ORGANIC LETTERS

2012
Vol. 14, No. 23
5972–5975

A General Organocatalytic Approach toward the Enantioselective Total Synthesis of Indolizidine Based Alkaloids

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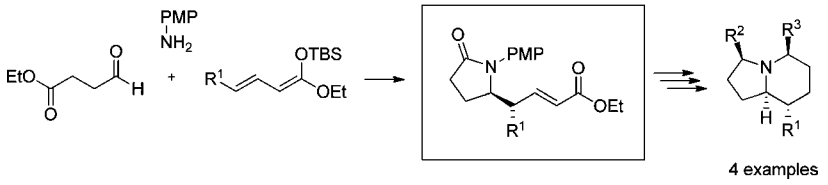
Received October 19, 2012

ABSTRACT



Four indolizidine based alkaloids (IBAs) have been synthesized in a highly enantioselective, straightforward, and flexible manner. As a key step our previously developed Brønsted acid catalyzed vinylogous Mannich reaction was employed which easily afforded gram amounts of an optically pure central intermediate which can be converted into a wide range of diversely substituted IBAs.

Lipid soluble indolizidine based alkaloids (IBAs) are commonly found in amphibian skin and display a wide range of biological activities. Among them significant inhibitory effects are observed on nicotinic acetylcholine receptors,[1] which make them promising candidates, e.g., for control of Alzheimer's disease, schizophrenia, epilepsy, and Parkinson's disease.[2,3] The structural diversity of IBAs is quite broad, as over 240 different members of this natural product class have been isolated thus far, which only differ in their substitution pattern and in the relative configuration of the substituents.[4] In particular, 5-mono-, 3,5-di-, and 5,8-disubstituted indolizidines represent a large portion of this group with over 100 members (Scheme 1). The relative configuration of some IBAs has been established whereas their absolute configuration remains largely unknown. Thus, IBAs depicted in Scheme 1 are drawn in a convenient manner as described by Daly and co-workers[5] but do not necessarily represent the correct absolute configuration. In several cases all stereoisomers have been isolated. Only microgram amounts of IBAs are typically available from natural sources, and therefore they have often been characterized merely by vapor-phase FT-IR and mass spectrometry.[6] In addition, due to this low availability, some structures have not yet been confirmed to be of natural origin (e.g., **1** and **2**). For further structure elucidation/validation and biological testing, a straightforward and flexible synthetic access toward sufficient quantities of optically pure material is highly desirable.

Accordingly, a wide range of different strategies toward IBAs have been developed which have been reviewed extensively on a regular basis since 1984.[7]

However, most of the reported procedures employ ex-chiral-pool strategies starting from amino acids and

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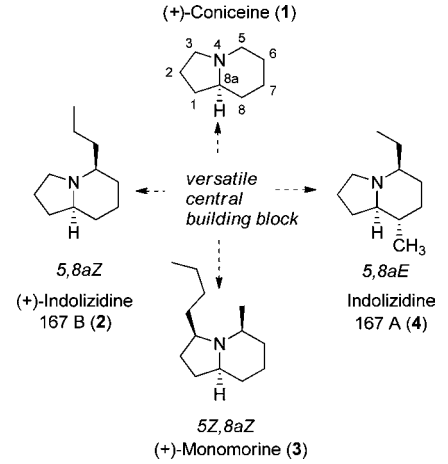
10.1021/ol302871u
Published on Web 11/19/2012

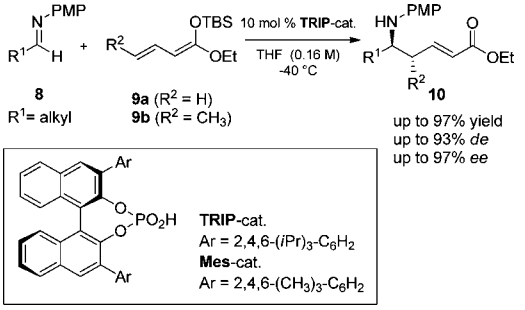
Scheme 1. Access toward Differently Substituted IBAs from a Versatile, Central Building Block



their derivatives which are directly incorporated into the final products.[8] Alternatively, chiral auxiliary-based strategies (e.g., with SAMP/RAMP,[9] carbohydrates,[10] amino alcohols,[11] or *N*-sulfinylimines[12]) have been developed and provide optically active IBAs with excellent diastereoselectivity.[13] An elegant three-component linchpin coupling of 2-silyl-1,3-dithianes with an optically pure epoxide and aziridine has been developed toward indolizidine 223AB.[14] Very few catalytic enantioselective approaches based upon the asymmetric Sharpless dihydroxylation,[15] the iridium-catalyzed allylic amination,[16] or the asymmetric Heck[17] reaction are known. Organocatalytic procedures such as the proline-catalyzed asymmetric α-amination/Horner–Wadsworth–Emmons olefination approach[18] by Kalkote et al. or the α-aminoxylation[19] of aldehydes by the Kumar group also lead to some IBAs. Most of these strategies, however, are limited to specific substitution patterns within the indolizidine core and, in addition, typically require further functional group manipulations to assemble the bicyclic framework.

Recently, we have documented the Brønsted acid catalyzed, enantioselective vinylogous Mukaiyama–Mannich reaction (VMMR) of acyclic silyl dienolates **9a** and **9b** to furnish δ-amino-α,β-unsaturated esters **10** in good yields and excellent enantio- and diastereoselectivities.[20]

Scheme 2. Brønsted Acid Catalyzed, Enantioselective, Vinylogous Mannich Reaction with Aliphatic Imines



Whereas our initially disclosed protocol[21] was best suited for aromatic and heteroaromatic aldimines, we have recently been able to extend this reaction to aliphatic aldimines **8** by a slight modification of the reaction conditions (Scheme 2). Functional groups such as ester moieties, halogen atoms, and alkynes were readily tolerated in this process. The use of the γ-methyl substituted dienolate **9b** furnished the corresponding vinylogous Mannich products carrying a second stereogenic center with good *anti*-diastereoselectivity as well. We report herein a generally applicable, flexible, catalytic, and enantioselective synthetic access to gram amounts of optically pure IBAs with the VMMR as the key step. In addition, this strategy at the same time provides the opportunity for a late-stage incorporation of substituents at various positions within the indolizidine core from a versatile central building block.

We envisioned an ester-substituted imine as a suitable reaction partner for the VMMR under the consideration that it should readily undergo a subsequent cyclization into the corresponding γ-lactam. This transformation would not only form the five-membered ring and set the first bridgehead stereogenic center but also provide a functionalized carbon chain required for the assembly of the bicyclic framework at the same time. To put these plans

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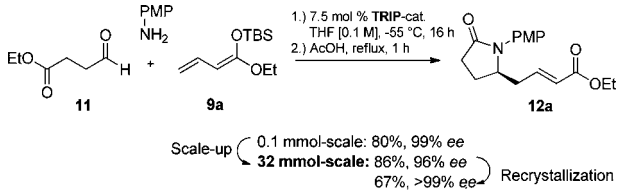
into practice, we treated bifunctional aldehyde **11**, *para*-anisidine, and vinylketene silyl-*O*,*O*-acetal **9a** with catalytic amounts of the TRIP phosphoric acid[22] (TRIP-cat.) for only 10 min at −55 °C which yielded the corresponding vinylogous Mannich product with 99% *ee*. Without further isolation the reaction mixture was subsequently stirred in acetic acid under reflux for 1 h which eventually afforded the desired lactam **12a** in 80% yield over two steps on a laboratory scale (Scheme 3).

Scheme 3. Synthesis of Chiral Lactam **12a**



The scale-up of this process was easily possible simply by prolonging the reaction time to 16 h which furnished **12a** in 86% yield over two steps and with a slightly decreased enantioselectivity of 96% *ee*.

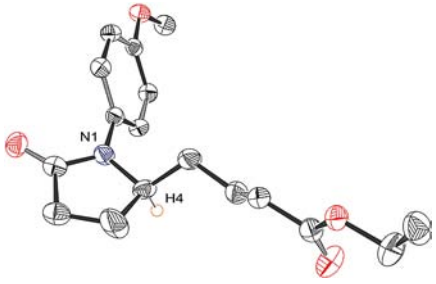


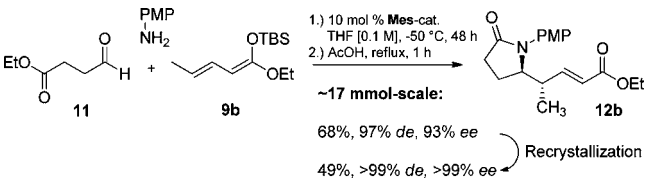
Figure 1. X-ray structure of **12a**. Elipsoid level at 50%; H-atoms are ommited for clarity except H^4.

The optical purity of lactam **12a** was further enhanced to >99% *ee* through a single recrystallization from a biphasic toluene/hexane solution which also provided material suitable for X-ray crystallography thereby proving its absolute configuration[23] (Figure 1; for further information, please see the SI).

The vinylogous Mannich reaction could also be employed advantageously to introduce a second stereogenic center at the 8-position of the indolizidine ring with good diastereoselectivity when the γ-methyl-substituted dienolate **9b** was used as the starting material.

The vinylogous Mannich product **12b** was obtained with very good diastereo- and enantioselectivity and an overall yield of 68% using the 3,3′-*bis*mesityl-substituted BINOL-phosphoric acid (Mes-cat.) as the Brønsted acid catalyst which proved superior over the TRIP-cat. in this particular case. **12b** was subsequently recrystallized to give a single diastereomer with >99% *ee* (Scheme 4, for the X-ray structure of **12b**, please see the SI). With multigram amounts of optically pure lactams **12a** and **12b** in hand, conversion into the target IBAs was undertaken. Compound **12a** was first transformed into the saturated Boc-protected lactam **13a** *via* a high-yielding three-step sequence and further elaborated in two distinct ways depending upon the substitution pattern of the final product (Scheme 5).

Scheme 4. Synthesis of Chiral Lactam **12b**



For 3-unsubstituted indolizidines, a chemoselective reduction of the imide *via* the hemiaminal furnished Boc protected pyrrolidine **14** in excellent yield[24] which was further converted into indolizidinone **16** through a deprotection–cyclization protocol in a quantitative yield.[25] In order to access 3-substituted indolizidines, Grignard addition on **13a** and subsequent reduction of the in situ generated *N*-acyl iminium ion, using a combination of *tris*pentafluorophenyl borane and triphenylsilane, occurred with complete *cis*-diastereoselectivity, to deliver pyrrolidine **15** which was converted into indolizidinone **17** in a very good yield over the two steps.[26]

For the 8-substituted indolizidines, lactam **12b** was employed as the starting material, which was first transformed into the imide **13b** and subsequently fully reduced, deprotected, and cyclized to furnish 8-methyl substituted indolizidinone **18** in 71% overall yield (Scheme 6).

The 5-substituent could now easily be installed *via* organometallic addition to indolizidinones **16**–**18** and subsequent diastereoselective iminium ion reduction.[27] Following this protocol, (+)-indolizidine 167B (**2**), (+)-monomorine (**3**), and indolizidine 167A (**4**), differing in their substitution at C3, C5, and C8, were obtained from their respective precursors as their TFA-salts in excellent yields as single stereoisomers (Scheme 7).[28]

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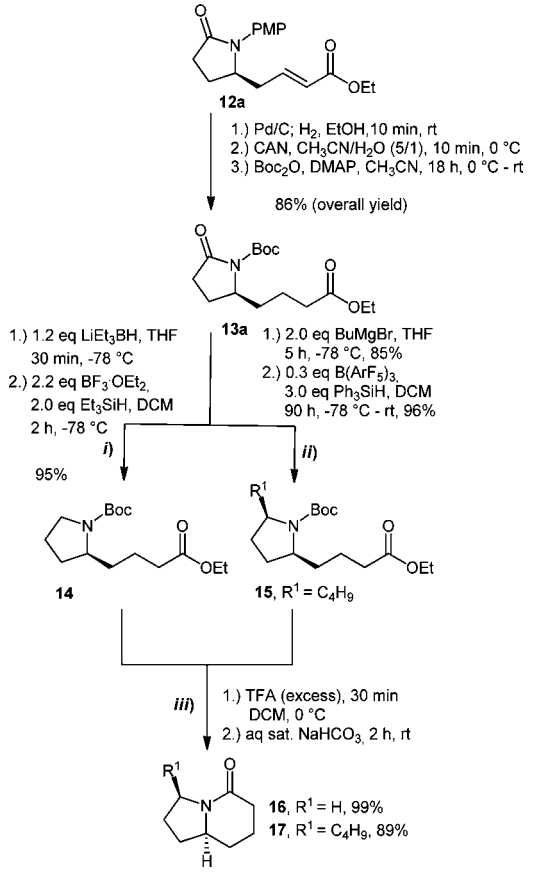
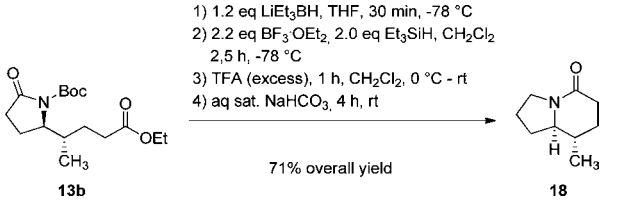
Scheme 5. Elaboration in Two Distinct Ways

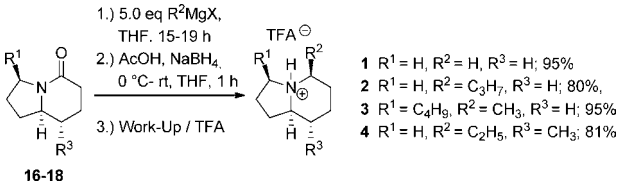


Scheme 6. Synthesis 8-Methyl-indolizidinone **18**



The yields of this final transformation exceed those reported in the literature quite significantly and are most likely due to the facile and quantitative isolation of the nonvolatile TFA salts. (+)-Coniceine (**1**) was obtained after complete reduction of **16** using lithium aluminum hydride.[29]

Scheme 7. Syntheses of Various IBAs **1**–**4**



In conclusion, we have established a novel, catalytic, enantioselective, and at the same time highly flexible synthetic access toward differently substituted IBAs **1**–**4** using our previously developed Brønsted acid catalyzed vinylogous Mannich reaction (VMMR). Both key intermediates **12a** and **12b** were formed on a large scale in good overall yields with excellent enantioselectivity, which was further enhanced through a single recrystallization to >99% *ee*. Further manipulations gave rise to (*S*)-coniceine and indolizidines 167A, 167B, and 195B as their TFA-salts in optically pure form, documenting the versatility of this approach. Hence, this strategy could conceivably be used to synthesize an even broader variety of naturally and non-naturally occurring IBAs using a parallel synthesis format. Further studies in this direction are currently ongoing in our laboratories.

Acknowledgment. We are grateful to the Deutsche Forschungsgemeinschaft and the Evonik-Stiftung (graduate fellowship to F.A.) for the generous financial support of this work. The donation of chemicals from Evonik, Chemetall, and BASF is gratefully acknowledged. We would like to thank J. Sieler for providing X-ray crystallographic data for compounds **12a** and **12b**.

Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for all new compounds, and CIF data for compounds **12a** and **12b**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.