dihydro-2*H*-pyrazines



Some years ago we reported a general, robust, and highly stereoselective method for the preparation of enantiomerically enriched 5-substituted oxopiperazines **7**.[34] These oxopiperazines were selectively reduced, using $LiAlH_4$, into the dihydro-2*H*-pyrazines **8** (Scheme 1).[35] The latter compounds were previously unreported, and only very recently an alternative synthesis of unsubstituted analogs has been proposed.[36] However, they can be very useful building blocks as for instance in the preparation of enantiomerically enriched 3-substituted 2,5-diazabicyclo[4.1.0]heptane cores[37] using the Simmon–Smith cyclopropanation protocol.

To further exploit their reactivity, we decided to investigate the use of 3,4-dihydro-2*H*-pyrazines **8** as starting material for the preparation of modified pyrazinoisoquinolines. It is well-known that aryl radicals are able to promote ring closure onto acyclic enamides[38−40] and that radical cyclizations can lead to highly diastereoselective processes.[41−43] Such reactivity, when applied to bromophenyl dihydropyrazinones, provided an easy and diastereoselective way to prepare fused tetrahydropiperazine[2,1-*a*]isoquinoline-4-ones, and this approach has been successfully applied to the synthesis of Praziquantel.[27] Consequently, the intramolecular radical cyclization of suitably protected 2-substituted 3,4-dihydropyrazines (Scheme 2)

Scheme 2. Synthesis of 3,4,6,7-Tetrahydro-1*H*-pyrazino [2,1-*a*]isoquinolines 13



appears to be a very promising strategy to obtain advanced intermediates for the diastereoseletive preparation of azaemetine analogs. The cyclization process, in fact, should allow the controlled installation of the ring junction, being that it is the relative configuration of the new generating stereogenic centers driven by the stereochemistry of the 2-substituted carbon in the starting material.

For this task, we prepared a series of 2-substituted 3,4-dihydro-2*H*-pyrazines **8a−e** having a 2-(2-bromophenyl) ethyl moiety on the nitrogen in the 4-position. This simultaneously plays the role of a protective group and a suitable radical precursor. All compounds **8a−e** were obtained by reduction of the corresponding oxopiperazines **7a−e**, in turn prepared following our usual synthetic sequence (Scheme 2) based on a reductive amination step which, in this case, is carried out using 2-(2-bromophenyl) ethylamine **12**.[34]

The radical reaction was performed in an argon atmosphere by refluxing the crude 2-substituted 3,4-dihydro-2*H*-pyrazines **8a−e** in degassed toluene (0.003 M), in the presence of tributyltin hydride and of a catalytic amount of AIBN. The desired intramolecular cyclization occurred smoothly, and we were pleased to observe that the expected compounds were obtained as the only reaction products with excellent diastereoselectivity. The title 3,4,6,7-tetrahydro-1*H*-pyrazino-[2,1-*a*]isoquinolines **13a−d** were recovered as a single diastereoisomer by UPLC and ^1H NMR analysis of the crude mixture and obtained in good to reasonable yields after

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purification by flash chromatography. In contrast, in the case of **8e** cyclization was unsuccessful and only traces of **13e** were found together with a complex mixture of byproducts.

The relative stereochemistry of the observed diastereoisomer was determined by 1D NOESY and 2D ROESY NMR experiments.[44] Accordingly, the absolute (3*S*, 11b*R*)-configuration of the piperazine core could be assigned from the known C-3 stereogenic center, derived from the naturally occurring L-alanine used as starting material.

A rationale for the high diastereoselectivity observed in this reaction can be put forward considering the models represented in Figure 3, where low energy conformers of substrate **8a** are depicted together with the cyclization reaction transition state models for the *exo* and *endo* conformations of compound **8a**.

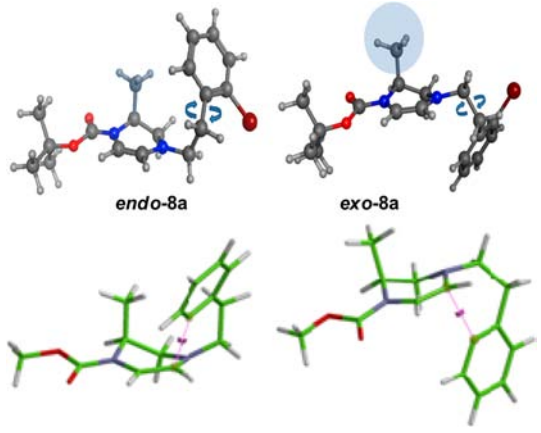


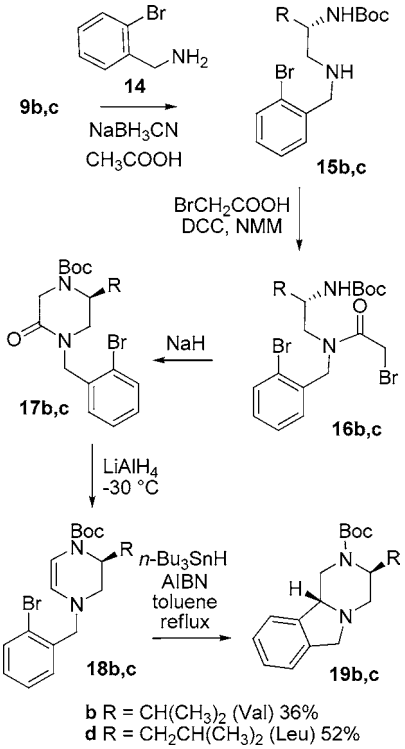
Figure 3. Low energy conformers and cyclization transition state models for the *exo* and *endo* conformations of compound **8a**.

As already observed for 6-alkyltetrahydropyridines,[45] the substituent might prefer to adopt an axial orientation, which favors the *exo* diastereoisomer, where there is no steric interaction between the substituent (methyl in case of **8a**) and the phenyl ring bearing the radical species. Indeed, the energy difference between the two transition states is ~0.75 kcal/mol, calculated at the DFT B3LYP/6-31G* level, in favor of the *exo* conformation. This energy gap, corresponding to an *endo*/*exo* ratio of about 10/90 at 298 K, can fully explain the *anti* selectivity of the radical addition observed and corresponds to the aryl radical adding onto the *Si* face of the olefin.[46]

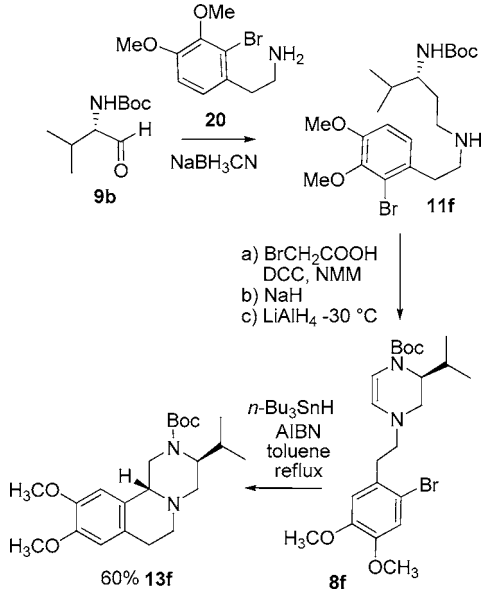
Such an approach could also be used to prepare hexahydropyrazino[2,1-*a*]isoindoles **19**. To prove this, we prepared 2-bromobenzyl 3,4-dihydropyrazines **18b,c** following the standard synthetic sequence previously described,[34] and using 2-(2-bromophenyl)benzylamine **14** in the reductive amination step. Radical cyclization was then performed under the same experimental conditions to give the [2,1-*a*] isoindoles **19b,c** in reasonable yields, and, once again, as a single diastereoisomer (Scheme 3). The relative stereochemistry for compounds **19b** and **19c** was determined, as discussed above, by NOE studies, and the (3*S*,10b*R*) configuration, derived from the *anti* addition, was confirmed.

Finally our procedure was successfully applied to prepare compound **13f** (Scheme 4) as a possible advanced intermediate for the synthesis of azaemetine or tetrahydropyrazinoisoquinolines analogs of Ipecac and Alangium alkaloids (see Figure 2). Dihydro-2*H*-pyrazine **8f** was prepared from valine aldehyde **9b** and 2-(2-bromo-3,4-dimethoxyphenyl) ethyl

Scheme 3. Synthesis of Hexahydropyrazino[2,1-*a*]isoindoles



Scheme 4. Synthesis of a Possible Intermediate for the Preparation of Ipecac and Alangium Alkaloids Analogs



amine **20**. The key radical cyclization occurred successfully, and compound **13f** was indeed recovered, as a single diastereoisomer, in 60% yield after purification by flash chromatography.

In summary, we have shown that suitably protected enantiomerically pure 2-substituted 3,4-dihydropyrazines are useful chiral building blocks for the stereoselective synthesis of highly decorated polycyclic structures, which might be transformed into different families of bioactive compounds. In particular both the 3-substituted tetrahydropyrazinoisoquinolines and hexahydropyrazino[2, 1-*a*]isoindoles have

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efficiently been obtained from this starting material through a diastereoselective intramolecular radical cyclization, in which the configuration of the newly formed stereogenic center resulted in being *trans* with respect to the pre-existing C-3 stereogenic center of the dihydro-2*H*-pyrazine scaffold. This original synthetic protocol has been successfully applied to the preparation of an advanced intermediate in the synthesis of Ipecac and Alangium alkaloid analogs.

■ ASSOCIATED CONTENT

Supporting Information

All experimental procedures, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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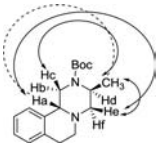

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