BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

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Edited by Joseph Philip Michael

Generated on 02 November 2026, 02:47

Imprint

Beilstein Journal of Organic Chemistry
www.bjoc.org
ISSN 1860-5397
Email: journals-support@beilstein-institut.de

The *Beilstein Journal of Organic Chemistry* is published by the Beilstein-Institut zur Förderung der Chemischen Wissenschaften.

Beilstein-Institut zur Förderung der Chemischen Wissenschaften
Trakehner Straße 7–9
60487 Frankfurt am Main
Germany
www.beilstein-institut.de

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Beilstein Journal of Organic Chemistry

Indolizidines and quinolizidines: natural products and beyond

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Editorial

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Beilstein Journal of Organic Chemistry **2007**, 3, No. 27.
doi:10.1186/1860-5397-3-27

Received: 24 September 2007
Accepted: 26 September 2007
Published: 26 September 2007

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Alkaloids occur in such astonishing profusion in nature that one tends to forget that they are assembled from a relatively small number of structural motifs. Among the motifs that are most frequently encountered are bicyclic systems containing bridgehead nitrogen, especially 1-azabicyclo[4.3.0]nonanes and 1-azabicyclo[4.4.0]decanes or their unsaturated analogues – the indolizidines and quinolizidines to which this Thematic Series is devoted. These two azabicyclic systems may occur in the natural products either in isolation (the so-called 'simple izidine' alkaloids) or, more commonly, embedded within fused polycyclic arrays. Just how widespread they are was pointed out over two decades ago in a review in which it was estimated that between 25% and 30% of all alkaloids possess structures incorporating one or other of these motifs. [1] As might be expected of systems that are so pervasive, their natural sources are extremely diverse: they occur in organisms as widely different as bacteria, fungi, higher plants, invertebrates and vertebrates; and both terrestrial and marine sources are represented. For example, two of the best-known and most widely investigated groups of 'simple izidine' alkaloids are the plant-derived polyhydroxylated indolizidines that function as potent glycosidase inhibitors, [2-4] and the alkylindolizidines and analogues sequestered from dietary sources in the skins of amphibians. [5,6] It is thus hardly surprising that both the structural elucidation and the total synthesis of these and related alkaloids continue to attract the attention of eminent chemists, as borne out by the seemingly inexhaustible flow of publications in prominent journals. [7] Several general reviews on these alkaloids have also appeared in recent years. [8-11]

The interest in indolizidines and quinolizidines, although inspired by alkaloids, nowadays extends far beyond natural product chemistry. Considerable effort is being invested in the development of innovative methods for preparing the parent bicyclic systems and, more especially, for the stereocontrolled attachment of substituents. Studies on the biological activity of compounds containing azabicyclic building blocks (for example, rigid bicyclic peptidomimetics) are gaining momentum. Structural, spectroscopic and computational studies on both natural and synthetic indolizidines and quinolizidines are also reported regularly. In this Thematic Series, there are representative articles covering several of these aspects. A number of authors have contributed reviews in which their own contributions to the development of indolizidine and quinolizidine chemistry are highlighted. There are articles on the total synthesis of relevant natural products, as well as articles

describing novel methodological approaches to the systems of interest. That what may appear to be a marginal, passé or recondite outpost of chemistry still attracts a healthy measure of international attention bears testimony to the durability of a topic that is sure to retain its fascination for the foreseeable future.

Jo Michael

Guest Editor

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The definitive version of this article is the electronic one which can be found at:
doi:10.1186/1860-5397-3-27

Beilstein Journal of Organic Chemistry

Flexible synthetic routes to poison-frog alkaloids of the 5,8-disubstituted indolizidine-class I: synthesis of common lactam chiral building blocks and application to the synthesis of (-)-203A, (-)-205A, and (-)-219F

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Full Research Paper

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Beilstein Journal of Organic Chemistry **2007**, 3, No. 29.
doi:10.1186/1860-5397-3-29

Received: 19 July 2007
Accepted: 28 September 2007
Published: 28 September 2007

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Abstract

Background

The 5,8-disubstituted indolizidines are the largest class of poison-frog alkaloids found in anuran skin, and are of considerable interest because of their inhibitory effects on the neuronal nicotinic acetylcholine receptors. Many synthetic strategies for the construction of this nucleus have been reported: however, a flexible route has not been reported to date.

Results

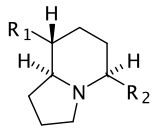
Synthesis of lactam chiral building blocks for the flexible synthesis of the title alkaloids has been achieved using a Michael-type conjugate addition reaction to a chiral cyclic enamine ester as the key step in constructing the trisubstituted piperidine ring system. To demonstrate the usefulness of these chiral building blocks, syntheses of (-)-**203A**, (-)-**205A** from **1**, and (-)-**219F** from **2** have been achieved.

Conclusion

The total synthesis of (-)-**203A**, (-)-**205A**, and (-)-**219F** was achieved, and the absolute stereochemistry of natural **203A** was determined to be 5*S*, 8*R*, 9*S*. In addition, the relative stereochemistry of natural **219F** was determined.

Introduction

The indolizidine ring system has been widely found in microbial, plant, and animal sources, and many natural products containing this ring system show interesting biological activities. [1] The skin extracts of poison-frogs are a rich source of indolizidines. [2] There are about 20 examples of 3,5-disubstituted indolizidines and about 80 of the 5,8-disubstituted indolizidines. Furthermore, many of such poison-frog alkaloids show significant activities, for example with nicotinic acetylcholine receptors (nAChRs) of the central nervous system. [3] Our syntheses and then biological evaluations of poison-frog alkaloids, [4-10] revealed that the 5,8-disubstituted indolizidine (-)-**235B'**, exhibited selective and potent blockade of α4β2-nAChRs. [11] Alkaloids of this class with various substituents at the 5- and 8-positions that have been synthesized are shown in Figure 1. All side-chain double bonds in these synthetic compounds have the *cis* (*Z*) configuration. Our flexible synthetic strategy provides a powerful tool for the synthesis of 5,8-disubstituted indolizidines, permitting detailed investigation of structure activity relationships for blockade of nAChRs by this class of alkaloids.



203A: $R_1 = Me$, $R_2 = CH_2CH{=}CHC{\equiv}CH$
205A: $R_1 = Me$, $R_2 = (CH_2)_3C{\equiv}CH$
207A: $R_1 = Me$, $R_2 = (CH_2)_3CH{=}CH_2$
209B: $R_1 = Me$, $R_2 = n\text{-}C_5H_{11}$
209I: $R_1 = n\text{-}Pr$, $R_2 = n\text{-}Pr$
219F: $R_1 = Et$, $R_2 = (CH_2)_3C{\equiv}CH$
221I: $R_1 = Et$, $R_2 = (CH_2)_2CH{=}CHCH_3$
223J: $R_1 = n\text{-}Pr$, $R_2 = n\text{-}Bu$
223V: $R_1 = n\text{-}Bu$, $R_2 = n\text{-}Pr$
231C: $R_1 = Me$, $R_2 = (CH_2)_3CH{=}CHC{\equiv}CH$
233D: $R_1 = Me$, $R_2 = (CH_2)_3CH{=}CHCH{=}CH_2$
235B': $R_1 = Me$, $R_2 = (CH_2)_5CH{=}CH_2$
235B": $R_1 = Me$, $R_2 = (CH_2)_3CH{=}CHCH_2CH_3$
237D: $R_1 = Me$, $R_2 = n\text{-}C_7H_{15}$
251N: $R_1 = n\text{-}Bu$, $R_2 = n\text{-}C_5H_{11}$

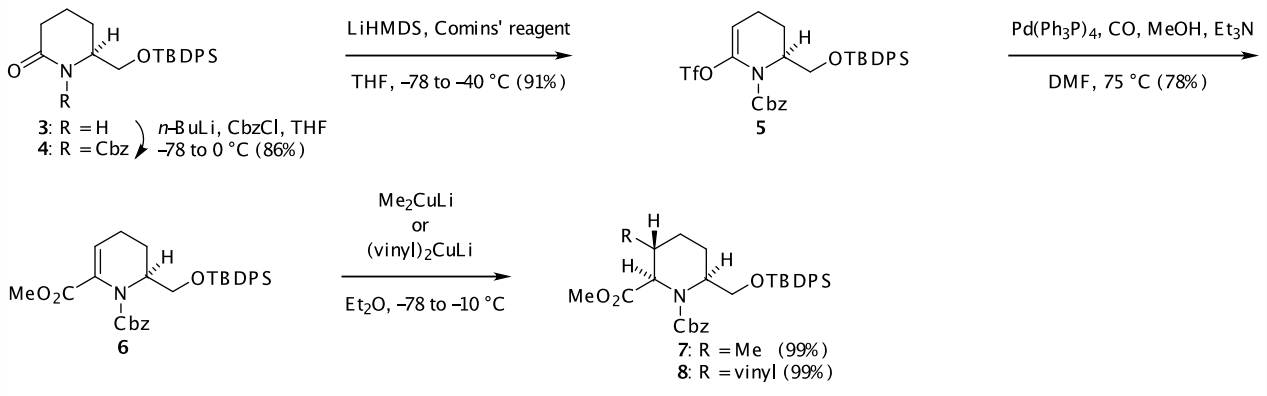
Figure 1: Representative examples of 5,8-Disubstituted Indolizidines.

In this contribution, we describe the synthesis of the common lactam chiral building blocks that permit the flexible synthesis of 5,8-disubstituted indolizidines. Their application to the synthesis of (-)-**203A**, (-)-**205A**, and (-)-**219F** illustrates in detail the synthetic procedures employed. [12]

Results and Discussion

To realize the versatile synthesis of the 5,8-disubstituted indolizidine class of poison-frog alkaloids, we designed two lactam chiral building blocks (**1**, **2**). The substituent at the 8-position is stereoselectively created by our original Michael-type conjugate addition reaction. [13,14] Various substituents at the 5-position would be introduced using the protected hydroxymethyl side-chain (Figure 2).

The synthesis began with the known piperidone **3**, [15] which was treated with *n*-BuLi and then CbzCl to provide the Cbz-urethane **4**. Treatment of **4** with LiHMDS followed by 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins' reagent) [16] gave the enoltriflate **5** in good yield. The palladium-catalyzed carbon monoxide insertion reaction [17] in the presence of MeOH afforded the enaminoester **6**. The key Michael-type conjugate addition reaction of **6** with lithium dimethylcuprate or divinylcuprate proceeded smoothly to



Scheme 1: Construction of tri-substituted piperidine ring systems (**7**, **8**).

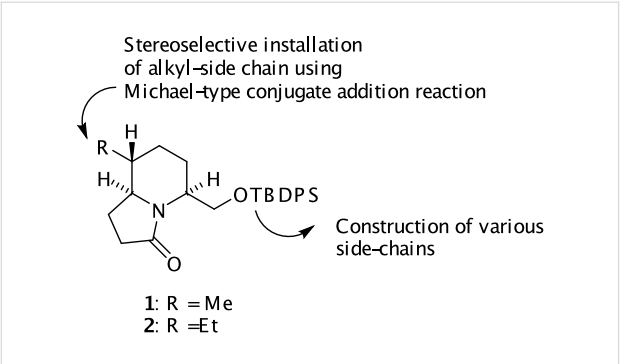
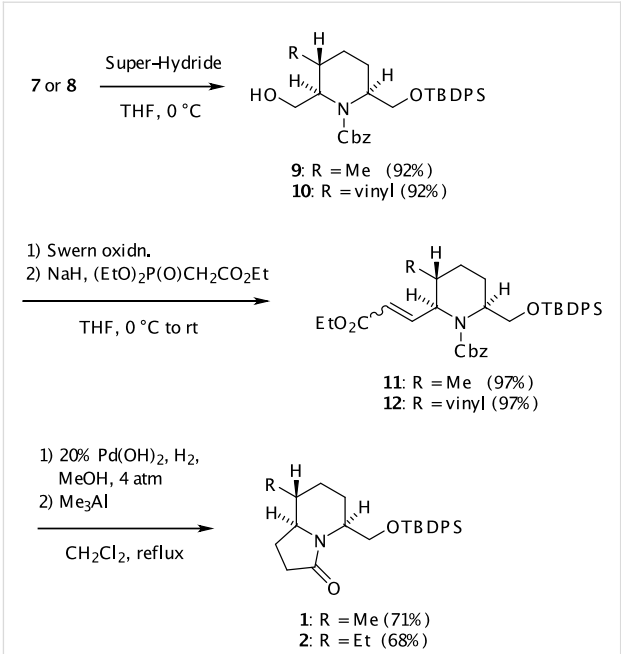


Figure 2: Synthetic Strategies to 5,8-Disubstituted Indolizidines from Chiral Building Blocks (**1**,**2**).

provide the trisubstituted piperidines (**7**, **8**) as single stereoisomers in excellent yields.

The stereochemical course of the above addition reaction can be rationalized as follows: The enamine ester **6** would adopt conformation **A** owing to $A^{(1,3)}$ strain [18] between the benzyloxycarbonyl group on nitrogen and the substituent at the α-position, The methyl or vinyl anion then attacks from the α-orientation controlled by a stereoelectronic effect [19] producing the desired trisubstituted piperidine as a single isomer. This argument can also be explained by the Cieplak's hypothesis [20] as shown in Figure 3. Reduction of the ester moiety in **7** and **8** with Super-Hydride gave the corresponding alcohols (**9**, **10**) in good yield. Swern oxidation of **9** or **10** followed by Horner-Emmons reaction of the resulting aldehydes afforded the α,β-unsaturated esters (**11**, **12**) each in 97% yield. Hydrogenation of the double bond in **11** or **12** over 20% $Pd(OH)_2$ and then treatment of the resulting deblocked amino alcohols with trimethylaluminum under Weinreb's conditions [21] gave rise to the lactams **1** and **2** in 71% and 68% overall yields, respectively.



Scheme 2: Synthesis of common lactam-type chiral building blocks (**1**, **2**).

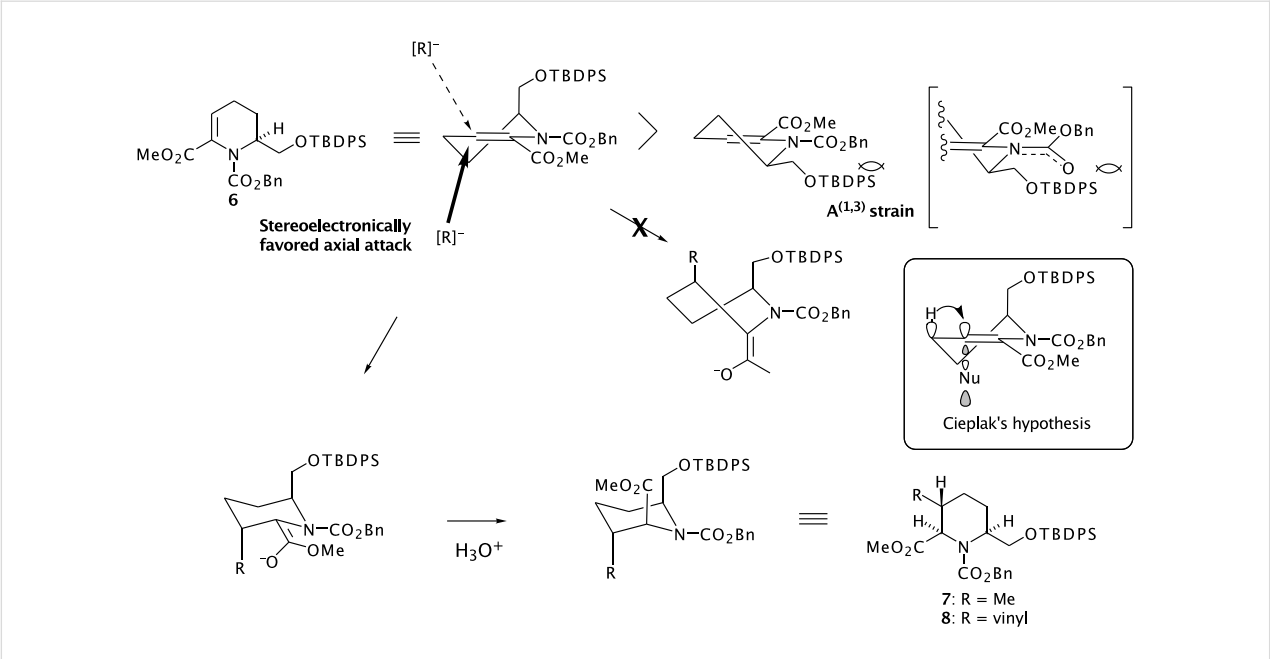
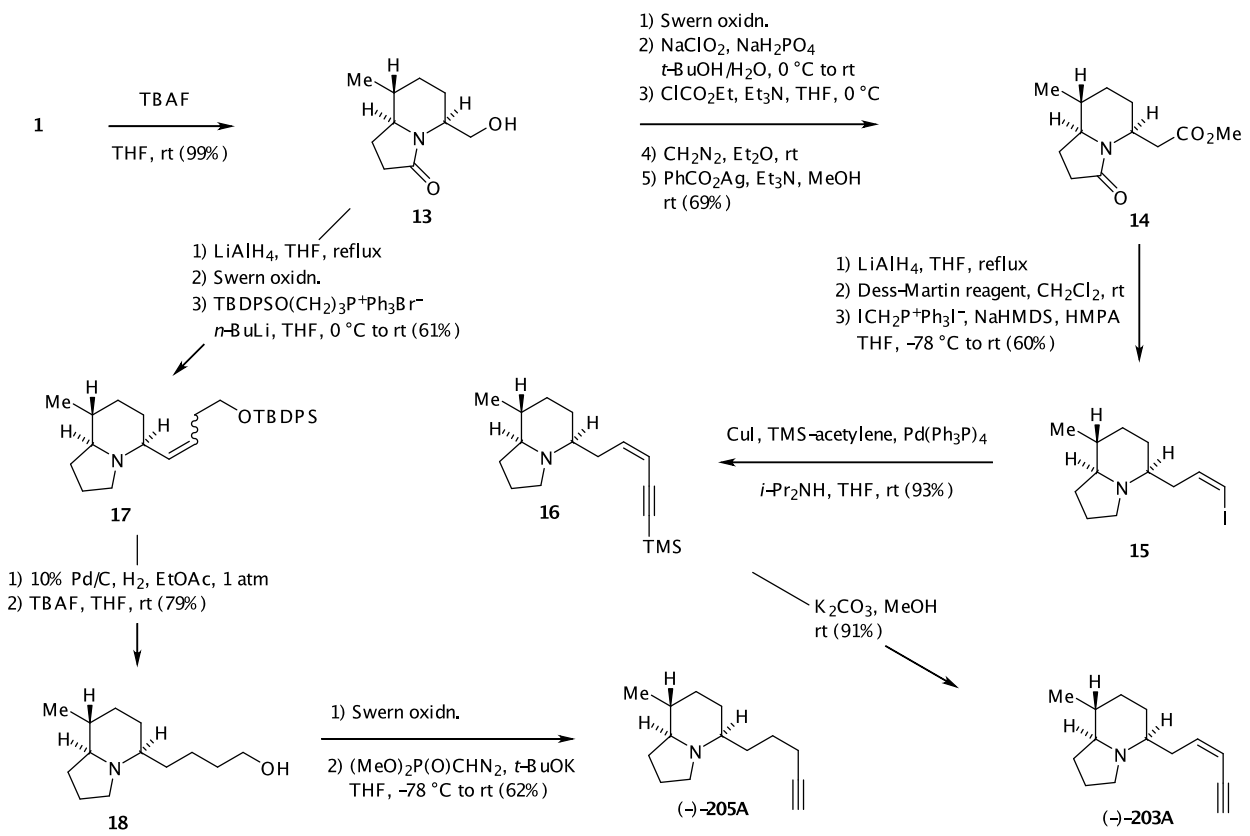


Figure 3: Stereochemical Course of Key Michael-type Conjugate Addition Reaction of **6**.



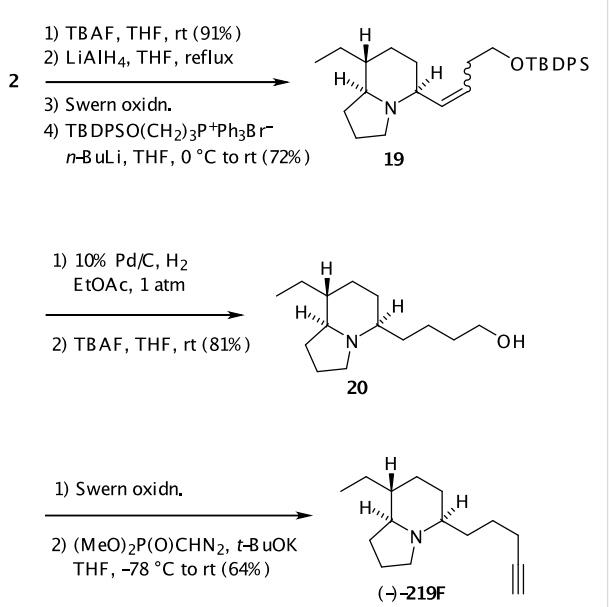
Scheme 3: Synthesis of (-)-**203A** and (-)-**205A**.

To demonstrate the utility of the chiral lactam building blocks, we conducted the total synthesis of indolizidines (-)-**203A** [22] and (-)-**205A** [23] from **1**, and (-)-**219F** [2] from **2**, respectively (Scheme 3, Scheme 4). Removal of the silyl protecting group in **1** was performed by treatment with TBAF to afford the corresponding alcohol **13**, which was converted to the homologated ester **14** via a two-step oxidation, followed by an Arndt-Eistert sequence of the resulting carboxylic acid. Reduction of both carbonyl groups in **14** with lithium aluminum hydride provided the alcohol, which was directly used for formation of *Z*-iodoolefin **15**. Thus, the Dess-Martin periodinane oxidation [24] of the alcohol, followed by Wittig reaction of the resulting aldehyde under Stork's reaction conditions, [25] gave the olefin. Purification by silica gel column chromatography afforded pure **15** in 60% isolated yield. The coupling reaction of **15** with TMS-acetylene under Sonogashira's conditions [26] gave rise to the product **16**. Finally, treatment of **16** with K_2CO_3 in MeOH provided (-)-**203A**. The GC-MS and GC-FTIR spectra of synthetic (-)-**203A** were identical with those of the natural product, and comparison of the optical rotation of the synthetic material ($[\alpha]_D^{26}$ -94.5 (c 2.0, $CHCl_3$) with the natural product, lit. [22] $[\alpha]_D$ -23.3 (c 0.3, $CHCl_3$)) suggest that the absolute stereochemistry of natural **203A** is 5*S*, 8*R*, 9*S*.

We achieved the total synthesis of (-)-**205A** starting from **1** via **13** (Scheme 3). Lithium aluminum hydride reduction of **13** followed by Swern oxidation and Wittig reaction of the resulting aldehyde gave the olefin **17**. Hydrogenation of **17** over Pd/C, and treatment of the resulting indolizidine with TBAF provided the homologated alcohol **18**. Finally, the terminal triple bond was constructed by Seyferth-Gilbert reaction. [27] After oxidation of **18** under the Swern conditions, treatment of the resulting aldehyde with Seyferth-Gilbert reagent in the presence of *t*-BuOK furnished (-)-**205A**, whose spectral data were identical with reported values. [22,28]

In addition, (-)-**219F**, a 5,8-disubstituted indolizidine with an ethyl group at C-8, [2] was synthesized from **2** (Scheme 4). The lactam **2** was converted to the homologated alcohol **20** via **19** as used with **1** in the synthesis of (-)-**205A**, which was then transformed into (-)-**219F** using the Seyferth-Gilbert reaction after Swern oxidation of **20**.

Although the direct comparison of the NMR spectra of the synthetic alkaloid with the natural product was not possible due to the scarcity of natural product, the GC-MS and GC-FTIR spectra of the synthetic material were identical with those of



Scheme 4: Synthesis of (-)-**219F**.

natural product detected in the Madagascan mantellid frog, *Mantella betsileo*. Thus, the relative stereochemistry of natural **219F** was established.

In conclusion, we succeeded in the construction of chiral lactam building blocks (**1**, **2**) for the synthesis of three representative poison-frog alkaloids of the 5,8-disubstituted indolizidine class; these were alkaloids (-)-**203A**, (-)-**205A**, and (-)-**219F (**experimental details can be found in Supporting Information File 1). This flexible synthetic route starting from **1** or **2** will be amenable to any side-chain at the 5-position of these alkaloids. Such indolizidines are expected to show inhibitory effects on the nAChRs, and the biological results will be reported in due course.

Supporting Information

Supporting Information File 1

Experimental details for the synthesis of (-)-**203A**, (-)-**205A**, and (-)-**219F**. Experimental data which includes experimental details on the spectral instruments, elemental analyzer.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-29-S1.doc]

Acknowledgments

This work was supported in part by a grant-in-aid for Scientific Research (C, No. 17590004) by the Japan Society for the Promotion of Science (JSPS). Work at NIH was supported by the intramural research program of NIDDK.

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Flexible synthesis of poison-frog alkaloids of the 5,8-disubstituted indolizidine-class. II: Synthesis of (-)-209B, (-)-231C, (-)-233D, (-)-235B", (-)-221I, and an epimer of 193E and pharmacological effects at neuronal nicotinic acetylcholine receptors

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Beilstein Journal of Organic Chemistry **2007**, 3, No. 30.
doi:10.1186/1860-5397-3-30

Received: 19 July 2007
Accepted: 28 September 2007
Published: 28 September 2007

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Abstract

Background

The 5,8-disubstituted indolizidines constitute the largest class of poison-frog alkaloids. Some alkaloids have been shown to act as noncompetitive blockers at nicotinic acetylcholine receptors but the proposed structures and the biological activities of most of the 5,8-disubstituted indolizidines have not been determined because of limited supplies of the natural products. We have therefore conducted experiments to confirm proposed structures and determine biological activities using synthetic compounds. Recently, we reported that one of this class of alkaloids, (-)-**235B'**, acts as a noncompetitive antagonist for α4β2 nicotinic receptors, and its sensitivity is comparable to that of the classical competitive antagonist for this receptor, dihydro-β-erythroidine.

Results

The enantioselective syntheses of (-)-**209B**, (-)-**231C**, (-)-**233D**, (-)-**235B"**, (-)-**221I**, and what proved to be an epimer of natural **193E**, starting from common chiral lactams have been achieved. When we performed electrophysiological recordings to examine the effects of the synthetic alkaloids on two major subtypes of nicotinic receptors (α4β2 and α7) expressed in *Xenopus laevis* oocytes, (-)-**231C** effectively blocked α4β2 receptor responses (IC_{50} value, 1.5 μM) with a 7.0-fold higher potency than for blockade of α7 receptor responses. In contrast, synthetic (-)-**221I** and (-)-epi-**193E** were more potent in blocking α7 receptor responses (IC_{50} value, 4.4 μM and 9.1 μM, respectively) than α4β2 receptor responses (5.3-fold and 2.0-fold, respectively).

Conclusion

We achieved the total synthesis of (-)-**209B**, (-)-**231C**, (-)-**233D**, (-)-**235B"**, (-)-**221I**, and an epimer of **193E** starting from common chiral lactams, and the absolute stereochemistry of natural (-)-**233D** was determined. Furthermore, the relative stereochemistry of (-)-**231C** and (-)-**221I** was also determined. The present asymmetric synthesis of the proposed structure for **193E** revealed that the C-8 configuration of natural **193E** should be revised. The selectivity for α4β2 and α7 nicotinic receptors differed markedly for the 5,8-disubstituted indolizidines tested, and thus it appears that the nature of the side chains in these indolizidines is crucial with regard to subtype-selectivity.

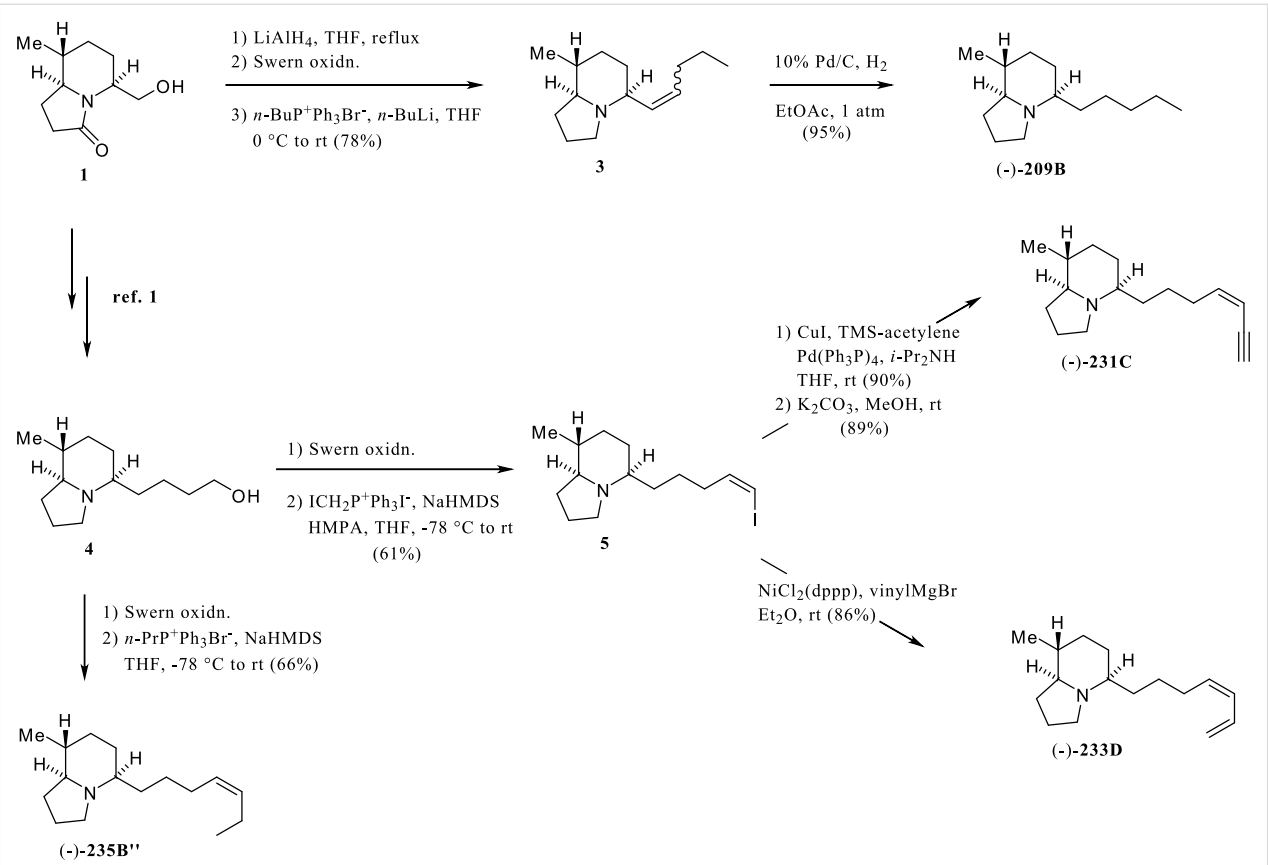
Introduction

In the preceding paper [1], we have reported the synthesis of the chiral lactam building blocks (**1**, **2**, Scheme 1, Scheme 2) for the flexible synthesis of poison-frog alkaloids of the 5,8-disubstituted indolizidine class. The utility of these chiral building blocks was demonstrated by the synthesis of alkaloids (-)-**203A**, (-)-**205A** from **1**, and of (-)-**219F** from **2**. Although the biological activity of most of the 5,8-disubstituted indolizidines has not been investigated, certain 5,8-disubstituted indolizidines have been shown to act as noncompetitive blockers of nicotinic acetylcholine receptors. [2,3]

Nicotinic receptors are ligand-gated ion channels composed of five subunits. [4] To date, 12 nicotinic receptor subunits (α2-α10, β2-β4) have been identified. Subtypes of neuronal nicotinic receptors are constructed from numerous subunit combinations, which confer varied functional and pharmacological characteristics. [5] Nicotinic receptors have been implicated in a wide range of neuronal dysfunctions and mental illness, such as epilepsy, Tourette's syndrome, Alzheimer's disease, Parkinson's disease, and schizophrenia. [5,6] Since different subtypes of nicotinic receptors are involved in different neurological disorders, subtype-selective nicotinic ligands would be valuable for investigation and potentially for treatment of cholinergic disorders of the central nervous system. However, there are only a limited number of compounds that elicit subtype-selective blockade of nicotinic receptors because of the similarity of receptor-channel structure among the subtypes. Recently, we have investigated the effect of synthetic (-)-**235B'**, one of the 5,8-disubstituted indolizidine class of poison-frog alkaloids, on several subtypes of nicotinic receptors, and found that this alkaloid exhibits selective and potent blocking effects at the α4β2 nicotinic receptor. [3] The potency of (-)-**235B'** for this receptor is comparable to that of the classical α4β2 competitive antagonist, dihydro-β-erythroidine. In this study, we have synthesized 5,8-disubstituted indolizidines (-)-**209B**, (-)-**231C**, (-)-**233D**, (-)-**235B"**, (-)-**221I**, and an alkaloid that proved to be an epimer of natural indolizidine **193E**. The alkaloids (-)-**209B** and (-)-**235B"** are known to be noncompetitive nicotinic blockers [2], but effects of the other compounds have not yet been tested. To explore possible subtype selectivity, we examined the effects of (-)-**231C**, (-)-**221I** and (-)-epi-**193E** on α4β2 and α7 nicotinic receptors, the most abundant subtypes in the mammalian brain. [4]

Results and Discussion

Reduction of the lactam **1** [1] with $LiAlH_4$ followed by Swern oxidation of the resulting alcohol and Wittig reaction gave the olefin **3** in 78% overall yield (Scheme 1). Hydrogenation of the double bond in **3** with 10% Pd/C provided (-)-**209B**, whose spectral data were identical with reported values. [7] The lactam **1** was also converted to the alcohol **4**, [1] which was transformed into (-)-**235B"** by Swern oxidation followed by Wittig reaction under high dilution and 'salt free' conditions (Scheme 1). The spectral data of synthetic (-)-**235B"** were identical with reported values. [8,9] Indolizidines (-)-**231C** [10] and (-)-**233D** [10] were synthesized from common intermediate **5** prepared from the alcohol **4**. Thus, the Swern oxidation of **4** and then the Wittig reaction of the resulting aldehyde under Stork's conditions [11] provided the *Z*-iodoolefin **5** in a highly stereoselective manner. The Sonogashira coupling reaction [12] of **5** with TMS-acetylene followed by cleavage of the trimethylsilyl



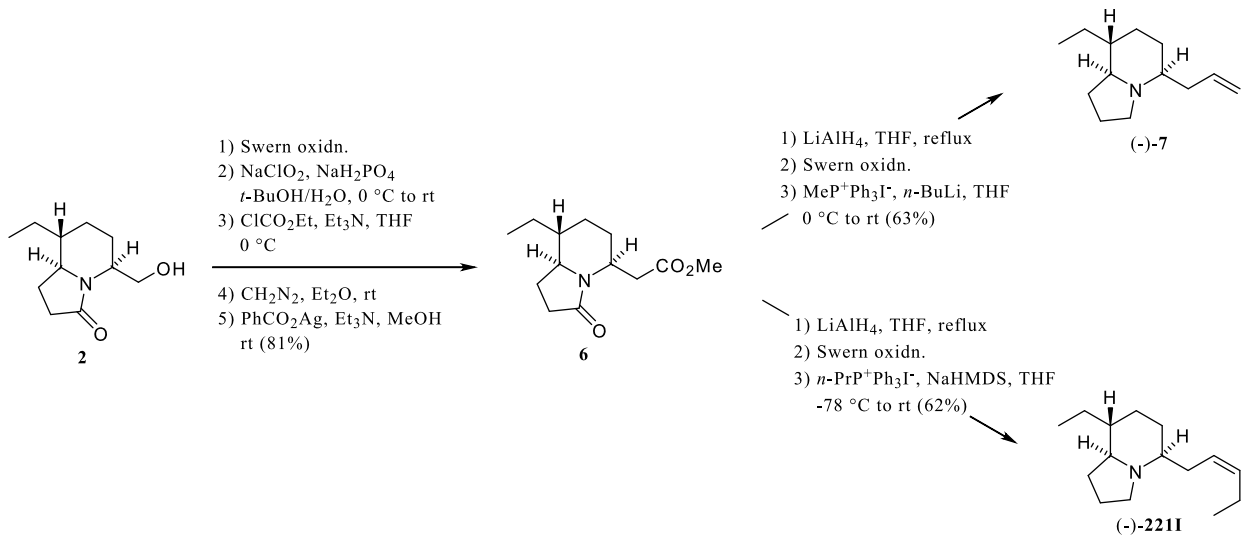
Scheme 1: Syntheses of (-)-**209B**, (-)-**231C**, (-)-**233**D, and (-)-**235B''**.

group with K_2CO_3 afforded (-)-**231C**. Although the rotation of the natural alkaloid is unknown, the relative stereochemistry was determined to be 5,8-*E* and 5,9-*Z* by GC-MS and GC-FTIR comparison with natural **231C** in extracts from a Panamanian dendrobatid frog, *Dendrolbates pumilio*. A similar, Ni-catalyzed cross coupling [13] reaction of **5** with vinylmagnesium bromide provided the (-)-**233D**, whose spectral data were identical with values reported for the natural alkaloid isolated from the Panamanian dendrobatid frog. [10] Although differing in magnitude, the HCl salts of both synthetic (-) **233D** and the natural alkaloid had negative optical rotations.

Indolizidine (-)-**7** with the relative stereochemistry proposed for **193E** [14] and indolizidine (-)-**221I** [14] were synthesized from the lactam **2** [1] via the ester **6** (Scheme 2). The two-step oxidation of **2** followed by Arndt-Eistert homologation of the resulting carboxylic acid provided the ester **6**. Reduction of both lactam and ester moieties of **6** with $LiAlH_4$ followed by Swern oxidation and Wittig reaction of the resulting aldehyde furnished the indolizidine (-)-**7**. Coinjections of synthetic material with an alkaloid fraction from a Madagascan mantellid frog, *Mantella viridis* that contained natural **193E**, revealed that the synthetic material had a slightly longer GC retention time than the natural product. The GC-mass spectra of (-)-**7** and natural product were virtually identical and their GC-FTIR spectra were very similar in the Bohlmann band region (indicating 5,9-*Z* configurations in both), although differing slightly in their fingerprint regions. These results indicate that the natural **193E** is most likely the 8-epimer of (-)-**7** and that the proposed configuration [14] of the ethyl substituent at C-8 was in error. The indolizidine (-)-**221I** was also synthesized from **6** following a procedure similar to that used for the synthesis of (-)-**7** as shown in Scheme 2.

The relative stereochemistry of natural **221I** was determined to be the same as that of synthetic (-)-**221I** by GC-MS and GC-FTIR comparison with natural **221I**, in the alkaloid fraction from the Madagascan mantellid frog, *Mantella viridis* (See Supporting Information File 1 for experimental details relating to all syntheses).

We then conducted electrophysiological experiments to examine the effect of three of the synthetic alkaloids on nicotinic receptors. When *Xenopus laevis* oocytes expressing the α4β2 nicotinic receptor were treated with 3 μM (-)-**231C**, the peak amplitude of the acetylcholine (ACh)-elicited currents



Scheme 2: Syntheses of (-)-**221I** and (-)-**7** (an epimer of **193E**).

was greatly decreased, whereas the responses elicited in oocytes expressing the α7 nicotinic receptor were not strongly affected (Figure 1A). When the concentration-response curves were compared between these receptor subtypes, (-)-**231C** blocked the α4β2 receptor-mediated currents [50% inhibitory concentration (IC_{50}) = 1.5 μM, 95% confidence intervals (CI): 1.1 to 2.1 μM] with 7.0-fold higher sensitivity than blockade of the α7 receptor-mediated currents (IC_{50} = 10.7 μM, 95% CI: 8.6 to 13.3 μM) (Figure 1B). These results indicate that (-)-**231C** selectively blocked the responses mediated by the α4β2 receptor.

The 5,8-disubstituted indolizidine (-)-**231C** is an analogue of (-)-**235B'**, both of which have a seven-carbon unsaturated side-chain at C-5 and a methyl at C-8. Both synthetic compounds have the same absolute stereochemistry (5*R*, 8*R*, 9*S*). Our previous [3] and present data demonstrate that both (-)-**235B'** and (-)-**231C** produce potent blockade of the α4β2 nicotinic receptor with a similar selectivity of 6- to 7-fold over blockade of the α7 receptor. However, the potency of (-)-**235B'** in blocking the α4β2 receptor is approximately 20-fold greater than that of (-)-**231C**. These results suggest that either flexibility or degree of unsaturation of the seven-carbon side-chain at C-5 in these 5,8-disubstituted indolizidines is crucial for potent interaction with the α4β2 receptor.

The synthetic (-)-**221I** and (-)-epi-**193E** are 5,8-disubstituted indolizidines with an ethyl rather than a methyl at C-8 and a five-carbon or three-carbon side-chain, respectively, at C-5. The alkaloid (-)-**221I** blocked α7 receptor responses (IC_{50} = 4.4 μM, 95% CI: 3.1 to 6.1 μM) with 5.3-fold higher potency than for blockade of the α4β2 receptor responses (IC_{50} = 23.1 μM, 95% CI: 18.5 to 28.9 μM) (Figure 2). Synthetic (-)-epi-**193E** was more potent in blocking the α7 receptor response (IC_{50} = 9.1 μM, 95% CI: 7.5 to 11.1 μM) compared to blockade of the α4β2 receptor (IC_{50} = 18.0 μM, 95% CI: 12.2 to 26.7 μM) (Figure 3). Previously, we examined the effects of three synthetic 5,8-disubstituted indolizidines with an *n*-butyl group at C-8 and an *n*-propyl group at C-5 in blocking different subtypes of nicotinic receptors. [3] Two of these compounds, namely (+)-8,9-diepi-**223V** and (-)-9-epi-**223V** were 6.7-fold and 11.2-fold more potent in blocking α7 receptor compared to blockade of α4β2 receptor, while the third, (-) **223V**, was only slightly more potent at blocking the responses mediated by the α7 receptor. [3,15] These results suggest that the α4β2 receptor does not interact well with indolizidines having substituents larger than methyl at C-8, while the α7 receptor is more accepting of larger side-chains at C-8. Further analogous synthetic alkaloids need to be tested. Overall, the side chains of 5,8-disubstituted indolizidines appear to be of critical importance in determining selectivity and potency in blocking responses mediated by subtypes of neuronal nicotinic receptors. Further study of structure-activity relationships of synthetic 5,8-disubstituted indolizidines at nicotinic subtypes could lead to even more subtype-selective ligands as research probes and as potentially useful drugs.

Neuronal nicotinic receptors have been implicated in the physiological processes of reward, cognition, learning and memory. [5,6] Some ligand-binding and autoradiography studies with postmortem human brain suggest that loss of neuronal nicotinic receptors is related to central cholinergic disorders such as Alzheimer's disease, Parkinson's disease and schizophrenia. [4,6] For instance, in schizophrenic patients,

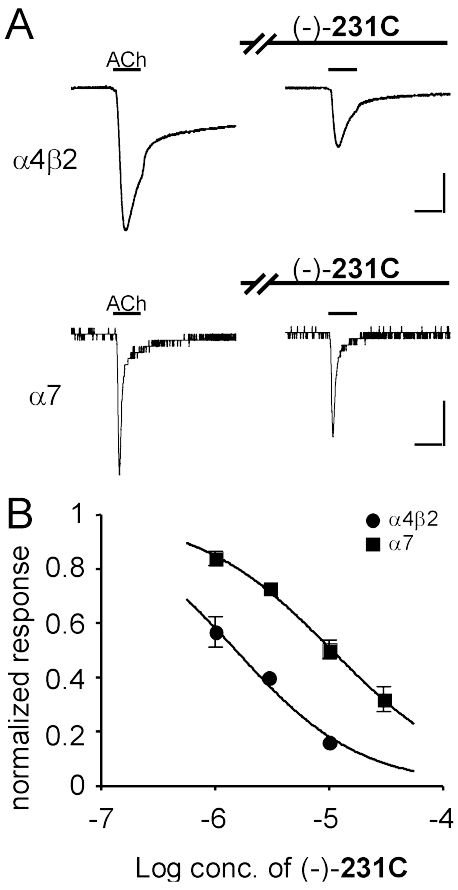


Figure 1: Inhibitory effect of (-)-**231C** on ACh-induced currents in *X. laevis* oocytes expressing recombinant nicotinic receptors. Currents were recorded in the voltage-clamp mode at -60 mV. Concentrations of ACh used were 1 μM for the α4β2 receptor and 100 μM for the α7 receptor. For test responses, oocytes were preincubated with (-)-**231C** for 3 min and then exposed to ACh with (-)-**231C**. A, representative traces showing the ACh-elicited currents in the absence and presence of (-)-**231C** (3 μM). Horizontal bars indicate the period of perfusion with ACh for 5 s. Vertical scale bars represent 0.5 μA on the α4β2 receptor, and 0.1 μA on the α7 receptor. B, concentration-response curves for (-)-**231C** on recombinant nicotinic receptors. Current responses to ACh in the presence of (-)-**231C** in each oocyte were normalized to the ACh responses (control responses) recorded in the same oocytes. Values represent the mean ± S.E.M. for five to six separate experiments.

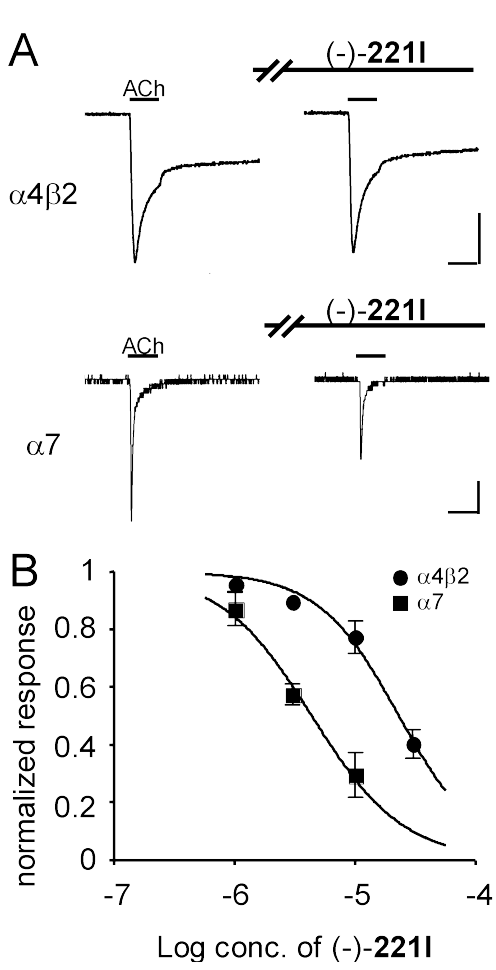


Figure 2: Inhibitory effect of (-)-**221I** on ACh-induced currents in *X. laevis* oocytes expressing recombinant nicotinic receptors. Currents were recorded in the voltage-clamp mode at -60 mV. Concentrations of ACh used were 1 μM for the α4β2 receptor and 100 μM for the α7 receptor. For test responses, oocytes were preincubated with (-)-**221I** for 3 min and then exposed to ACh with (-)-**221I**. A, representative traces showing the ACh-elicited currents in the absence and presence of (-)-**221I** (3 μM). Horizontal bars indicate the period of perfusion with ACh for 5 s. Vertical scale bars represent 0.5 μA on the α4β2 receptor, and 0.1 μA on the α7 receptor. B, concentration-response curves for (-)-**221I** on recombinant nicotinic receptors. Current responses to ACh in the presence of (-)-**221I** in each oocyte were normalized to the ACh responses (control responses) recorded in the same oocytes. Values represent the mean ± S.E.M. for five separate experiments.

decrease in binding of α-bungarotoxin (α-Bgt), a major specific ligand for α7 nicotinic receptors, has been detected in hippocampus, thalamus and frontal cortex [16,17]. Therefore, loss of α7 nicotinic ligand-binding appears to be an early presymptomatic diagnostic marker for schizophrenia. For *in vivo* mapping of brain receptors, positron emission tomography (PET) and single photon emission computed tomography (SPECT) using specific ligands are powerful, non-invasive techniques. Although ^{125}I-methyllycaconitine has been used for α7-selective binding in rat brain, [18] neither PET nor SPECT ligand of α7 nicotinic receptors has been available so far. Radiolabeled α-Bgt could not be used for *in vivo* mapping because of the large molecular weight, high toxicity and poor blood-brain barrier permeability. [19] Indolizidines are low molecular weight, lipophilic compounds that should penetrate well into brain and, as shown in our research, some exhibit high affinity and selectivity for either α4β2 or α7 nicotinic receptors. Further structure-activity relationship studies of synthetic indolizidines may lead to the development of radioactive α4β2-selective or α7-selective ligands useful for *in vivo* mapping of these important central nicotinic receptors.

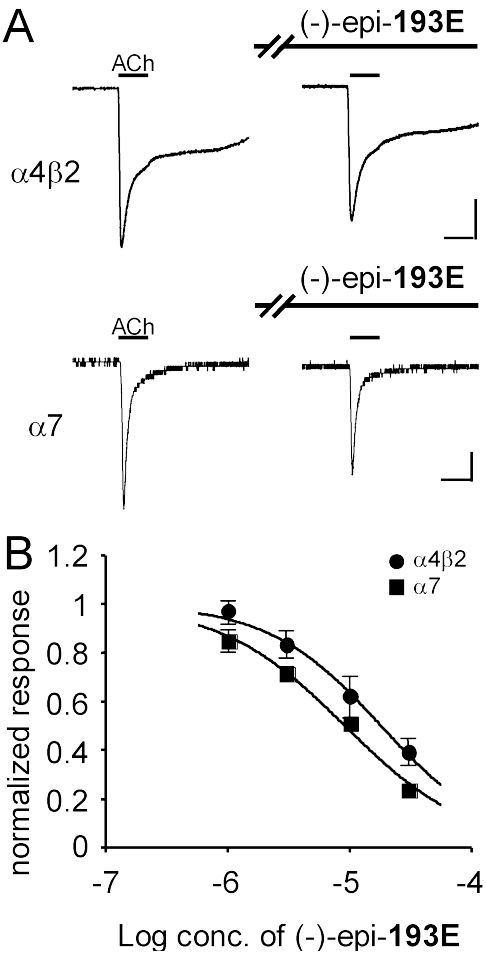


Figure 3: Inhibitory effect of (-)-epi-**193E** on ACh-induced currents in *X. laevis* oocytes expressing recombinant nicotinic receptors. Currents were recorded in the voltage-clamp mode at -60 mV. Concentrations of ACh used were 1 μM for the α4β2 receptor and 100 μM for the α7 receptor. For test responses, oocytes were preincubated with (-)-epi-**193E** for 3 min and then exposed to ACh with (-)-epi-**193E**. A, representative traces showing the ACh-elicited currents in the absence and presence of (-)-epi-**193E** (3 μM). Horizontal bars indicate the period of perfusion with ACh for 5 s. Vertical scale bars represent 0.5 μA on the α4β2 receptor, and 0.1 μA on the α7 receptor. B, concentration-response curves for (-)-epi-**193E** on recombinant nicotinic receptors. Current responses to ACh in the presence of (-)-epi-**193E** in each oocyte were normalized to the ACh responses (control responses) recorded in the same oocytes. Values represent the mean ± S.E.M. for five separate experiments.

Supporting Information

Supporting Information File 1

Experimental details for the synthesis of (-)-**209B**, (-)-**231C**, (-)-**233D**, (-)-**235B"**, (-)-**221I**, and an epimer of **193E** and pharmacological effects at neuronal nicotinic acetylcholine receptors. Experimental data which includes experimental details on the spectral instruments, elemental analyzer.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-30-S1.doc]

Acknowledgments

We are grateful to Dr. John A. Dani (Baylor College of Medicine, Houston, TX, USA) for his support with electrophysiological data acquisition, and to Dr. Jerry A. Stitzel (University of Colorado) for providing us with plasmid DNA. This work was supported in part by a grant-in-aid for Scientific Research (C, No. 17590004, and No. 16590435) by the Japan Society for the Promotion of Science (JSPS). Work at NIH was supported by the intramural research program of NIDDK.

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Beilstein Journal of Organic Chemistry

A convenient allylsilane-*N*-acyliminium route toward indolizidine and quinolizidine alkaloids

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Review

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Beilstein Journal of Organic Chemistry **2007**, 3, No. 32.
doi:10.1186/1860-5397-3-32

Received: 21 June 2007
Accepted: 02 October 2007
Published: 02 October 2007

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Abstract

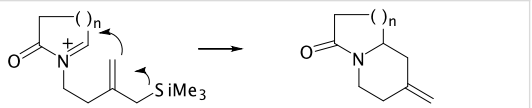
This review relates all the results that we obtained in the field of the total synthesis of indolizidine and quinolizidine alkaloids using a strategy of the addition of an allylsilane on an *N*-acyliminium ion. In this paper, we describe the synthesis of racemic indolizidine 167B and chiral indolizidines: (-)-indolizidines 167B, 195B, 223AB, (+)-monomorine, (-)-(3*R*,5*S*,8a*S*)-3-butyl-5-propyl-indolizidine and (-)-dendroprimine. Next, we relate the synthesis that we have developed in the quinolizidines field: (±)-myrtine and epimyrtine, (±)-lasubines I and II and chiral quinolizidines: (+)-myrtine, (-)-epimyrtine, (-)-lasubines I and II and (+)-subcosine II.

Background

Bicyclic indolizidines and quinolizidines are commonly occurring structural skeleta found in natural alkaloids. Such compounds have been isolated from animals: poison frogs of the family *Dendrobatidae* have provided a rich source of novel pharmacologically active alkaloids, including a variety of bicyclic nitrogen heterocyclic compounds such as indolizidines. [1,2] Several quinolizidine alkaloids have been isolated from plants: *Lythraceae* family (Lasubines), [3]*Vaccinum myrtillus* (myrtine, epimyrtine). [4,5]

Firstly, most of these compounds are frequently found in concentrations too low to allow complete structural elucidation; secondly, the biological activities for most of them make these alkaloids ideal targets for total synthesis.

We have developed a new method to generate bicyclic indolizidine and quinolizidine compounds based on an intramolecular cyclisation of acyliminium ions substituted by an allylsilyl side chain as an internal π-nucleophile (Scheme 1). [6]



Scheme 1: Allylsilane-*N*-acyliminium cyclisation.

This reaction has proven to be a very powerful method for construction of indolizidine and quinolizidine ring systems with efficient control of stereochemistry.

I Indolizidines

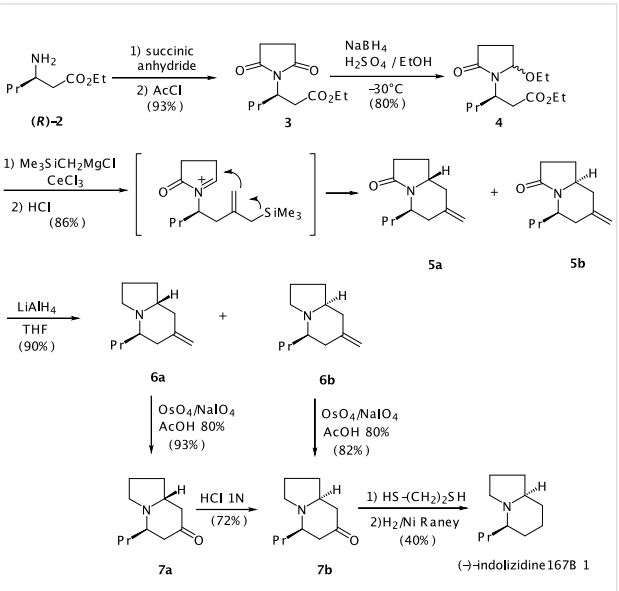
I 1. Indolizidine 167B

Indolizidine 167B, one of the simplest amphibian indolizidine alkaloids, was originally found as a trace component in the skin secretions of a frog belonging to the genus Dendrobates captured on the Isla Colon Panama. [7] The structure and relative stereochemistry shown in **1** are now accepted as correct although the absolute configuration of the natural product remains uncertain. [8] The lack of availability of the natural material and the important biological activities of the compound make this alkaloid an ideal target for total synthesis. [9-16]

I 1.1 Intramolecular cyclisation

We have found that intramolecular cyclisation of an allylsilane on an acyliminium ion constituted an excellent route to nitrogen bicyclic ring systems. [6] This method represents an efficient and stereoselective strategy for the preparation of 5-substituted indolizidines.

The source of chirality was the aminoester **(*R*)-2** which was prepared according to Davies'methodology. [17] Synthesis of the indolizidine skeleton was carried out as shown in Scheme 2. Reaction of **(*R*)-2** with succinic anhydride and then with acetyl chloride in refluxing toluene gave imide **3**, then, **3** was reduced into ethoxylactam **4**. In the next step, **4** was treated with two equivalents of the cerium reagent derived from trimethylsilymethylmagnesium chloride and $CeCl_3$. The mixture was then hydrolysed with 1N HCl to give methylenindolizidinones **5a** and **5b** in a 4:1 ratio. Reduction of the mixture of lactams **5a** and **5b** with lithium aluminium hydride gave methylenindolizidines **6a** and **6b** which were separated by flash chromatography.

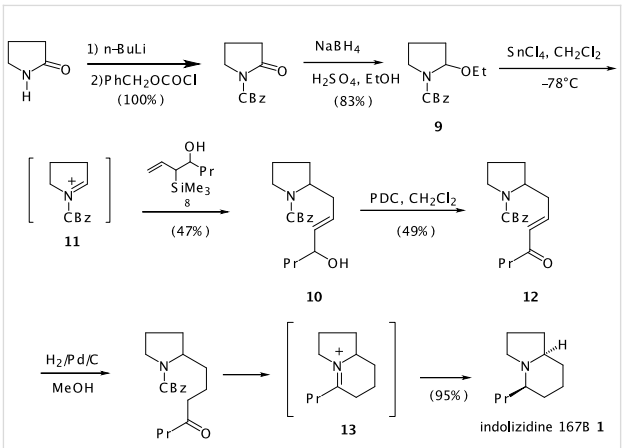


Scheme 2: Enantioselective synthesis of (-)-indolizidine 167B by intramolecular allylsilane-*N*-acyliminium cyclisation.

Osmium tetroxide catalysed periodate oxidation of the olefinic bond of **6a** and **6b** led respectively to indolizidin-3-ones **7a** and **7b**. Upon treating an aqueous solution of **7a** with 1N HCl the thermodynamically more stable indolizidinone **7b** was obtained through a retro-Mannich fragmentation-cyclisation process. The last two steps were the conversion of **7b** into its dithiolane and subsequent desulfurisation using Raney nickel. The synthesis of (-)-indolizidine 167B **1** has been achieved in 7 steps with a 17% overall yield from ethyl (3*R*)-3-aminohexanoate **2** with an enantiomeric excess of 93%. [19]

I 1.2 Intermolecular cyclisation

The intermolecular reaction between hydroxyalkyl-substituted allylsilanes and the acyliminium ion coming from pyrrolidin-2-one constitutes a new route to 5-substituted indolizidines (Scheme 3).



Scheme 3: Synthesis of (±)-indolizidine 167B by intermolecular cyclisation of allylsilane-*N*-acyliminium cyclisation.

Hydroxyallylsilane **8** was synthesised as described [18] by reaction of the reagent prepared from allyltrimethylsilane, *sec*-butyllithium and titanium tetraisopropoxide with aldehydes. The key step of the synthesis is the intermolecular addition of the allylsilyl functional group of alcohol **8** on the acyliminium ion derived from ethoxycarbamate **9**.

Treatment of a mixture of ethoxycarbamate **9** and hydroxyallylsilane **8** with one equivalent of stannic chloride resulted in the formation of **10** via the acyliminium ion intermediate **11**. Subsequent oxidation of alcohol **10** with pyridinium dichromate, then catalytic hydrogenation (H_2 over Pd/C) of ketone **12** induced hydrogenolysis of the CBz group, reduction of the

double bond of the side chain and reduction of the iminium ion intermediate **13** to give the indolizidine 167B **1.** [20]

The synthesis of (±)-indolizidine 167B has been achieved in five steps in 18% overall yield from pyrrolidin-2-one.

I 2. 3,5-Disubstituted indolizidines

Most of the indolizidine alkaloids are disubstituted by alkyl chains at the 3,5 positions. These compounds have been attractive targets for synthesis because of their potential biological activities. [7] Accordingly, novel strategies for the preparation of substituted indolizidines have received considerable attention. [21-27]

The allylsilyl functional group is a weak carbon nucleophile for trapping *N*-acyliminium ions, thus providing a useful method for intramolecular carbon-carbon bond formation. [28,29] We have applied this methodology towards the synthesis of indolizidine alkaloids. (*vide supra*) We describe here a new approach to 3,5-disubstituted indolizidines based on an intermolecular addition of allylsilanes on an *N*-acyl iminium starting from *L*-pyroglutamic acid used as the chiral precursor.

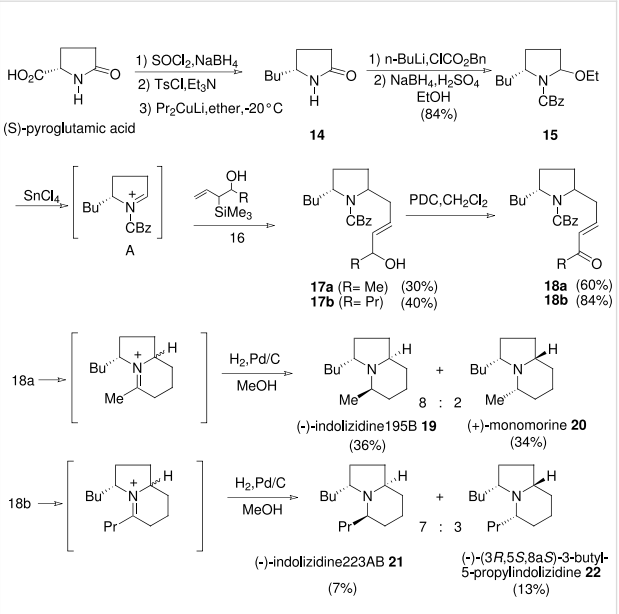
Preparation of lactam **14** was accomplished starting from the commercially available *S*-(-)-pyroglutamic acid according to a previously described procedure. [30,31] Next, lactam **14** was protected (*n*-BuLi, benzyl chloroformate) then converted to ethoxycarbamate **15**, isolated as a mixture of two diastereomers according to Hiemstra's procedure. [32,33] Condensation of allylsilanes **16** onto iminium ion **A** generated *in situ* by treatment of **15** with stannous chloride led to compounds **17a** and **17b**. The next two steps were straightforward: oxidation (pyridinium dichromate) of **17a** and **17b** afforded α,β-ethylenic ketones **18a** and **18b**.

On hydrogenation over palladium on carbon, **18a** gave a mixture of indolizidines **19** and **20** which were separated by flash chromatography. They were identified as (-)-indolizidine 195B and (+)-monomorine respectively. In the same manner, the hydrogenation of **18b** provided a mixture of isomers **21** and **22** respectively identified as (-)-indolizidine 223AB and (-)-(3*R*,5*S*,8a*S*)-3-butyl-5-propylindolizidine. [34] These four indolizidines were obtained in five steps with overall yields of about 8%.

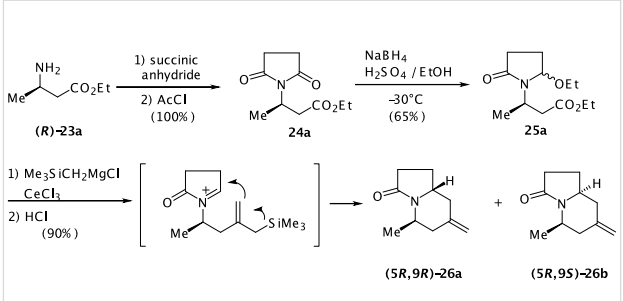
I 3 (-)-Dendroprimine

(-)-Dendroprimine **22** is an alkaloid isolated from *Dendrobium primulinum* Lindl (*Orchidaceae*) and shown to be a 5,7-dimethylindolizidine. [35] Its relative configuration was determined after the synthesis of the four racemic diastereomers of this indolizidine and a conformational analysis of these diastereomers has been discussed. [36,37] Its identification as (5*R*,7*S*,9*R*)-5,7dimethylindolizidine has been firmly established. [38] We describe here the first asymmetric synthesis of this alkaloid; [39] two other syntheses were recently published. [40,41]

The first steps of our synthesis were carried out as shown in Scheme 5. The starting material was ethyl 2-aminopropanoate **23**. Chirality was introduced with isomers **(*R*)-23a** and **(*S*)-23b**, which were prepared by a Michael reaction according to Davies' procedure from ethyl crotonate and respectively (*R*)- and (*S*)-*N*-benzyl-α-methylbenzylamine. [17] Reaction of **23a** with succinic anhydride and then with acetyl chloride gave imide **24a**, it was then reduced into ethoxylactam **25a**. Compound **25a** was treated with the cerium reagent derived from trimethylsilylmagnesium chloride and cerium chloride.



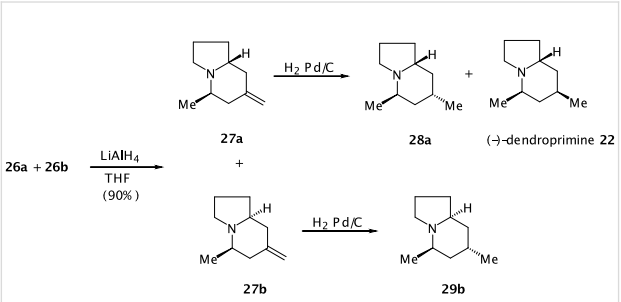
Scheme 4: Synthesis of 3,5-disubstituted indolizidines from *L*-pyroglutamic acid.



Scheme 5: Access to indolizidine precursors of dendroprimine starting from chiral 2-aminopropanoate.

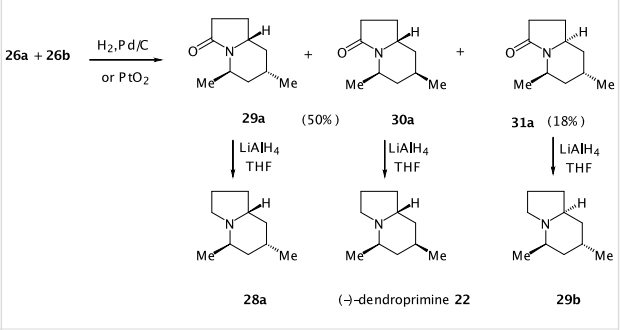
The mixture was then hydrolysed with 1N HCl to give methylenindolizidinones **26a** and **26b** in a 4:1 ratio.

These diastereomers could not be separated. According to Scheme 6, in the first step the reduction of the lactam functional group of cyclisation products **26a** and **26b** with lithium aluminium hydride afforded a 4:1 mixture of methylenindolizidines **27a** and **27b** in quantitative yield. These isomers were separated. Palladium-catalysed hydrogenation of **27a** was found to be stereoselective, giving a mixture of **28a** and (-)-(dendroprimine) **22** in a 3:1 ratio. Using similar conditions, **27b** led to compound **29b**.



Scheme 6: Access to (-)-dendroprimine by reduction with $LiAlH_4$ of indolizidinones 26.

Another way (cf. Scheme 7) was studied to access (-)-dendroprimine **22**: hydrogenation of the crude mixture of cyclisation products **26a** and **26b** over palladium on carbon provided a mixture of lactams **29a**, **30a** and **31a** in which isomer **30a** was preponderant (**29a**/**30a**/**31a** = 15:65:20). Flash column chromatography gave pure **31a** in 18% yield, but **29a** and **30a** could not be separated (50% yield). A mixture of the three isomers was used without purification for the next step. This mixture was then reduced with lithium aluminium hydride to give the indolizidines **28a**, **22** and **29b.** In conclusion, (-)-dendroprimine was obtained in five steps with overall yields of 17 and 20%.



Scheme 7: Access to (-)-dendroprimine by catalytic hydrogenation of indolizidinones 26.

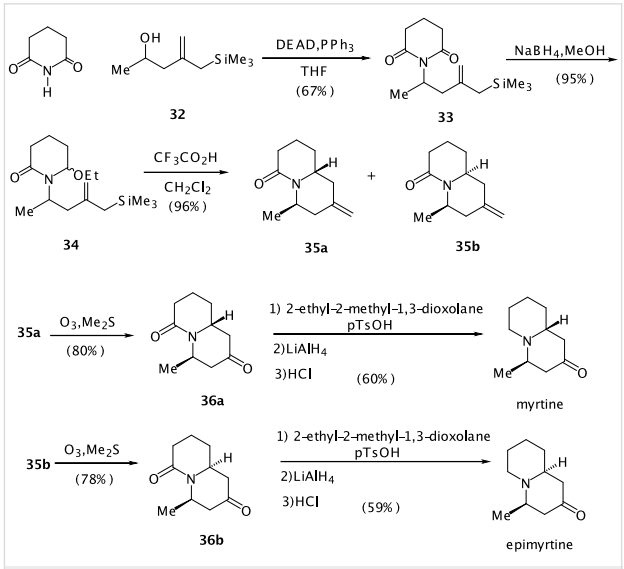
II Quinolizidines

II 1-Myrtine and epimyrtine

(+)-Myrtine and (-)-epimyrtine are quinolizidine alkaloids isolated from *Vaccinium myrtillus* (Ericaceae). [4,5] Several syntheses of these compounds as racemic mixtures have been described, [5,42-44] but only three enantioselective syntheses of (+)-myrtine [43,45] and three syntheses of (-)-epimyrtine have been published. [46,47]

II 1.1 Synthesis of (±)-myrtine and (±)-epimyrtine

These compounds have been prepared according to Scheme 8, the synthesis of hydroxyalkylallylsilane **32** is accomplished in 40% yield following Trost's procedure. [48] Reaction of glutarimide with alcohol **32** under Mitsunobu reaction conditions afforded imide **33** in 67% yield. Reduction of **33** was carried out with an excess of sodium borohydride in methanol at 0°C to give **34** as a mixture of two diastereomers which were not separated. The hydroxylactam **34** was then cyclised to the quinolizidine isomers **35a** and **35b** on treatment with 4 equiv. of trifluoroacetic acid in a 7:3 ratio. Then, ozonolysis of **35a** and **35b** followed by reduction with dimethylsulfide furnished respectively **36a** and **36b**. Protection of the carbonyl group by ketalisation with 2-ethyl-2-methyl-1,3-dioxolane and *p*-toluenesulfonic acid, reduction of the amide function with lithium aluminium hydride then quantitative removal of the protecting group (HCl treatment) afforded (±)-myrtine and (±)-epimyrtine. These syntheses were achieved in seven steps and 20% overall yield. [49]

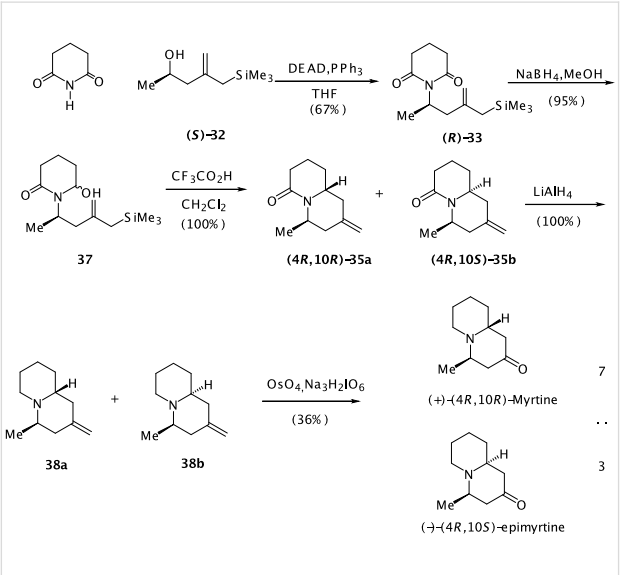


Scheme 8: Synthesis of (±)-myrtine and (±)-epimyrtine.

II 1.2 Synthesis of (+)-myrtine and (-)-epimyrtine

We used a similar strategy to prepare the enantiopure compounds starting from (*S*)-2-(hydroxypropyl)allyltrimethyl-

silane **32** (cf. Scheme 9). Compound **32** was obtained in quantitative yield by cerium mediated trimethylsilylmethylmagnesium chloride addition to ethyl (*S*)-3-hydroxybutanoate as we described. [50] The first three steps of the enantioselective synthesis were those previously described for the synthesis of racemic compounds (*vide supra*). Condensation of alcohol **32** with glutarimide under Mitsunobu conditions led to (+)-imide **(*R*)-33** in 67% yield. Reduction of **(*R*)-33** with sodium borohydride afforded hydroxylactam **37** as a 1:1 mixture of isomers in 95% yield. Treatment of hydroxylactam **37** with trifluoroacetic acid in methylene chloride gave a 7:3 mixture of the two isomeric bicyclic compounds **(4*R*,10*R*)-35a** and **(4*R*,10*S*)-35b** in quantitative yield. Reduction of this mixture of lactams with lithium aluminium hydride gave a 7:3 mixture of methylenquinolizidines **38a** and **38b** in quantitative yield. Osmium tetroxide-catalysed periodate oxidation of the olefinic bond of quinolizidines **38a** and **38b** under carefully controlled conditions led to a 7:3 mixture of the two diastereomeric alkaloids (+)-myrtine and (-)-epimyrtine. These alkaloids were obtained in five steps from (*S*)-2-(2-hydroxypropyl)allylsilane **32** with an overall yield of 23% and a high enantiomeric purity. This synthesis constitutes the first total synthesis of naturally occurring (-)-epimyrtine and confirms the configuration 4*R*,10*S* which was assigned previously to this compound. [51]



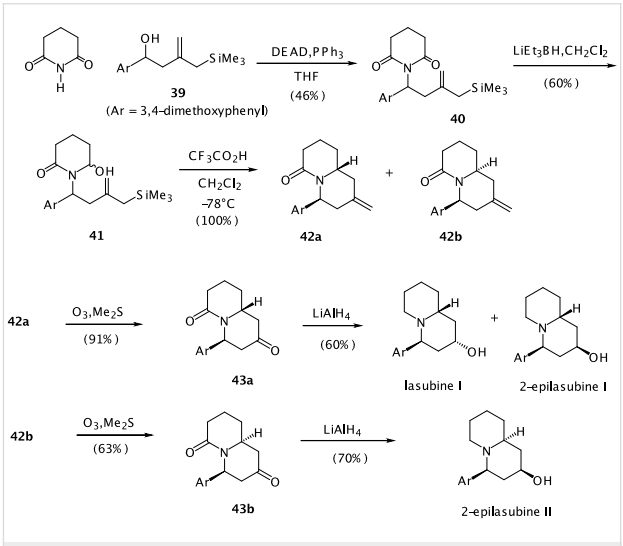
Scheme 9: Enantioselective synthesis of (+)-myrtine and (-)-epimyrtine.

II 2. Lasubines

The Lythraceae alkaloids constitute a large family of natural products, most of which contain 4-arylquinolizidine substructures. Among them are the quinolizidine alkaloids lasubine I and lasubine II which have been isolated from *Lagerstroemia subscotata* Koehne. [3] Numerous racemic [44,52-54] and asymmetric total syntheses of these alkaloids have been described. [43,55-64]

II 2.1. Synthesis of (±)-lasubine I and (±)-lasubine II

The first steps of our synthesis were carried out as shown in Scheme 10. The starting material was 2-(2-hydroxyethyl) allylsilane **39** which was prepared in 86% yield by indium mediated allylsilylation of 3,4-dimethoxybenzaldehyde, as already described. [65] Condensation of alcohol **39** with glutarimide under Mitsunobu conditions led to imide **40** in 46% yield. Reduction of **40** with diisobutylaluminium hydride afforded hydroxylactam **41** isolated as a mixture of isomers, a higher yield of a single isomer was obtained when using lithium triethylborohydride as reducing regent. The reduction had to be performed at -78°C to prevent formation of ring opening products. [66] Treatment of hydroxylactam **41** with trifluoroacetic acid in methylene chloride gave a mixture of isomeric bicyclic compounds **42a** and **42b** in a quantitative yield and a 4:1 ratio when the reaction was performed at -78°C.

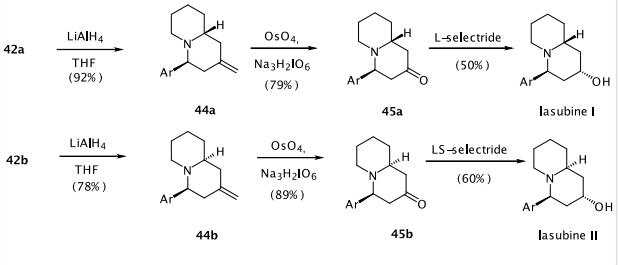


Scheme 10: Synthesis of (±)-lasubines I and II and (±)-2-epilasubine II.

Then, we examined two routes to the quinolizidine alkaloids lasubine I and lasubine II from methylenquinolizidinones **42a** and **42b**. They involved oxidation of the methylene group into a carbonyl which was then stereoselectively reduced to the hydroxyl group. The shortest route consisted of the ozonolysis of the methylene group followed by the simultaneous reduction of the two carbonyl groups of keto lactams **43a** and **43b**. Thus, treatment of **42a** with ozone then with dimethyl sulfide afforded the expected keto lactam **43a** in 91% yield. Ozonolysis of **42b** led to keto lactam **43b** in 63% yield. Reduction of **43a** with lithium aluminium hydride afforded in 60% yield a 1:1.2 mixture of lasubine I and 2-epilasubine I which

were separated as their acetates. In the same way, reduction of **43b** gave 2-epilasubine II in 70% yield.

In order to circumvent the stereochemical difficulty we decided to reduce first the lactam group (cf. Scheme 11) to obtain quinolizidines whose conformation should not be distorted by the junction with the piperidone ring. Lactams **42a** and **42b** were reduced with lithium aluminium hydride to give methylenquinolizidines **44a** and **44b** in 92% and 78% yields respectively. Osmium tetroxide catalysed periodate oxidation of the olefinic bond of methylenquinolizidines **44a** and **44b** under carefully controlled conditions led to the already described 2-oxoquinolizidines **45a** and **45b** in 79% and 89% yields respectively. The final step is a reduction of the carbonyl group. The use of borohydride in the reduction of **45a** has been described to give lasubine in an excellent yield. [67,68] In our hands, this reaction afforded a 1:1 mixture of (±)-lasubine I and (±)-epilasubine I. Stereoselective reduction of quinolizidin-2-one **45a** to (±)-lasubine I was achieved in 50% yield with lithium tri-*sec*-butylborohydride (L-selectride). Quinolizidinone **45b** was selectively converted to (±)-lasubine II with lithium trisamylborohydride (LS-selectride) in 60% yield.



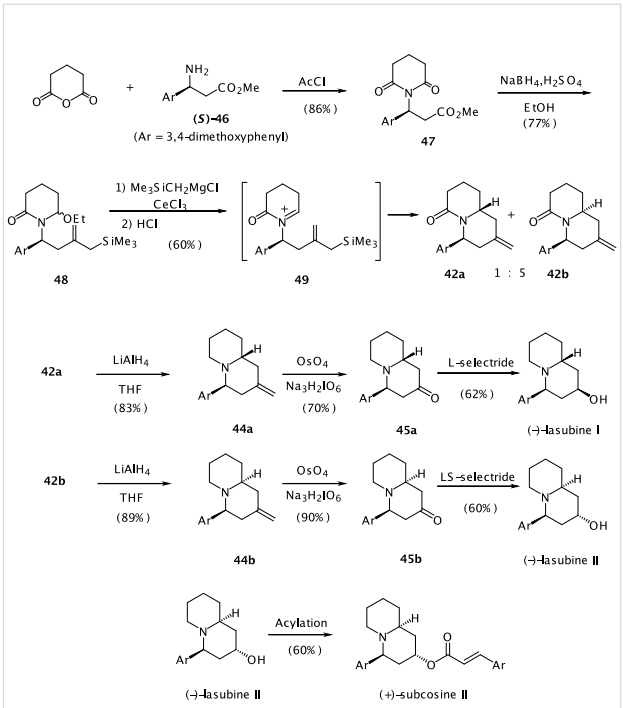
Scheme 11: Synthesis of (±)-lasubine I and II.

In conclusion, (±) lasubine I and (±)-lasubine II were obtained in six steps from 2-(2-hydroxyethyl)allylsilane **39** in 8% and 7.4% yields respectively.

II.2.2 Synthesis of (-)-lasubine I, (-)-lasubine II and (+)-subcosine II

A similar strategy was attempted from (+)-(3*R*)-ethyl 3-hydroxy-3-(3,4-dimethoxyphenyl)propionate but racemisation was observed during the Mitsunobu reaction. [69] So we developed another strategy to prepare these natural optically active compounds based on the intramolecular acyliminium ion allylsilane cyclisation of intermediate **49** generated from ethoxylactam **48**. Chirality is introduced with the β-aminoester **46**.

(*S*)-β-Aminoester **46** was prepared according to Davies'procedure. [17] Reaction of **46** with glutaric anhydride



Scheme 12: Enantioselective synthesis of (-)-lasubines I and II and (+)-subcosine.

then with acetyl chloride in refluxing toluene gave imide **47** in 86% yield. Imide **47** was reduced into ethoxylactam **48** which was isolated as a mixture of two diastereomers. In the next step, ethoxylactam **48** was treated with the cerium reagent derived from $CeCl_3$ and trimethylsilylmethylmagnesium chloride. The mixture was then hydrolysed with 1N HCl to give methylenquinolizidinones **42a** and **42b** in a 1:5 ratio and 60% yield. Reduction of lactams **42a** and **42b** with lithium aluminium hydride in refluxing THF for 12 h gave methylenquinolizidines **44a** and **44b** in 83% and 92% yields respectively. Osmium tetroxide catalysed periodate oxidation of the olefinic bond of **44a** and **44b** under carefully controlled conditions led to quinolizidin-2-ones **45a** and **45b** in 70 and 90% yields. The final step is a reduction of the carbonyl group. Stereoselective reduction of **45a** with L-selectride provided (-)-lasubine I in 62% yield. Quinolizidin-2-one **45b** was selectively converted to (-)-lasubine II with LS-selectride in 65% yield. Acylation of (-)-lasubine II with 3,4-dimethoxycinnamic anhydride gave (+)-subcosine II in 60% yield.(Scheme 12)

In conclusion, we have described the total synthesis of (-)-lasubine I, (-)-lasubine II and (+)-subcosine II using intramolecular cyclisation of *N*-acyliminium ion **(*S*)-49**. (-)-Lasubine I and (-)-lasubine II were obtained in six steps with overall yields of 7 and 14% respectively. (+)-Subcosine was prepared in seven steps with an overall yield of 9%. These

three compounds were obtained with high enantiomeric purity. These results constitute the first total synthesis of naturally occurring (-)-lasubine II and (+)-subcosine II and unambiguously establish their absolute configuration as 2*S*,4*S*,10*S*.

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Beilstein Journal of Organic Chemistry

An asymmetric synthesis of all stereoisomers of piclavines A1-4 using an iterative asymmetric dihydroxylation

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Full Research Paper

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Beilstein Journal of Organic Chemistry **2007**, 3, No. 37.
doi:10.1186/1860-5397-3-37

Received: 05 September 2007
Accepted: 29 October 2007
Published: 29 October 2007

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Abstract

The asymmetric synthesis of both enantiomers of piclavines A1, A2, A3, and A4 has been achieved using an iterative asymmetric dihydroxylation with enantiomeric enhancement.

Background

Indolizidine units are frequently found in many natural products and designed bioactive molecules. [1] Among these alkaloids, piclavines A1-4 (Figure 1), extracted from the tunicate *Clavelina picta* and the first indolizidine alkaloids to be found in the marine biosphere, exhibit interesting antimicrobial activities. [2] However, very little effort has been made to synthesize the piclavines. So far, among the four isomers shown in Figure 1, the synthesis of piclavine A4 [3] and a mixture of piclavines A1 and A2 [4] has been reported, but the synthesis of all four isomers has never been reported. In addition, their biological activities have been evaluated as a mixture of piclavines A1-4. [2] Therefore, we were inspired to develop a comprehensive synthetic program for these alkaloids.

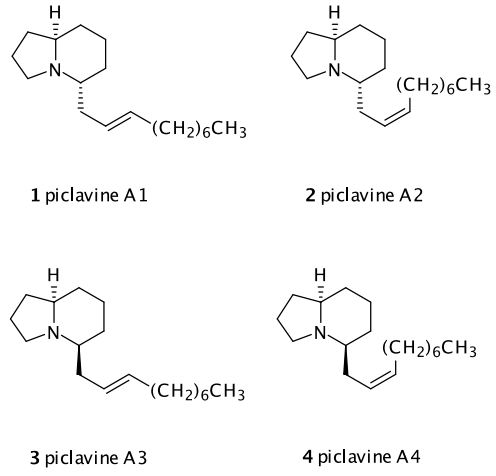
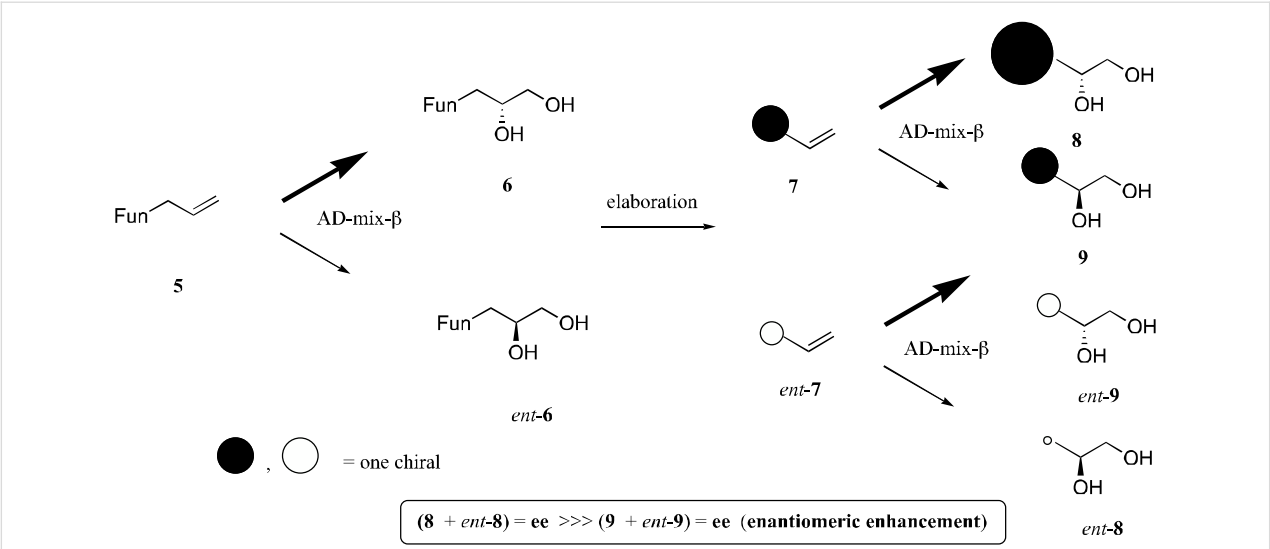


Figure 1: Piclavines A1-A4.

The asymmetric synthesis of an indolizidine ring remains a great challenge. Our interest in this field has been focused on potential strategies based on the enantiomeric enhancement

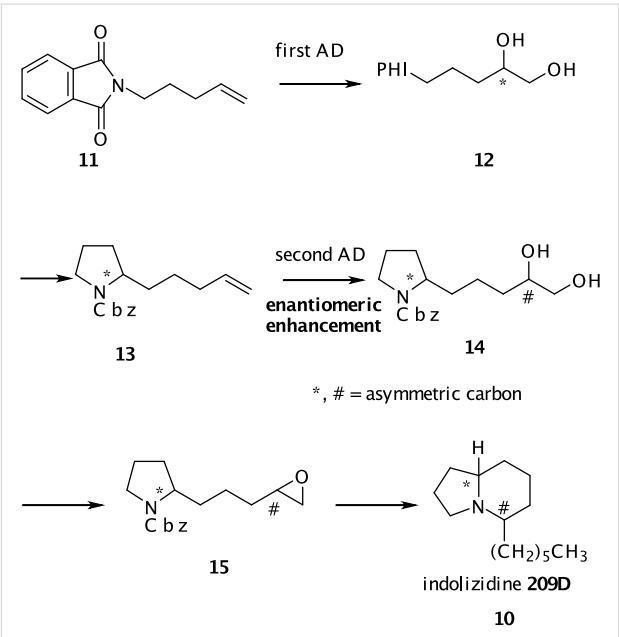


Scheme 1: Enantiomeric enhancement by iterative AD.

caused by the twofold or more application of the Sharpless asymmetric dihydroxylation (AD) [5,6] or Brown's asymmetric allylboration[7] reactions. In general, the enantiomeric excesses (ees) obtained for AD of terminal olefins are lower than for *trans* disubstituted olefins. However, it is expected that iterative AD terminal olefins will give products with high ees based on the following consideration. The first AD (AD-mix-β) of **5** produces major and minor enantiomers, **6** and *ent*-**6**, which are elaborated by introduction of terminal olefins to afford **7** and *ent*-**7**, respectively. The second AD of a mixture of **7** and *ent*-**7** provides four products **8**, **9**, *ent*-**9**, and *ent*-**8**. The relationship between **8** and **9** is diastereomeric. Since very little of the mirror image compound *ent*-**8** is prepared, the ee of the major product **8** will be very high. On the other hand, the ee of the minor diastereomer **9** or *ent*-**9** will be a low (Scheme 1). In most cases, when the products prepared by the iterative AD are acyclic and their asymmetric centers are remote, it is difficult to separate two diastereomers. Since transformation of acyclic compounds to cyclic derivatives provides rigid conformation and causes close proximity between two chiral centers, it is expected to greatly facilitate separation of two diastereomers. In this line, we report a full paper describing a new synthesis of all stereoisomers of piclavines A1-4 with high enantiomeric purity (amplification) for the major diastereomer via iterative AD reaction of terminal olefins. [8]

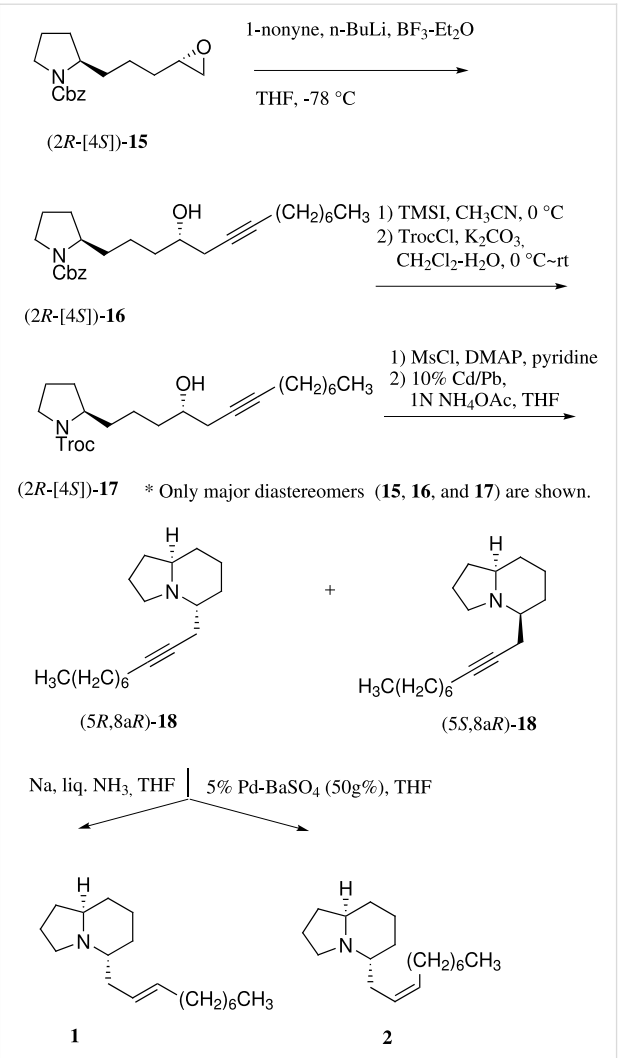
Results

Actually we developed a general access to 5-substituted indolizidines **10** (all four stereoisomers of indolizidine 209D) with high enantio-enhancement (92–98% ee) via a sequence of iterative AD reactions starting from an achiral *N*-pentenylphthalimide (**11**). [9] The two stereogenic centers in **10** were constructed with high enantio-enhancement via a sequence of twofold AD reactions as shown in Scheme 2.

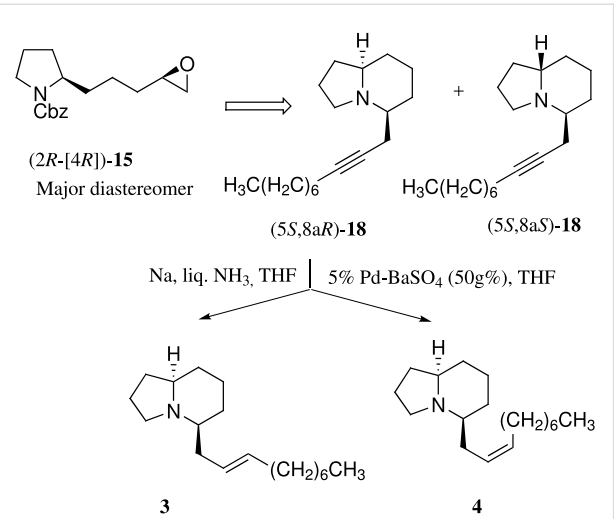


Scheme 2: Asymmetric synthesis of indolidines **209D** using an iterative AD.

We embarked on the synthesis of piclavines A1-4 using the four stereoisomers of the epoxides **15**[9] derived from **11** according to our reported procedure as synthetic intermediates. Regioselective cleavage of the epoxide (2*R*-[4*S*])-**15** rings with lithium acetylide generated from 1-nonyne with *n*-butyl lithium in combination with BF_3-Et_2O[10] gave the secondary alcohols (2*R*-[4*S*])-**16** in 94%. It is impossible to utilize hydrogenolysis



Scheme 3: Asymmetric synthesis of piclavines A1 and A2 from (2*R*-[4*S*])-**15**.



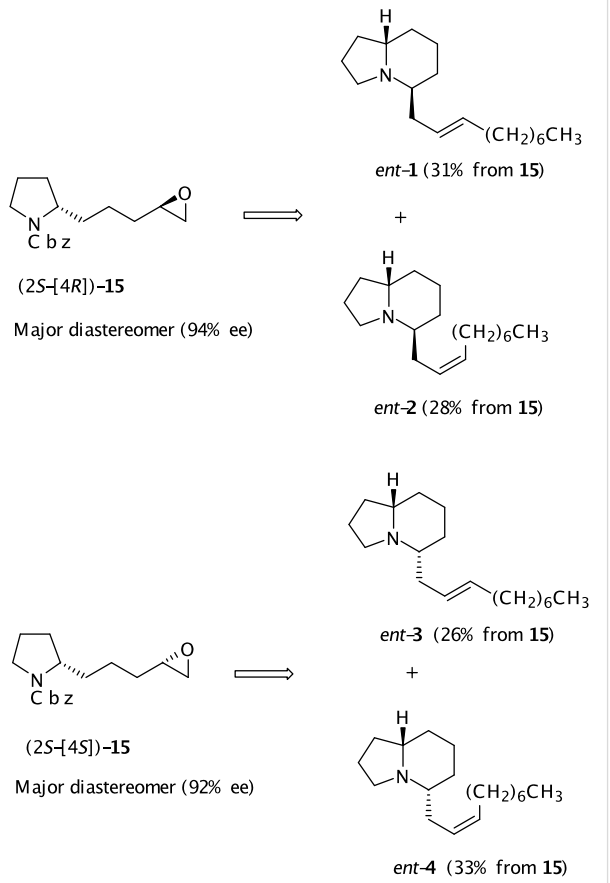
Scheme 4: Asymmetric synthesis of piclavines A3 and A4 from (2*R*-[4*R*])-**15**.

due to reactivity of the acetylene unit. Indeed, the *N*-protecting group exchange of benzyloxycarbonyl (Cbz) for 2,2,2-trichloroethoxycarbonyl (Troc) in **17** was examined. The use of basic reagents such as $Ba(OH)_2$[11] and KOH[12] failed to afford clean deprotection of Cbz. However, treatment of (2*R*-[4*S*])-**16** with iodotrimethylsilane (TMSI)[13] in CH_3CN provided the amine (75%), which was treated with TrocCl/K_2CO_3 to afford the Troc carbamates (2*R*-[4*S*])-**17**. After mesylation of [2*S*-(4*R*)]-**17**, *N*-deprotection of the resulting mesylate with 10% Cd-Pb[14] gave the desired (5*R*,8a*R*)-**18** {[α]$^{25}_D$ +9.03 (*c* 0.32, CH_3OH)} as a major product and (5*R*,8a*S*)-**18** {[α]$^{25}_D$ −22.7 (*c* 1.54, CH_2Cl_2)} as a minor product in a ratio of 2.3:1 in 25% overall yield. As expected, at this stage it was possible to separate the two diastereomers because transformation of monocyclic compounds (pyrrolidines) to bicyclic derivatives (indolizidines) provides rigid conformation and causes close proximity (a change from 1,5- to 1,3-relationship) between the two asymmetric centers. With indolizidine (5*R*, 8a*R*)-**18** in hand, we examined partial-reduction of their triple bonds. First, treatment of (5*R*, 8a*R*)-**18** with sodium in liquid ammonia gave the desired piclavine A1 (**1**) {[α]$^{25}_D$ −5.6 (*c* 0.84, CH_2Cl_2)} containing a *trans*-olefin in 71% yield. Exposure of hydrogen to (5*R*, 8a*R*)-**18** in the presence of Lindlar catalyst (Pd/$CaCO_3$/Pb) or Rosenmund catalyst (5% Pd-$BaSO_4$) was carried out in order to obtain a *cis* olefin product. However, hydrogenation using 10 g% catalysts scarcely proceeded, because the tertiary amine in indolizidine presumably works as a poison of the catalyst. Accordingly, the use of a large amount (50 g%) of 5% Pd-$BaSO_4$ took place with semi-reduction of (5*R*,8a*R*)-**18** to provide piclavine A2 (**2**) {[α]$^{25}_D$ +4.03 (*c* 0.21 CH_2Cl_2)} in 53% yield (Scheme 3). The ^1H and ^{13}C NMR spectra of synthetic piclavines A1 and A2 are in good agreement with those of a mixture of natural piclavines A1 and A2. [2]

A similar sequence of the epoxide (2*R*-[4*R*])-**15** prepared by $(DHQD)_2$-PYR ligand-induced AD reaction of (*R*)-**13** afforded the desired (5*S*,8a*R*)-**18** {[α]$^{25}_D$ −67.5 (*c* 1.11, CH_2Cl_2)} as a major product and (5*S*,8a*S*)-**18** {[α]$^{25}_D$ −3.11 (*c* 0.62, CH_3OH)} as a minor product in a ratio of 3.6:1 in 46% overall yield from (2*R*-[4*R*])-**15**. Similar semi-reduction of (5*S*, 8a*R*)-**18** with Na/NH_3 and H_2/10%Pd-$BaSO_4$ gave piclavine A3 (**3**) (76%) {[α]$^{25}_D$ −74.3 (*c* 1.30, CH_2Cl_2) and piclavine A4 (**4**) [α]$^{25}_D$ −76.5 (*c* 0.63 CH_2Cl_2)} lit. [3] [α]$^{20}_D$ −74.8 (*c* 0.5 CH_2Cl_2)} in 84% yield, respectively (Scheme 4). Spectral data of **4** were completely consistent with values reported. [3]

With two diastereomers (2*S*-[4*R*])- and (2*S*-[4*S*])-**15** in hand, [9] the enantiomers of piclavines A1-4 were prepared according to the procedure described above (Scheme 5). However, the abso-

lute configuration of natural products remains unassigned. [2]



Scheme 5: Asymmetric synthesis of enantiomers of piclavines (**1–4**).

Conclusion

In summary, we accomplished the asymmetric synthesis of both enantiomers of piclavines A1, A2, A3, and A4 with high enantio-enhancement via iterative AD reactions starting from an achiral *N*-pentenylphthalimide **11**.

Supporting Information

Supporting Information File 1

Synthetic details, spectral properties and HRMS data. Experimental details for an asymmetric synthesis of all stereoisomers of piclavines A1-4 using an iterative asymmetric dihydroxylation. Experimental data which includes experimental details on the spectral instruments.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-37-S1.doc]

Acknowledgments

This work was supported in part by the High Technology Research Program from the Ministry of Education, Sciences, Sports and Culture of Japan

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doi:10.1186/1860-5397-3-37

Beilstein Journal of Organic Chemistry

Vinylogous Mukaiyama aldol reactions with 4-oxy-2-trimethylsilyloxypyrroles: relevance to castanospermine synthesis

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Full Research Paper

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Beilstein Journal of Organic Chemistry **2007**, 3, No. 38.
doi:10.1186/1860-5397-3-38

Received: 28 July 2007
Accepted: 03 November 2007
Published: 03 November 2007

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Abstract

Background

The diastereoselectivity of a vinylogous Mukaiyama aldol reaction of a series of *N*-substituted 4-oxy-2-trimethylsilyloxypyrroles with a tartrate-based aldehyde has been explored as a model reaction for castanospermine synthesis.

Results

The study has revealed that the reaction is sensitive to the nature of the combination of *N*- and 4-oxy substituents. With a *N*-PMB or *N*-Bn and 4-methoxy combination, the reaction generates an aldol adduct with the correct absolute configurations for C-8 and C-8a of the indolizidine alkaloid castanospermine. The adduct was transformed to an indolizidine, whose ketal could not be transformed appropriately for the target alkaloid.

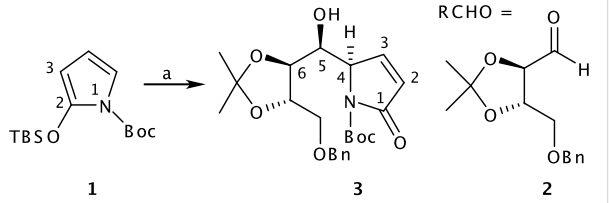
Conclusion

The first successful diastereoselective Mukaiyama aldol strategy for the C-8 and C-8a stereogenic centres of castanospermine is presented using silyloxypyrrole chemistry. The results suggest that a full enantioselective synthesis can be realized provided that C-1 functionalisation is accomplished early in the synthesis, post-coupling.

Background

N-Protected silyloxypyrroles have emerged in recent years as powerful synthetic building blocks for synthesis, particularly of pyrrolizidine and indolizidine alkaloids.[1-3] Following the pioneering work of Casiraghi, *N*-(*t*-Boc)-2-(*t*-butyldimethylsilyloxy)pyrrole TBSOP **1** has established itself as the reagent of choice for promoting extended (vinylogous) Mukaiyama addition reactions to aldehydes,[4] imines [5] and conjugatively to enones [6,7] under Lewis-acid mediated dissociative reaction conditions. Many of these reactions reveal high diastereoselectivities, which has been exploited to access a range of

natural products and their derivatives.[8,9] An example of Casiraghi's from the castanospermine repertoire showing the numbering system used in this article is shown in Scheme 1.[4]



Scheme 1: An example of a vinylogous Mukaiyama aldol in a natural product synthesis. *Reagents and conditions*: a) RCHO **2**, $SnCl_4$ (1.2 equiv), ether, -85°C.

While TBSOP **1** can be prepared, isolated and stored (at low temperature) for general use, its synthesis involves usage of the relatively expensive TBSOTf. From the outset of this work, we were interested in developing a cost-effective alternative using TMS rather than TBS as the silylating source and changing the *N*-Boc group to Bn or PMB. As expected, such changes precluded isolation of the silyloxypyrrole and resulted in us developing a one-pot methodology involving its *in situ* generation. We have recently demonstrated the applicability of *N*-protected-4-methoxy-2-trimethylsilyloxy pyrroles **5** to the synthesis of key intermediates for the alkaloids lepadiformine [10] and castanospermine [11] using vinylogous Mukaiyama aldol reactions. For the latter, silyloxypyrrole **5a** was shown to give adduct **6a** with the correct stereogenicities at C-4 and C-5 (C-8a and C-8 respectively in the alkaloid) for castanospermine.

This paper reports on the influence of substitution changes in **5** (R_1 and R_2) on the outcome of extended Mukaiyama reactions with aldehyde **7**, and demonstrates how one of the adducts can be transformed into an advanced intermediate for castanospermine synthesis (Scheme 2).

Results and Discussion

Changing the N-protecting group

Synthesis of pyrrolinones **4a** and **4b** was straightforward involving condensing the appropriate amine ($PMBNH_2$ or $BnNH_2$ respectively) with ethyl *E*-4-chloro-3-methoxybut-2-enoate.[11] Reaction of **4b** with *n*-BuLi as before followed by TMSCl to generate **5b**, and reaction with aldehyde **7** (0.7 equiv) as limiting reagent using $SnCl_4$ (2 equiv) as the Lewis-acid promoter with rapid stirring of the reaction gave a single crystalline diastereomer **6b** as the major product (57%) together with a mixed fraction (33%) following chromatography. The latter revealed a complex array for the H-4 and H-5 signals in its ^{1}H NMR spectrum, and no conclusive stereochemical assignments could be made. By comparison and as with **6a**,[11] the key NMR signals of H-4 and H-5 in the ^{1}H NMR and C-4 and C-5 in the ^{13}C NMR of **6b** suggested an identical stereochemistry to that of adduct **6a**, and this was unambiguously confirmed for **6b** as the 4,5-*erythro*-5,6-*threo* adduct by a single crystal X-ray determination (Figure 1).

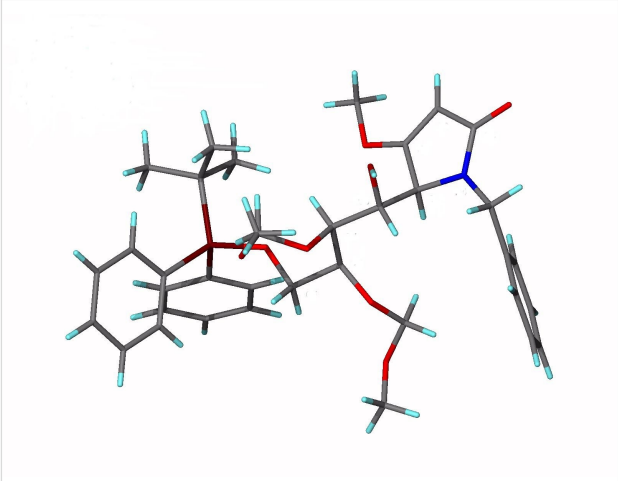
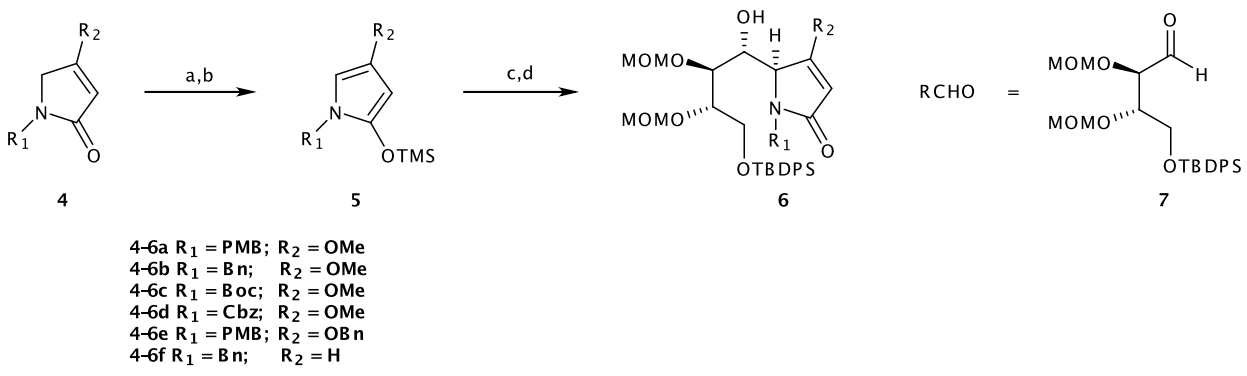


Figure 1: X-ray crystal structure of **6b**.



Scheme 2: Our vinylogous Mukaiyama aldol reaction with different substituents. *Reagents and conditions*: a) *n*-BuLi, (1.5 equiv), THF, -78°C, 30 mins; b) TMSCl (3 equiv), -78°C, 30 mins; c) **7** (0.7 equiv), THF, -78°C; d) $SnCl_4$ (2 equiv), -78°C to -20°C.

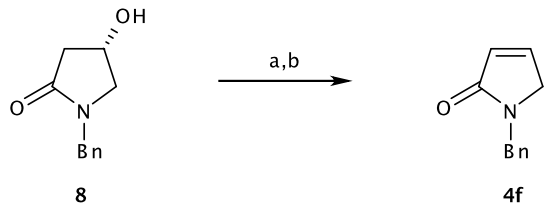
CCDC 653714 contains the Supplementary Crystallographic Data for compound **6b**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. Such a result confirmed the unimportance of the *p*-methoxy group of the *N*-PMB protecting group on the diastereoselectivity of the reaction. Given that tlc indicated that reaction only begins at around -50°C, and that the reaction is quenched at -20°C, we believe the major adduct to be the kinetic product. However, a more comprehensive study is needed to support this view beyond reasonable doubt.

Attention was then turned to changing the *N*-protecting group to a carbamate in line with TBSOP **1**. The pyrroline precursor **4** (R_1 = H, R_2 = OMe) was readily prepared via condensation of ethyl *E*-4-chloro-3-methoxybut-2-enoate with ammonia, and then transformed to carbamates **4c** and **4d** under the standard conditions of $(Boc)_2O$/DMAP and NaH/CBzCl respectively. Each was independently subjected to our *in situ* Mukaiyama sequence involving *n*-BuLi followed by TMSCl, and then addition of aldehyde **7** and $SnCl_4$. However, following the normal work-up, tlc analysis in each case revealed consumption of starting pyrrolinone with formation of a multitude of products. This was attributed to the instability of the pyrrolinone carbamates **4c** and **4d** towards *n*-BuLi, and indicated the need to resort to the Casiraghi conditions of 2,6-lutidine and TBSOTf for silyloxypyrrole generation.[12] However, in view of our objective of developing a cost-effective method, this option was not pursued.

Changing the 4-oxy substituent

In terms of synthetic design, the 4-methoxy substituent was envisaged as having implications for reactivity of the silyloxypyrrole as well as relevance to installation of the C-1 hydroxyl in a convergent castanospermine synthesis using a Mukaiyama aldol reaction as a key step. Thus it was decided to investigate the influence of changing both the O-protecting group as well as substituting the 4-oxy substituent with hydrogen. Deprotection of a methyl ether to its hydroxyl group requires aggressive conditions that can present problems in end-game aspects of total synthesis. Thus it was decided to change methyl to the more deprotection-friendly benzyl group. Synthesis of benzyl pyrrolinone **4e** was readily achieved by heating **4a** with excess benzyl alcohol at 80°C in an acid-catalysed (*p*-TsOH) exchange with *in vacuo* (water pressure) removal of methanol as it formed. Thus **4e** was isolated in 65% yield after chromatography. Subjecting **4e** to the standard silyloxypyrrole formation conditions as before to afford **5e** *in situ* followed by reaction with aldehyde **7** resulted in isolation of a major diastereoisomeric adduct in 63% yield following conventional work-up and chromatography. Although an X-ray structure determination was not carried out, the tlc and spectral characteristics provided strong evidence that adduct **6e** had the same $C_{4/5}$ stereochemistry as **6a, b**. For example, the coupling constant between H-5/H-6 of **6e** of 6.0 Hz compared to 7.2 and 7.3 Hz for **6a** and **6b** respectively indicated the same relative 5/6 stereochemistry (*threo*)[9] as in **6a**/**b**. Unfortunately, the signals for H-4 and H-5 were part of a complex signal and thus ascertaining the relative stereochemistry at H-4 was more difficult. However, the $[\alpha]_D$ found in this case had a positive value, as it was for **6a** and **6b**. Casiraghi has demonstrated that the sign of the rotation is dependent on C-4 absolute configuration,[4] and it is likely that the same holds here, thus since the ^{13}C values of **6e** for C-4, C-5 and C-6 were similar within 1 ppm to those for **6a** and **6b**, the absolute stereochemistries at C-4 and C-5 of **6e** were taken as likely to be the same as those for **6a** and **6b**.

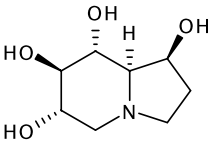
Finally, the role of the C-4 methoxy group was investigated. Thus, pyrrolinone **4f** (R_2 = H) was prepared from the known 4-hydroxy lactam **8** [13-15] via elimination of its mesylate (Scheme 3). Subsequent to this we became aware of a much shorter sequence for realising **4f** via condensation of dimethoxydihydrofuran with benzylamine [16] or *via* a ring-closing metathesis reaction.[17]



8 **4f**

Scheme 3: Synthesis of *N*-benzyl-3-pyrrolin-2-one **4f**. *Reagents and conditions*: a) MsCl, Et_3N, DMAP, 90%; b) Et_3N, THF, Δ, 70%.

Pyrrolinone **4f** was then subjected to the standard Mukaiyama aldol sequence (Scheme 2), but tlc indicated that no reaction to form an aldol adduct had taken place. The reaction sequence was repeated and each time starting pyrrolinone was recovered. Assuming that formation of the silyloxypyrrole occurred in this sequence, which we feel to be likely in this case, this outcome came as an interesting and unexpected result, particularly since chiral *N*-alkyl silyloxypyrroles are known to undergo asymmetric vinylogous Mukaiyama aldol reactions with simple aldehydes.[3,18] It would appear that in our case in the *N*-benzyl series, a C-4 methoxy group is essential for reactivity by raising the energy of the silyloxypyrrole HOMO. However, this still leaves the question of why Casiraghi's TBSOP **1** with an *N*-carbamate protecting group is so effective compared to our case **5f** with the *N*-benzyl group in which the nitrogen lone pair



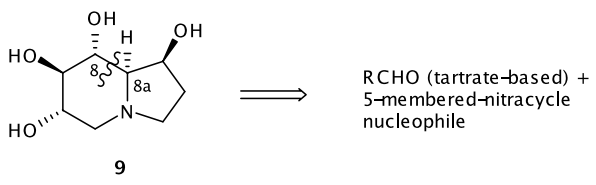
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Figure 2: Structure of (+)-castanospermine **9**.

is more delocalized into the pyrrole ring. Possible interference of the Lewis-acid at the nitrogen of **5f** (not likely in TBSOP) is a possible explanation, which presumably changes in the presence of the methoxy group of **5a**. The latter possibility is in line with the transition-state model recently postulated by us in which it was suggested that the methoxy group plays a coordinating role in the extended Mukaiyama aldol addition resulting in an *endo*-like transition state.[11] In the known cases [3,18] of *N*-alkyl silyloxypyrroles successfully reacting with simple aldehydes just mentioned, a more hindered α-asymmetric benzyl centre on nitrogen was used which would have presented steric hindrance at nitrogen towards the Lewis-acid.

We have also previously reported on the use of 4-methoxy-2-trimethylsilyloxypyrroles for generating C-5 quaternary centres using trimethyl orthoformate as the electrophile and $BF_3{\cdot}OEt_2$ as the promoter.[10] Together with the present study, this confirms the usefulness of *N*-benzyl-4-oxy-2-trimethylsilyloxypyrroles in vinylogous Mukaiyama aldol reactions.

As a demonstration of the usefulness of the methodology described herein, adduct **6a** was transformed into an advanced intermediate for the synthesis of (+)-castanospermine **9** (Figure 2). The latter is an indolizidine alkaloid that has received significant attention from the synthetic organic community in view of its potent biological activity as an α- and β-glycosidase inhibitor with promising anti-diabetic,[19] anti-cancer,[20] anti-viral [21] and anti-AIDS activity.[22] The early castanospermine syntheses were carbohydrate-based, and used glucose or mannose as their starting materials. However, in more recent times there has been a trend towards using other building blocks from the chiral pool to introduce some of the chiral centres.[23,24] Of these approaches, a number have utilized a convergent stategy via a C-8/C-8a disconnection (Figure 3). Thus, Gallagher,[25] Martin [26,27] and Casiraghi [4] have all attempted syntheses involving either a carbanion at C-8a or a Lewis-acid promoted aldol reaction as in Scheme 1 to form the C-8/C-8a bond. All the syntheses have suffered from incorrect diastereoselectivity in the aldol step as well as a lack of provision for C-1 hydroxyl group installation, and none of the syntheses based on this disconnection to date have successfully synthesized the target **9**. Given our success [9] in synthesizing the 4,5-*erythro*-5,6-*threo* adduct **6a** (Scheme 2) with correct absolute configurations for castanospermine (C-8/C-8a), we sought to transform **6a** into the target alkaloid, and in this paper report on the synthesis of an advanced intermediate towards this goal.



9

Figure 3: C-8/C-8a disconnection stategy for castanospermine synthesis.

Thus, adduct **6a** underwent oxidative cleavage of the PMB protecting group under acid conditions with CAN to give lactam **10** in 82% yield with retention of the MOM groups (Scheme 4). The vinyl ether **10** was then converted to a ketal in order to preclude any epimerization occurring at C-4, and this was achieved by subjecting **10** to bromine in the presence of methanol to give bromoketal **11** in 91% yield as a mixture of diastereomers (4:1). The diastereomeric mixture of **11** then underwent zinc reduction in the presence of methanol/THF/ammonium chloride [28] to give ketal **12** in 90% yield as a single diastereomer as evidenced by ^1H and ^{13}C NMR spectra. Having developed C-1 functionality in a protected form, attention turned to lactam carbonyl group removal and cyclization. In order to avoid interference during cyclization from the C-5 hydroxyl group as well as to link up with the lactam reduction methodology, the C-5 hydroxyl group and lactam N-H were both converted to their Boc derivatives using standard conditions ($(Boc)_2O$ (4 equiv), THF, DMAP) to give **13** in 90% yield as a crystalline solid. *N*-Boc lactam **13** was then reduced

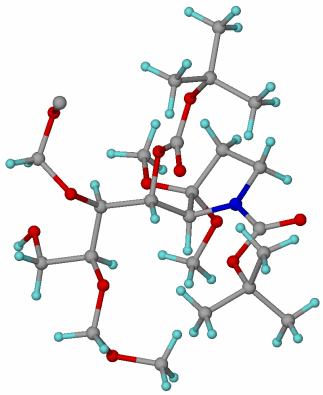
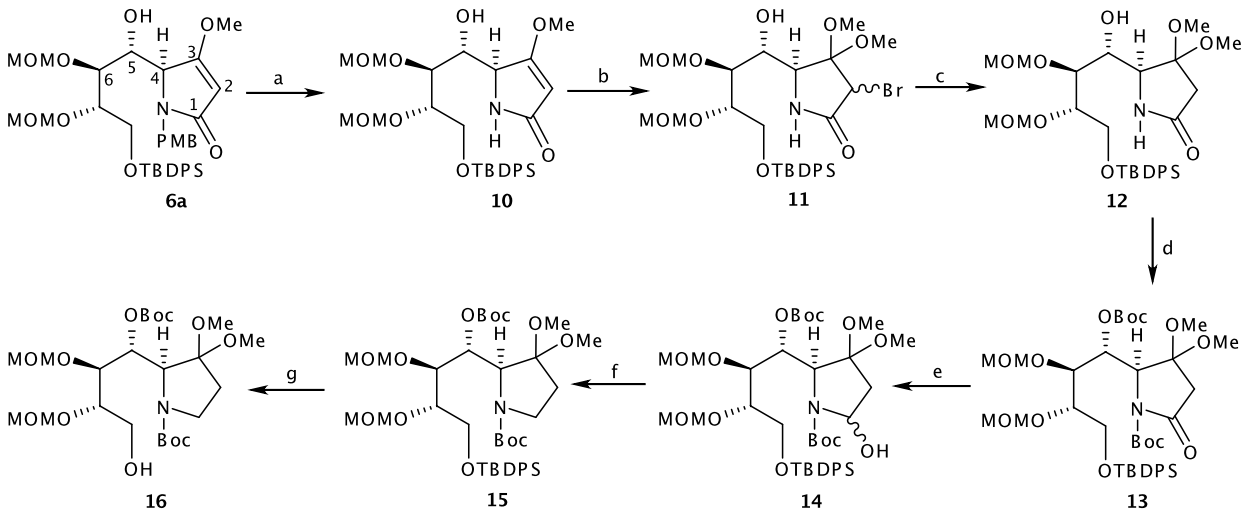
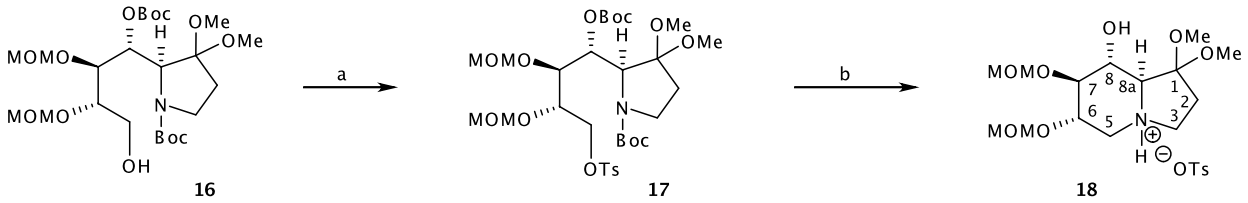


Figure 4: X-ray structure of **16**.



Scheme 4: Synthesis of Adduct **16** from adduct **6a**. *Reagents and conditions*: a) CAN, aq CH_3CN, -20°C to rt, 5 h, 82%; b) Br_2, MeOH, -20°C, 30 mins, 91%; c) Zn, aq NH_4Cl, THF, MeOH, RT, 30 mins, 90%; d) $(Boc)_2O$ (4 equiv), THF, DMAP (cat), rt, 18 h, 90%; e) DIBAL-H, THF, -78°C to -20°C, 2 h, 86%; f) Et_3SiH, $BF_3{\cdot}OEt_2$, DCM, -70°C, 1 h, 91%; g) TBAF, THF, 10°C, 5 days, 84%.



Scheme 5: Conversion of adduct **16** to indolizidine **18**. *Reagents and conditions* a) (1.5 equiv), Et_3N (2 equiv), DMAP (cat), DCM, 27°C, 24 h, 100%; b) i) TFA: DCM (1:4), 0°C 2 h; ii) Hünig's base (4 equiv), DCM, 0°C, 18 h, 56%.

to lactol **14** with DIBAL-H to afford a mixture of diastereomers in 86% yield, which was reduced with triethylsilane in the presence of $BF_3{\cdot}OEt_2$ to give carbamate **15** in 91% yield. This was then desilylated with TBAF at 10°C for 5 days to give alcohol **16** in 84% yield. These conditions were chosen, as by-products formed at higher temperature.

Adduct **16** was crystallized from ethyl acetate and hexane and used to obtain a single-crystal X-ray structure (Figure 4). CCDC 653715 contains the Supplementary Crystallographic Data for compound **16**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. The structure revealed the tartrate-derived centres C-6 and C-7 to be in their correct absolute configurations as derived from L-tartrate (both *S*-), and thus established the C-4 and C-5 absolute configurations to be *S*-, and *R*- respectively as shown in Scheme 4 and correct for castanospermine synthesis. The result also confirmed that the Mukaiyama adduct **6a** had not epimerized during this end-game sequence. Interestingly, the *N*-Boc group appears in its s-*trans* form, with the carbonyl oxygen pointing away from C-4. Compound **16** was then converted in high yield to tosylate **17** for the final cyclization, hydrolysis and reduction sequence to target (Scheme 5).

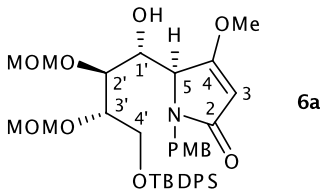
Exposure of **17** to TFA at 0°C followed by addition of Hünig's base resulted in cyclization to indolizidine **18**, which was isolated chromatographically as a tosylate salt in 56% yield. Compound **18** was identified from its NMR data. In particular, C-3(H-3), C-5(H-5) and C-8a(H-8a) resonated ≈ 10 ppm (C) and 1 ppm (H) downfield respectively compared to the signals in castanospermine as a result of deshielding by the quaternised nitrogen atom. Indolizidine **18** indicated concomitant hydrolysis of both MOM ethers to have occurred. A minor, less polar fraction was identified as a partially protected (C-6 or C-7) indolizidine (26%) that could independently be transformed into **18** by treatment with HCl. Unfortunately, attempts to hydrolyse the C-1 ketal of **18** to its carbonyl function under a variety of concentrations of acid (HCl) and at different temperatures all failed. Prolonged treatment led to decomposition. We attribute this unreactivity to destabilization of the intermediate oxocarbenium ion by the adjacent α-ammonium cation.

Conclusion

In summary, the present work has laid the foundation for a full enantioselective synthesis of castanospermine using a C-8/C-8a disconnection strategy. Future work will focus on C-1 transformation earlier in the sequence.

Experimental

See Supporting Information File 1 for full experimental data. Figure 5 describes the numbering system used in the experimental section.



6a

Figure 5: Structure of **6a** with numbering to demonstrate numbering system used in this section.

Supporting Information

Supporting Information File 1

General methods and Experimental. Experimental details for compounds **4** to **18**. Contains Figure 5.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-38-S1.doc]

Acknowledgments

We wish to thank the National Research Foundation, Pretoria (NRF) for their financial support.

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Beilstein Journal of Organic Chemistry

The enantiospecific synthesis of (+)-monomorine I using a 5-*endo*-trig cyclisation strategy

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Beilstein Journal of Organic Chemistry **2007**, 3, No. 39.
doi:10.1186/1860-5397-3-39

Received: 03 October 2007
Accepted: 08 November 2007
Published: 08 November 2007

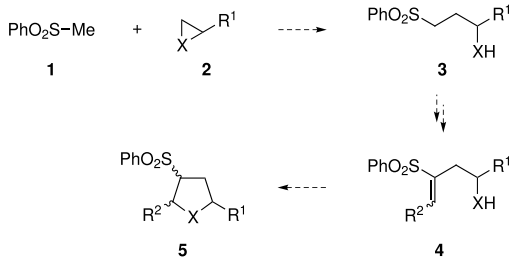
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Abstract

We have developed a general strategy for the synthesis of 2,5-*syn* disubstituted pyrrolidines that is based on the multi-faceted reactivity of the sulfone moiety and a 5-*endo*-trig cyclisation. This methodology was applied to the synthesis of indolizidine alkaloid monomorine I. Two factors were key to the success of this endeavour; the first was the choice of nitrogen protecting group whilst the second was the conditions for the final stereoselective amination step. Employing a combination of different protecting groups and an intramolecular reductive amination reaction we were able to prepare (+)-monomorine I in just 11 steps from commercially available D-norleucine in a completely stereoselective manner.

Background

The abundance in natural products and drug candidates of saturated five-membered heterocycles, such as tetrahydrofurans and pyrrolidines, makes these motifs attractive targets for synthesis. Over the last decade we have developed a powerful general strategy for the preparation of such compounds based upon the multi-faceted reactivity of the sulfone group and the formally disfavoured 5-*endo*-trig mode of cyclisation. [1-6] The methodology allows the conversion of epoxides (X = O) or aziridines (X = N-PG) (**2**) into the desired trisubstituted tetrahydrofurans or pyrrolidines (**5**) *via* a series of sulfone-mediated transformations (Scheme 1). Ring-opening **2** with the sulfone-stabilised anion of **1** forms the first C-C bond and furnishes **3**. Modifica-



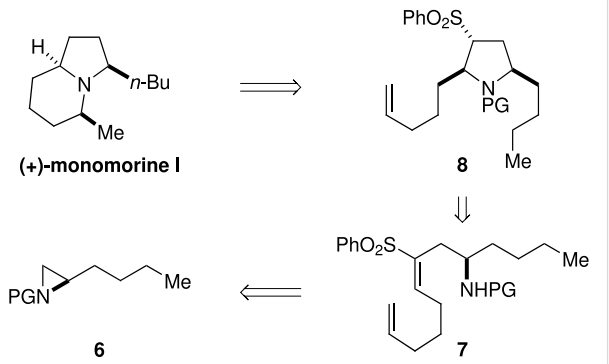
Scheme 1: General strategy for the synthesis of heterocycles *via* 5-*endo*-trig cyclisation

tion of the work of Julia [7-9] then utilises the sulfone to facilitate stereocontrolled alkenylation to give the cyclisation substrate **4**. Finally, 5-*endo*-trig cyclisation yields the desired heterocycles **5**. Overall, the sulfone moiety enables two C-C bond forming steps, allows stereocontrol of the alkene and activates the alkene to cyclisation. Furthermore, the sulfone can be used to elaborate the basic framework post-cyclisation.

In this publication we outline the application of this methodology to the synthesis of the indolizidine, (+)-monomorine I. [10-13] We have briefly described this work in a previous communication. [4]

Results and Discussion

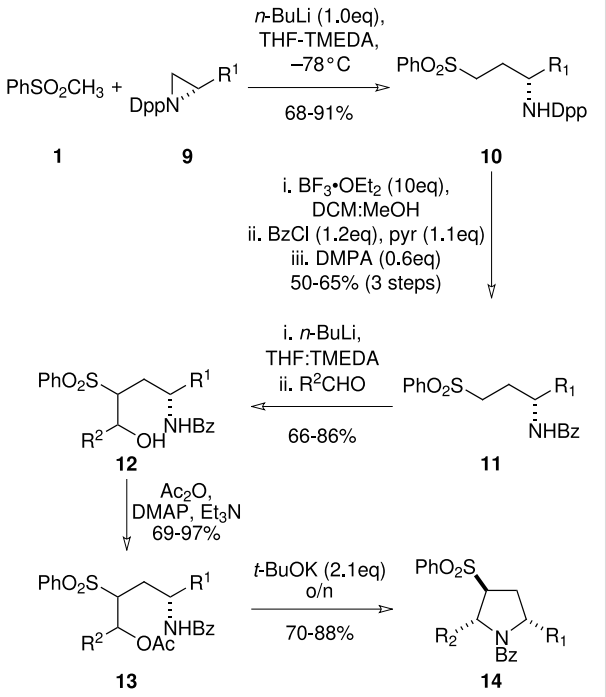
The pyrrolidine ring is an important structural motif that occurs in a range of pheromones, venoms and drug candidates. [14] In order to demonstrate the synthetic utility of the sulfone-mediated 5-*endo*-trig methodology. [3] we embarked on the total synthesis of the indolizidine alkaloid monomorine I, the trail pheromone of the Pharaoh worker ant *Monomorium pharaonis*. [10] Our initial synthetic plan is outlined in Scheme 2; aziridine **6**, prepared from D-norleucine by standard transformations, would be converted into the 2,5-*syn* disubstituted pyrrolidine core **8** *via* alkene **7**. With all the required carbon atoms in place, the final steps would involve deprotection, intramolecular hydroamination of the alkene and desulfonylation.



Scheme 2: Retrosynthesis of (+)-monomorine I

Initial studies directed towards this goal exploited the tosyl moiety as the nitrogen-protecting group (PG) and resulted in a succinct synthesis of alkenes of the type **4** (X = NTs; Scheme 1). [15] Disappointingly, all attempts to ring-close the sulfonamides proved fruitless, and it was found that desulfonylation was necessary before cyclisation could be achieved. Whilst the tosyl-based methodology permitted the synthesis of a range of simple, non-functionalised pyrrolidines **5** (X = NH), the harsh nature of the deprotection reaction, treatment with hydrobromic acid and phenol in acetic acid at reflux, led to the destruction of the the terminal alkene functionality of **7** (PG = Ts; Scheme 2) required for our synthesis of (+)-monomorine I. As a result of this set-back, a second nitrogen protecting group was assessed. The diphenylphosphinyl group (PG = $P(O)Ph_2$ = Dpp) overcame many of the problems encountered with the tosyl group; protected alkenes **4** (X = NDpp) underwent smooth 5-*endo*-trig cyclisation to furnish *N*-(diphenylphosphinyl)pyrrolidines **5** (X = Dpp) in good yields. [3,16] Furthermore, dephosphinylation was readily achieved under either Lewis acidic or Brønsted acid conditions compatible with a range of functional groups. This second-generation methodology was limited by the finding that acylation of **3** (X = NDpp) could only be achieved with non-enolisable acid chlorides, rendering it unsuitable for the synthesis of (+)-monomorine I. Ultimately, no single protecting group was found to be suitable and it was necessary to exploit a combination of protecting groups. The full evolution of the 5-*endo*-trig cyclisation-based pyrrolidine methodology will be described in a future publication.

Key to the successful synthesis of (+)-monomorine I was the use of the *N*-(benzoyl)aminosulfone **11** (Scheme 3). Benzamide **11** could be prepared from *N*-(diphenylphosphinyl)aziridine **9** by ring-opening with **1** followed by protecting group interchange. Although this strategy was not as elegant as utilising an *N*-benzoylaziridine directly, we deemed it prudent not to

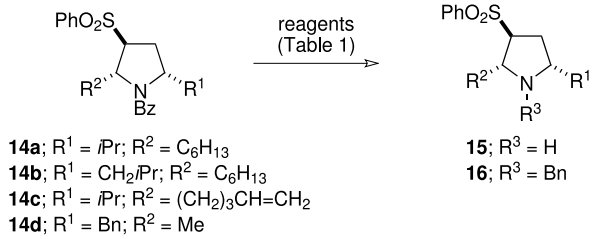


Scheme 3: The sulfone-mediated synthesis of 2,5-*syn* disubstituted pyrrolidines *via* a 5-*endo*-trig cyclisation

Table 1: Deprotection of *N*-benzoylpyrrolidines

Pyrrolidine	R^1	R^2	Reagent	R^3	Product	Yield (%)
14a	*i*Pr	C_6H_{13}	HCl	H	**15a**	69
14b	CH_2*i*Pr	C_6H_{13}	HCl	H	**15b**	60
14a	*i*Pr	C_6H_{13}	Super-Hydride®	H	**15a**	69
14c	*i*Pr	$(CH_2)_3CH=CH_2$	Super-Hydride®	H	**15c**	57
14c	*i*Pr	$(CH_2)_3CH=CH_2$	DIBAL	Bn	**16c**	70
14d	Bn	Me	DIBAL	Bn	**16d**	67

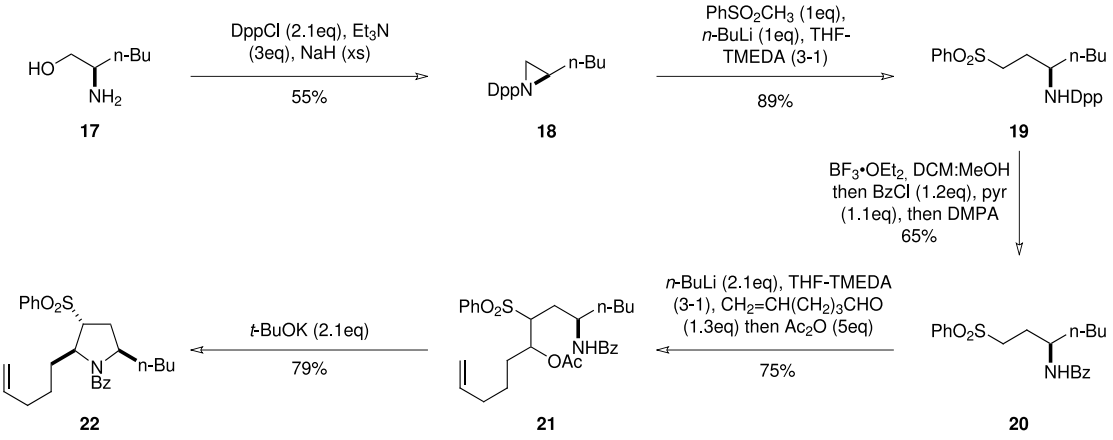
subject such a species to nucleophilic attack due to reported issues with chemoselectivity. [17] Careful optimisation obviated the need for chromatography following the protecting group exchange, and the benzamides **11** could be isolated in high purity and good yield. Hydroxyalkylation with a range of aldehydes proceeded without issue to give the β-hydroxysulfones **12** in excellent yields. The β-hydroxysulfones were then acylated under standard conditions to give **13**. Treatment of the β-acetoxysulfones **13** with two equivalents of base gave the pyrrolidines **14** directly as the product of a one-pot elimination-cyclisation cascade. The pyrrolidines were formed with complete diastereoselectivity for the 2,5-*syn* diastereoisomers. Although this stereochemical relationship could not be discerned from the ^{1}H NMR spectra of **14** due to peak broadening caused by amide rotamers, a combination of further elaboration and X-ray crystallographic analysis confirmed the assignment.



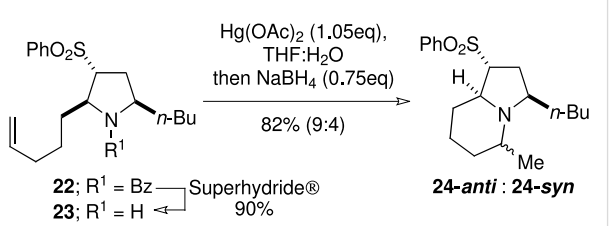
Scheme 4: The deprotection of *N*-benzoylpyrrolidines

Deprotection of simple benzoyl-protected pyrrolidines **14a** and **14b** could be achieved by acid hydrolysis (Scheme 4 and Table 1). However, as with the tosyl-based methodology, such reaction conditions were incompatible with the terminal alkene-substituted pyrrolidine **14c**. Therefore alternative deprotection conditions were investigated. Attempted base-mediated hydrolysis led to formation of the *N*-benzoylaminosulfone **11**, presumably by a sequence involving ring-opening by elimination, hydration of the electron-deficient alkenyl sulfone double bond and retro-aldol-like fragmentation. Reductive deprotection proved to be a more fruitful avenue of study. After considerable optimisation it was found that treatment of the *N*-benzoylpyrrolidines with Super-Hydride®[18] gave the free amines **15**, whilst the use of DIBAL in THF furnished the benzyl-protected pyrrolidines **16** in good yield (Scheme 4 and Table 1).

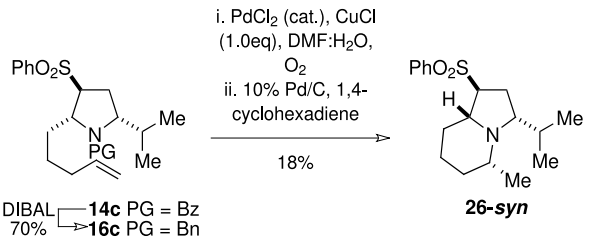
With the chemistry now in place to undertake the synthesis of (+)-monomorine I, the initial target, pyrrolidine **22**, was



Scheme 5: Synthesis of *N*-benzoyl protected pyrrolidine required for the preparation of (+)-monomorine I



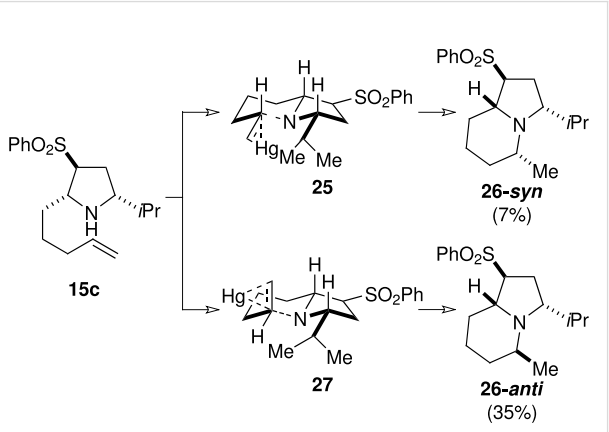
Scheme 6: Mercury-mediated hydroamination



Scheme 8: Model study for the reductive amination-based cyclisation

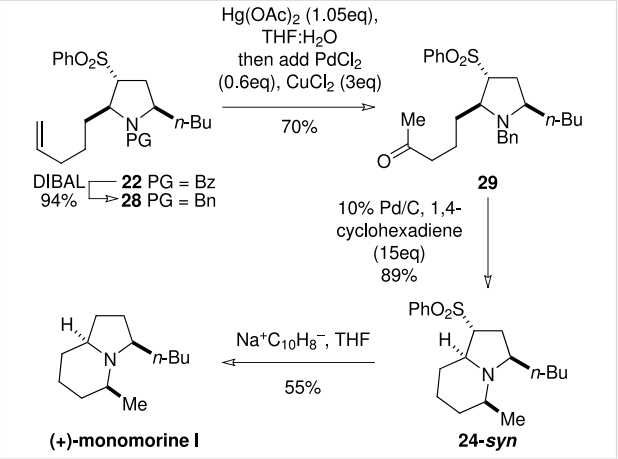
prepared. Commercially available D-norleucine was reduced to the amino alcohol **17**. [19] This was then converted into the benzoyl-protected aminosulfone **20** *via* the diphenylphosphinylaziridine **18,** which was ring-opened to give **19**, followed by protecting group exchange (Scheme 5). Formation of the dianion of **20** by exposure to two equivalents of *n*-butyllithium, followed by reaction with hex-5-enal and *in situ* trapping of the intermediate alkoxides gave the ester **21** as predominantly one diastereoisomer. Finally, one-pot elimination-cyclisation, promoted by two equivalents of potassium *tert*-butoxide, furnished the 2,5-*syn*-pyrrolidine **22** as a single diastereoisomer. Concurrently with the synthesis of **22**, the *iso*propyl model system, **14c**, was prepared using analogous chemistry.

Deprotection of **22** and **14c** was readily achieved with Super-Hydride® to give the free amines **23** and **15c**, which were subjected to mercury-mediated hydroamination (Scheme 6 and Scheme 7). [20] Cyclisation of **23** proceeded in good yield to give a 9:4 mixture of two indolizidines, epimeric at the C-5 methyl group **24-*anti*** and **24-*syn*** (Scheme 6). Cyclisation of the *iso*propyl analogue **15** proceeded with improved stereoselectivity to give a 5:1 mixture of epimeric indolizidines **26-*anti*** and **26-*syn*** (Scheme 7). Presumably, the increased steric bulk of the *iso*propyl group is responsible for the higher *anti*-selectivity. Assignment of the relative stereochemistry of the epimeric pairs proved problematic due to difficulties encountered during separation, and the presence of overlapping signals in the ^{1}H NMR spectrum. Finally, a combination of X-ray diffraction analysis and comparison of the ^{1}H NMR showed that the major diastereoisomer in each case was the undesired C-5 epimer, with the methyl group residing in the axial position. Naturally, we had assumed that the diastereoisomer in which all the substituents adopted a pseudo-equatorial orientation would have been formed preferentially. Yet inspection of the possible transition states for the cyclisation **25** *vs*. **27** reveals that the axial methyl may be favoured so as to minimize the strain associated with the eclipse of the C-3 and C-5 substituents (Scheme 7). Branching of the *iso*propyl substituent would cause greater interaction than the butyl group, and therefore would lead to an increase in selectivity.



Scheme 7: Proposed transition state for mercury-mediate hydroamination

The findings described above dictated that an alternative cyclisation strategy be investigated. It was anticipated that intramolecular reductive amination of a pendant methyl ketone would furnish the correct diastereoisomer, because the hydride source would be expected to approach the iminium ion from the less sterically demanding face, with the C-9 stereocentre being the controlling factor. [21] Both the benzoyl protecting group and the free amine were deemed incompatible with such a strategy. Therefore, **22** and **14c** were converted into the benzyl-protected pyrrolidines **28** and **16c** respectively by partial reduction with DIBAL-H (s Scheme 8 and Scheme 9). Wacker oxidation[22] of the *iso*propyl model compound **16c** gave the desired methyl ketone, which was subjected to transfer hydrogenation. [23] The latter reaction precipitated a reaction cascade commencing with deprotection of the *N*-benzylpyrrolidine followed by intramolecular reductive amination to give the desired indolizidine **26-*syn*** as a single diastereoisomer in 18% yield for the two steps. Whilst the yield of this unoptimised reaction was not satisfactory, we were pleased to observe that only the desired diastereoisomer was formed.



Scheme 9: The synthesis of (+)-monomorine I

Oxidation of the terminal alkene of **28** under Wacker conditions proved highly capricious and was ultimately abandoned in favour of a more reliable oxymercuration protocol. [24] Under these conditions the methyl ketone **29** was isolated in 70% yield (Scheme 9). Catalytic transfer hydrogenation led to sequential debenzylation and intramolecular reductive amination to furnish **24-*syn*** as a single diastereoisomer in excellent yield. Desulfonylation was achieved by brief exposure of **24-*syn*** to sodium naphthalenide in THF to furnish (+)-monomorine I, which showed ^{1}H and ^{13}C NMR, IR, mass spectral and optical rotation characteristics in agreement with published values. [25] Short reaction times were found to be crucial to the success of this reaction.

In summary, we have developed a highly stereoselective 5-*endo*-trig cyclisation reaction that facilitates the preparation of 2,5-*syn* disubstituted pyrrolidines. We have used this transformation as the key step in the synthesis of the indolizidine alkaloid, (+)-monomorine I. The synthesis was achieved in nine steps from the readily available aziridine **18**, and compares favourably with other total syntheses in the literature.

See Supporting Information File 1 for full experimental data.

Supporting Information

Supporting Information File 1

The enantiospecific synthesis of (+)-monomorine I using a 5-*endo*-trig cyclisation strategy: full experimental data. Full preparative details of all compounds prepared are reported, together with their spectroscopic data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-39-S1.doc]

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Beilstein Journal of Organic Chemistry

A divergent asymmetric approach to aza-spiropyran derivative and (1*S*,8a*R*)-1-hydroxyindolizidine

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Full Research Paper

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Beilstein Journal of Organic Chemistry **2007**, 3, No. 41.
doi:10.1186/1860-5397-3-41

Received: 23 September 2007
Accepted: 08 November 2007
Published: 08 November 2007

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Abstract

Background

Spiroketals and the corresponding aza-spiroketals are the structural features found in a number of bioactive natural products, and in compounds possessing photochromic properties for use in the area of photochemical erasable memory, self-development photography, actinometry, displays, filters, lenses of variable optical density, and photomechanical biomaterials etc. And (1*R*,8a*S*)-1-hydroxyindolizidine (**3**) has been postulated to be a biosynthetic precursor of hydroxylated indolizidines such as (+)-lentiginosine **1**, (−)-2-epilentiginosine **2** and (−)-swainsonine, which are potentially useful antimetastasis drugs for the treatment of cancer. In continuation of a project aimed at the development of enantiomeric malimide-based synthetic methodology, we now report a divergent, concise and highly diastereoselective approach for the asymmetric syntheses of an aza-spiropyran derivative **7** and (1*S*,8a*R*)-1-hydroxyindolizidine (*ent*-**3**).

Results

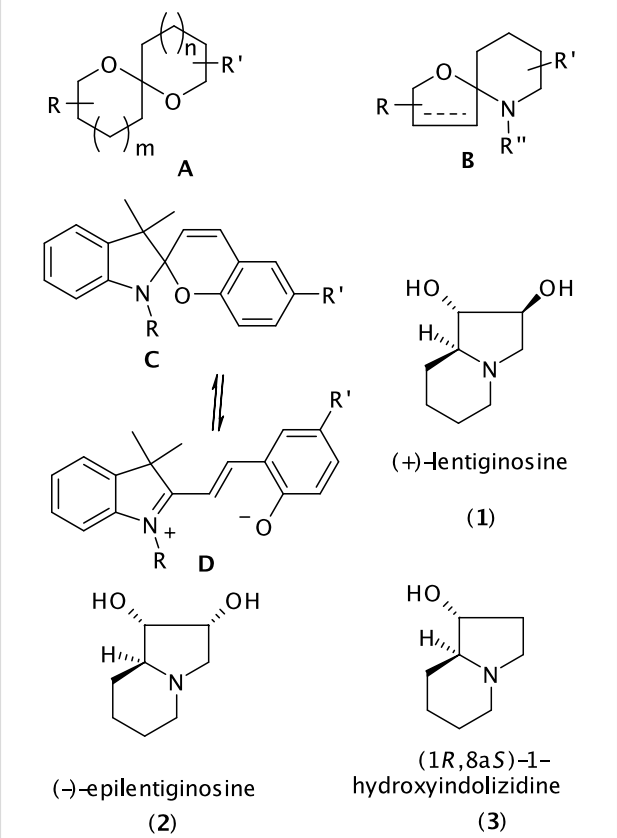
The synthesis of aza-spiropyran **7** started from the Grignard addition of malimide **4**. Treatment of the THP-protected 4-hydroxybutyl magnesium bromide with malimide **4** at −20°C afforded *N*,*O*-acetal **5a** as an epimeric mixture in a combined yield of 89%. Subjection of the diastereomeric mixture of *N*,*O*-acetal **5a** to acidic conditions for 0.5 h resulted in the formation of the desired functionalized aza-spiropyran **7** as a single diastereomer in quantitative yield. The stereochemistry of the aza-spiropyran **7** was determined by NOESY experiment. For the synthesis of *ent*-**3**, aza-spiropyran **7**, or more conveniently, *N*,*O*-acetal **5a**, was converted to lactam **6a** under standard reductive dehydroxylation conditions in 78% or 77% yield. Reduction of lactam **6a** with borane-dimethylsulfide provided pyrrolidine **8** in 95% yield. Compound **8** was then converted to 1-hydroxyindolizidine *ent*-**3** via a four-step procedure, namely, *N*-debenzylation/*O*-mesylation/Boc-cleavage/cyclization, and *O*-debenzylation. Alternatively, amino alcohol **8** was mesylated and the resultant mesylate **12** was subjected to hydrogenolytic conditions, which gave (1*S*,8a*R*)-1-hydroxyindolizidine (*ent*-**3**) in 60% overall yield from **8**.

Conclusion

By the reaction of functionalized Grignard reagent with protected (*S*)-malimide, either aza-spiropyran or (1*S*,8a*R*)-1-hydroxyindolizidine skeleton could be constructed in a concise and selective manner. The results presented herein constitute an important extension of our malimide-based synthetic methodology.

Background

Spiroketals of general structure **A** (Scheme 1) constitute key structural features of a number of bioactive natural products isolated from insects, microbes, fungi, plants or marine organisms. [1-3] The corresponding aza-spiroketal (cf: general structure **B**) containing natural products, while less common, are also found in plants, shellfish and microbes.[4,5] For example, pandamarilactone-1 and pandamarine were isolated from the leaves of *Pandanus amaryllifolius*;[6] solasodine and its derivatives were isolated from *Solanum umbelliferum*, which exhibited significant activity toward DNA repair-deficient yeast mutants;[7] azaspiracids are marine phycotoxins isolated from cultivated mussels in Killary harbor, Ireland;[8] and chlorofusin A is a novel fungal metabolite showing the potential as a lead in cancer therapy.[9] In addition, aza-spiropyrans **C**, being able to equilibrate with the corresponding non-spiro analogue **D**, is a well known class of compounds possessing photochromic properties for use in the area of photochemical erasable memory,[10] and also found applications as self-development photography, actinometry, displays, filters, lenses of variable optical density,[11] and photomechanical biomaterials etc.[12]



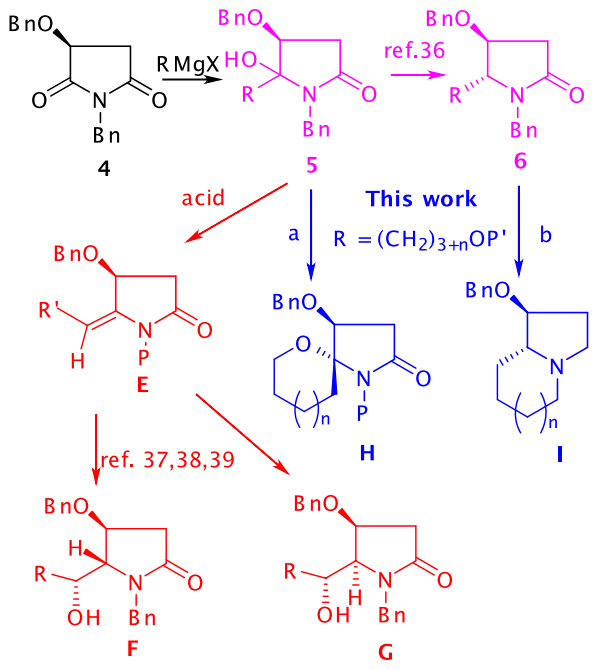
Scheme 1: The skeletons of useful aza-spiroketals and some naturally occurring hydroxylated indolizidines.

On the other hand, hydroxylated indolizidines [13-20] such as castanospermine, (−)-swainsonine, (+)-lentiginosine (**1**) [21-23] and (−)-2-epilentiginosine (**2**) [21-26] constitute a class of azasugars showing potent and selective glycosidase inhibitory activities. [13-20] (1*R*,8a*S*)-1-Hydroxyindolizidine **3** has been postulated as a biosynthetic precursor [21-26] of (+)-lentiginosine (**1**), (−)-2-epilentiginosine (**2**) and (−)-swainsonine, a potentially useful antimetastasis drug for the treatment of cancer.[15] In addition, these molecules serve as platforms for testing synthetic strategies, and several asymmetric syntheses of both enantiomers of 1-hydroxyindolizidine (**3**) have been reported. [27-34]In continuation of our efforts in the development of enantiomeric malimide-based synthetic methodologies, [35-38] we now report concise and highly diastereoselective syntheses of an aza-spiropyran derivative **7** and (1*S*,8a*R*)-1-hydroxyindolizidine (*ent*-**3**).

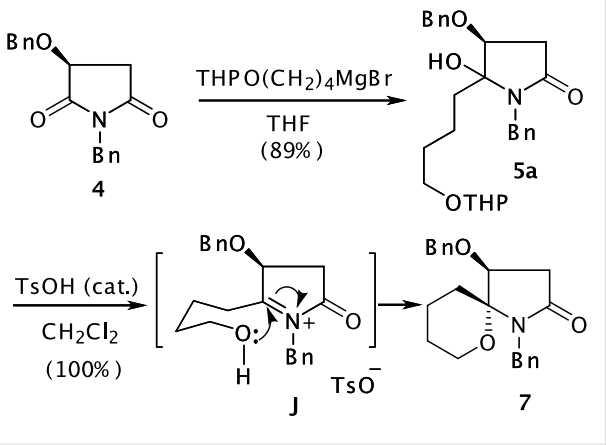
Results and discussion

Previously, we have shown that the addition of Grignard reagents to *N*,*O*-dibenzyl malimide (**4**) leads to *N*,*O*-acetals **5** in high regioselectivity (Scheme 2), and the subsequent reductive dehydroxylation gives **6** in high *trans*-diastereoselectivity.[35] On the other hand, treatment of *N*,*O*-acteals **5** with an acid furnished enamides **E**, which can be transformed stereoselectively to either hydroxylactams **F** or **G** under appropriate conditions. [36-38] It was envisioned that if a C_4-bifunctional Grignard reagent was used, both aza-spiroketal **H** (such as aza-spiropyran, n = 1, path a) and indolizidine ring systems **I** (path b) could be obtained.

The synthesis of aza-spiropyran **7** started from the Grignard addition of malimide **4**. Treatment of the THP-protected 4-hydroxybutyl magnesium bromide with malimide **4** at −20°C for 2.5 h afforded *N*,*O*-acetal **5a** as an epimeric mixture in 7:1 ratio and with a combined yield of 89% (Scheme 3). If the reaction was allowed to stir at room temperature overnight, the diastereomeric ratio was inversed to 1: 1.8. Subjection of the diastereomeric mixture of the *N*,*O*-acetal **5a** to acidic condi-



Scheme 2: Synthetic strategy based on *N*,*O*-dibenzylmalimide (**4**).



Scheme 3: Stereoselectivity synthesis of aza-spiropyran **7**.

tions [TsOH (cat.)/CH_2Cl_2, r.t.] for 0.5 h resulted in the formation of the desired functionalized aza-spiropyran derivative **7** as a single diastereomer in quantitative yield. The result means that a tandem dehydration-THP cleavage-intramolecular nucleophilic addition occurred. When the stirring was prolonged to 2 h, about 5% of another epimer (no shown) was also formed according to the ^{1}H NMR analysis.

The stereochemistry of the aza-spiropyran **7** was determined on the basis of the NMR analysis. This was done firstly by a ^{1}H-^{1}H COSY experiment to confirm the proton assignments, and then by NOESY experiment. As shown in Figure 1, the strong NOE correlation of H-9a (δ_H 3.59) and H-4 (δ_H 4.22) indicates clearly O_4/O_5-*trans* relationship in compound **7**.

These findings are surprising comparing with our recent observations. In our previous investigations, it was observed that the treatment of *N*,*O*-acetals **5** with an acid leads to the dehydration products **E** (Scheme 2), and the two diastereomers of **5** shows different reactivities towards the acid-promoted dehydration. [36-38] The *trans*-diastereomer reacts much more slower than the *cis*-diastereomer, and some un-reacted *trans*-epimer was

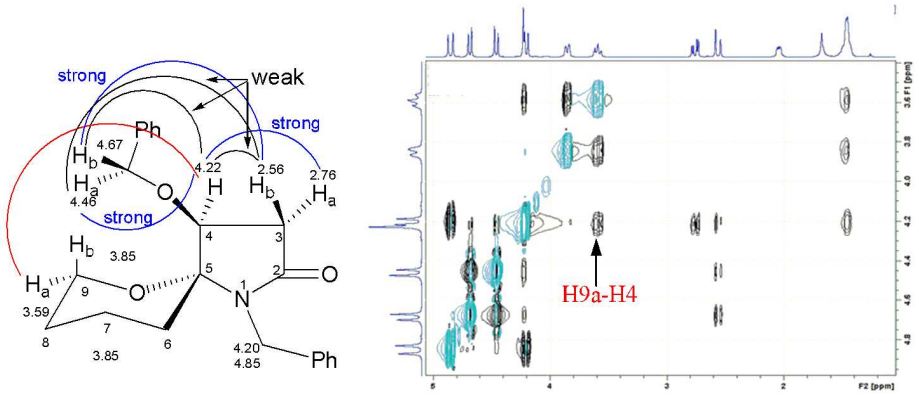
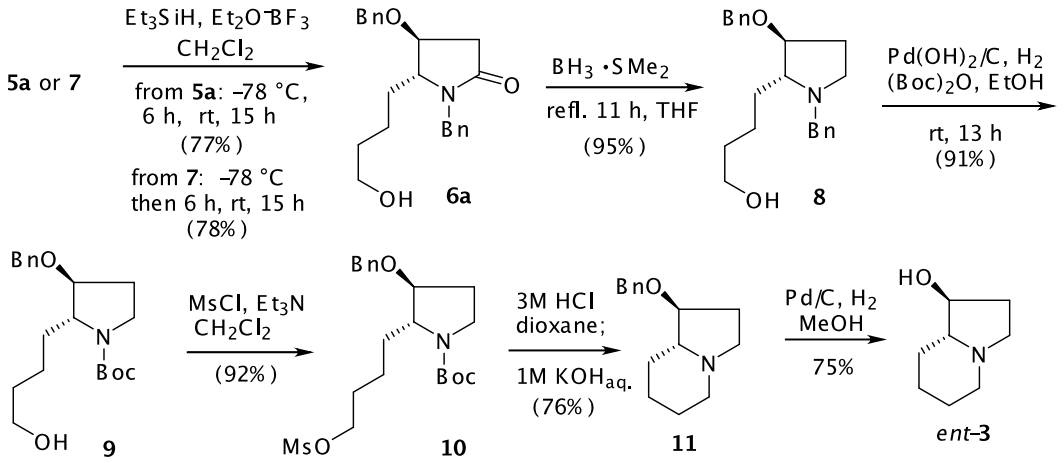


Figure 1: The observed NOE correlations (in part) and the region expanded NOESY spectrum of compound **7**.



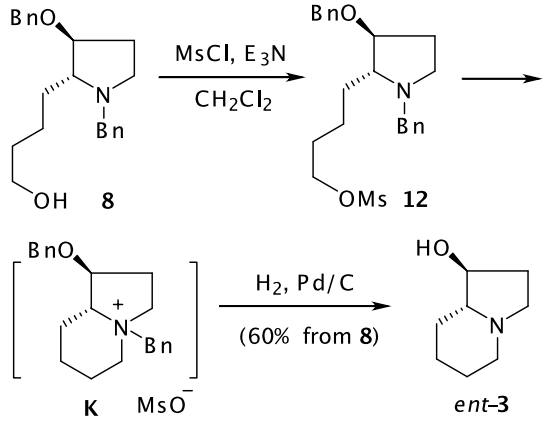
Scheme 4: Stereoselective synthesis of (1*S*,8a*R*)-1-hydroxyindolizidine (*ent*-**3**).

always recovered even starting with a pure *cis*-diastereomer. In the present study, not only both two diastereomers have been completely converted to the aza-spiropyran **7**, what is equally surprising is that no dehydration product was observed under acidic conditions!

For the synthesis of *ent*-**3**, aza-spiropyran **7**, a cyclic *N*,*O*-acetal, was converted to lactam **6a** under standard reductive dehydroxylation conditions (Et_3SiH, $BF_3{\cdot}OEt_2$, −78°C, 6 h; warm-up, yield: 78%) (Scheme 4). Under the same conditions, *N*,*O*-acetal **5a** was converted to lactam **6a** in 77% yield. It was observed that during the reaction of **5a**, **7** was first formed as an intermediate after the addition of Et_3SiH and $BF_3{\cdot}OEt_2$, and stirring for 1 hour.

Reduction of lactam **6a** with borane-dimethylsulfide provided pyrrolidine derivative **8** in 95% yield. Compound **8** was then converted to (1*S*,8a*R*)-1-hydroxyindolizidine (*ent*-**3**) {$[\alpha]_D^{27}$ +50 (*c* 0.90, EtOH); lit.[29] $[\alpha]_D$ +51.0 (*c* 0.54, EtOH); lit.[32] −49.7 (*c* 0.95, EtOH) for the antipode} via a four-step procedure, namely, one-pot *N*-debenzylation-*N*-Boc formation/*O*-mesylation/Boc-cleavage/cyclication, and *O*-debenzylation.

In searching for a more concise method, amino alcohol **8** was mesylated (MsCl, NEt_3, 0 °C) and the resultant labile mesylate **12** was subjected to catalytic hydrogenolysis (H_2, 1 atm, 10% Pd/C, r.t.), which gave (1*S*,8a*R*)-1-hydroxyindolizidine (*ent*-**3**) in 60% overall yield from **8** (Scheme 5).[39,40] The one-pot *N*,*O*-bis-debenzylation and cyclization of mesylate **12** deserves comment. Because the *N*-debenzylation generally required longer reaction time,[41] or using of Pearlman's catalyst (cf. Scheme 4). The easy debenzylation of **12** allows assuming that an intramolecular substitution occurred firstly, and the formation of the quaternary ammonium salt **K** [40] then favors the reductive debenzylation. This mechanism is supported by the following observations. First, in a similar case, Thompson et al observed that the formation of a mesylate resulted in spontaneous quarternization leading to the bicyclic indolizidine.[40] Second, we have also observed that the tosylate of **8** is too labile to be isolated, and mesylate **12** decomposed upon flash column chromatography on silica gel, which are due to the spontaneous formation of a polar quaternary ammonium salt. In addition, the presence of the *O*-benzyl group in **K** is an assumption based on our previous observation on a similar case.[42]



Scheme 5: One-pot synthesis of *ent*-**3** from amino alcohol **8**.

Conclusion

In summary, we have demonstrated that by the reaction of functionalized Grignard reagent with the protected (*S*)-malimide **4**, either aza-spiropyran derivative **7** or (1*S*,8a*R*)-1-hydroxyindolizidine skeleton (*ent*-**3**) can be constructed in a concise and selective manner. It is worthy of mention that in addition to the reductive dehydroxylation leading to 2-pyrrolidinones **6**, and

the acid-promoted dehydration leading to (*E*)-enamides **E** (and then **F**, **G**), acid treatment of the *N*,*O*-acetal **5a** could provide, chemoselectively and quantitatively, the aza-spiropyran ring system **7**. The results presented herein constitute a valuable extension of our malimides-based synthetic methodology.

See Supporting Information File 1 for full experimental procedures and characterization data of the synthesized compounds.

Supporting Information

Supporting Information File 1

Experimental. Experimental procedures for the synthesis of all compounds described, and characterization data for the synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-41-S1.doc]

Acknowledgments

The authors are grateful to the NSFC (20572088), NSF of Fujian Province and Xiamen City (2006J0268; 3502z20055019) and the program for Innovative Research Team in Science & Technology (University) in Fujian Province for financial support. We thank Professor Y. F. Zhao for the use of her Bruker Dalton Esquire 3000 plus LC-MS apparatus.

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Beilstein Journal of Organic Chemistry

Synthesis of the Benzo-fused Indolizidine Alkaloid Mimics

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Full Research Paper

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Beilstein Journal of Organic Chemistry **2007**, 3, No. 42.
doi:10.1186/1860-5397-3-42

Received: 04 October 2007
Accepted: 30 November 2007
Published: 30 November 2007

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Abstract

A general synthesis of various benzo-fused indolizidine alkaloid mimics has been developed. The indolizidine derivatives **8** were prepared via heteroaryl Grignard addition to *N*-acylpyridinium salts followed by an intramolecular Heck cyclization. Further substitution reactions were developed to demonstrate that heterocycles **8** are good scaffolds for chemical library preparation.

Background

As part of a program directed at studying the synthesis and synthetic utility of *N*-acyldihydropyridones, the heterocycles **1** were developed as useful building blocks for alkaloid synthesis (Figure 1). [1,2] Biologically active indolizidine alkaloids [3] such as (+)-allopumiliotoxin 267A (**2**) [4], (±)-indolizidine 209B (**3**) [5], (+)-indolizidine 209D (**4**) [6], and (±)-tylophorine (**5**) [7] were prepared in racemic or enantiopure form using these dihydropyridone intermediates. Herein we demonstrate the utility of this chemistry for preparing diverse benzo-fused indolizidine compounds.

Results and Discussion

The reaction of various kinds of heteroaryl Grignard reagents with the *N*-acylpyridinium salt prepared from 4-methoxypyridine (**6**) and 2-iodobenzoylchloride (**7a**) was studied (Table 1). The addition of 2-furyl [8], 2-thienyl [9] and 2-pyrrolyl [10,11] Grignard reagents gave *N*-acyldihydropyridones **1a-c** in good yields (entries 1–3). In addition, the *N*-methyl-2-indolyl [11] Grignard reagent gave **1d** in moderate yield (entry 4). In spite of trying various methods of preparing the 2-pyridyl [12-15] Grignard reagent, **1e** was obtained in only 15% yield (entry 5). Encouraged by these

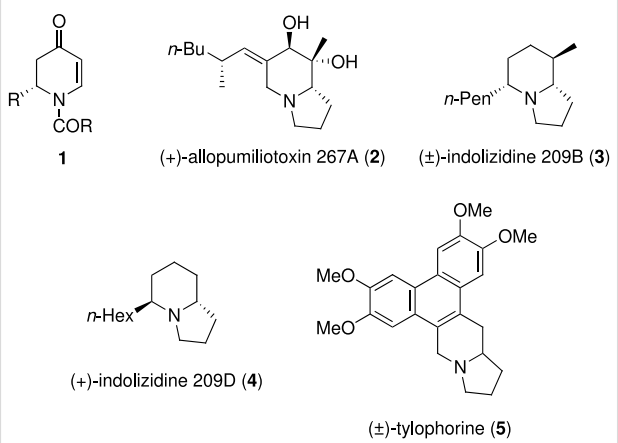
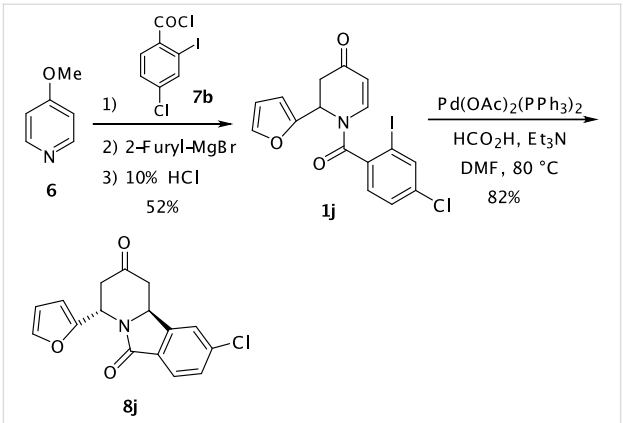


Figure 1: *N*-Acyldihydropyridone **1** and indolizidine alkaloids.

results, the reaction of 3-heteroaryl Grignard reagents was also examined (entries 6–9). The 3-furyl [16] and 3-thienyl [17] Grignard reagents were prepared from the corresponding 3-bromo compounds and gave **1f** and **1g** in moderate yields (entries 6,7). The compounds **1h** and **1i** were prepared in good yield from *N*-TIPS-3-bromopyrrole [18] and *N*-TIPS-3-bromoindole (entries 8,9).

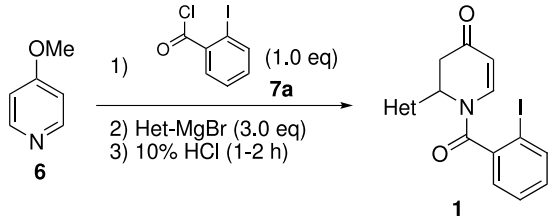
Next, the intramolecular reductive Heck cyclization with *N*-acyl-2,3-dihydropyridones **1a-i** was investigated (Table 2). A short synthesis of indolizidine alkaloids of type **8** by using Heck or anionic cyclization methods was developed. [6,19] In this reaction, only the trans diastereomer was obtained as determined by analysis of the ^{1}H-NMR spectrum of the crude product. This methodology is useful for the synthesis of various types of indolizidine alkaloids and their mimics. Treatment of **1a-i** with 5 mol% of palladium catalyst, 2 equiv of formic acid and 4 equiv of triethylamine at 80°C in DMF provided **8a-i** in good yields. THF could also be used as a solvent in this reaction. In the case of **1h** and **1i**, the *N*-TIPS group was cleaved under the reaction conditions (entries 8,9).



Scheme 1: Preparation of chloro-substituted compound 8j.

To add more points of diversity, the preparation of derivatives containing functionality in the benzene ring was examined. The chloro-substituted compound **1j** was prepared from **6** and 4-chloro-2-iodobenzoylchloride (**7b**). [20] The reductive Heck cyclization of **1j** proceeded without difficulty to provide compound **8j** in 82% yield (Scheme 1).

Table 1: Reaction with 2- and 3-substituted heteroaryl Grignard reagents



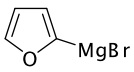
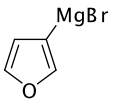
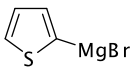
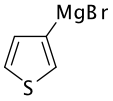
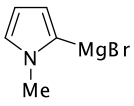
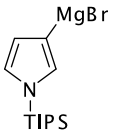
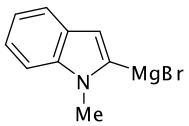
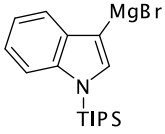
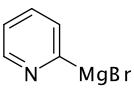
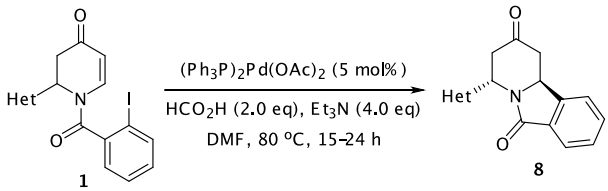
entry	Het-MgBr	Yield of **1**	entry	Het-MgBr	Yield of **1**
1		**1a** 83%	6		**1f** 55%
2		**1b** 86%	7		**1g** 58%
3		**1c** 69%	8		**1h** 9%
4		**1d** 51%	9		**1i** 77%
5		**1e** 15%			

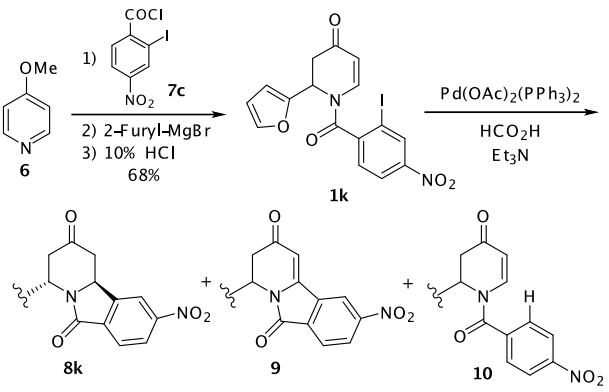
Table 2: Intramolecular reductive Heck cyclization



entry	1	yield of 8	entry	1	yield of 8
1	**1a**	**8a** 82%	6	**1f**	**8f** 78%
2	**1b**	**8b** 81%	7	**1g**	**8g** 79%
3	**1c**	**8c** 74%	8	**1h**	**8h** 57%[a]
4	**1d**	**8d** 48%	9	**1i**	**8i** 82%[a]
5	**1e**	**8e** 31%			

a TIPS group was cleaved.

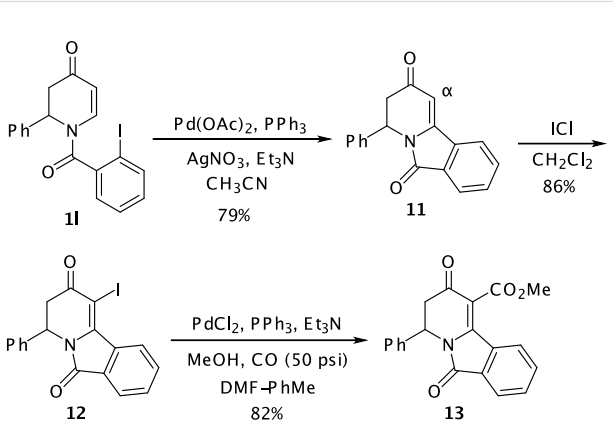
Next, the nitro-substituted compound **1k** was prepared from 4-methoxypyridine (**6)** and 2-iodo-4-nitrobenzoyl chloride (**7c**) (Scheme 2). [21] Although the reductive Heck cyclization of **1k** gave the desired compound **8k** in 17% yield, the non-reductive cyclized product **9** and uncyclized compound **10** were isolated in 26% and 17%, respectively (entry 1). The reaction in THF with 10 mol% of palladium catalyst at a lower reaction temperature gave **8k** in 67% yield (entry 3). [22]



entry	Pd (mol%)	solvent	condition	8k	9	10
1	5	DMF	80 °C, 9 h	17%	26%	17%
2	5	THF	80 °C, 6 h	13%	0%	7%
3	10	THF	R.T.→60 °C, 5 h	67%	5%	4%

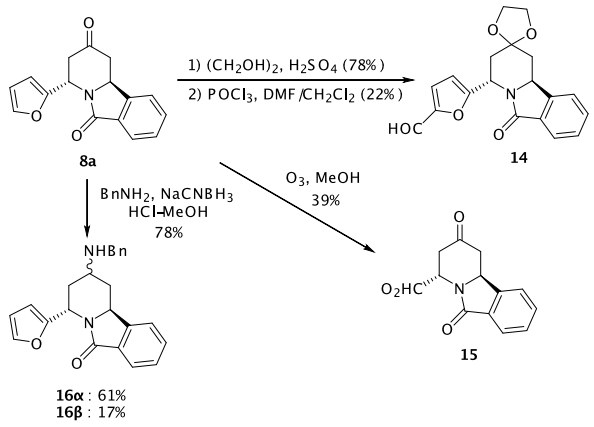
Scheme 2: Preparation of nitro-substituted compound 8k.

Scheme 3 shows a method for substitution at the α-position of *N*-acyldihydropyridone **11**. Our laboratories have reported C-5 substitution of 5-iodo-1,2-dihydropyridones via palladium mediated cross-coupling and carboalkoxylation. [23] Initially, non-reductive Heck cyclization of **1l** [24] was carried out in the presence of $Pd(OAc)_2$ and $AgNO_3$ in CH_3CN. [22] Treatment of the product **11** with ICl in CH_2Cl_2 at 0°C gave the iodinated dihydropyridone **12** in 86% yield. Palladium-catalyzed carboalkoxylation reaction of **12** gave the α-methoxycarbonyl dihydropyridone **13** in 82% yield.



Scheme 3: α-Methoxycarbonylation of 11.

The addition and modification of functional groups on **8a** were investigated (Scheme 4). The protection of the C-4 carbonyl of **8a** as a ketal followed by Vilsmeier-Haack formylation [25] furnished **14** in 22% yield. The furan ring of **8a** was converted to a carboxylic acid by ozonolysis to afford **15**. The reductive amination of **8a** with benzylamine provided **16α** and **16β** in good yield. The stereochemistry of these compounds was determined by NOESY NMR analysis. These functional groups, such as carboxylic acid and secondary amine, provide diversity which could be important for the development of biologically active derivatives.



Scheme 4: Modification of functional groups within 8a.

Conclusion

The synthesis and chemistry of indolizidine derivatives **8** was investigated with the goal of providing access to diverse heterocyclic compounds of potential biological activity. The various kinds of *N*-acyldihydropyridones **1** were conveniently prepared from heteroaryl Grignard reagents and *N*-acylpyridinium salts. Subsequently, dihydropyridones **1** were converted to **8** by use of an intramolecular Heck cyclization. The chloro- and nitro-substituted acyl chlorides **7** were also used to provide compounds with additional synthetic handles. The α-position of dihydropyridone **11** was halogenated and carbonylated to provide ester **13**. Compound **8a** was also converted to furylaldehyde **14**, carboxylic acid **15** and secondary amines **16**. Indolizidine alkaloids such as type **8** are readily synthesized in 2 steps from commercially available compounds. We have demonstrated that compound **8** can be substituted with functional groups, and provide useful scaffolds for the preparation of indolizidine alkaloid mimics.

Experimental

See Supporting Information File 1 for full experimental data.

Supporting Information

Supporting Information File 1

Experimental Section. Experimental details and full spectroscopic data for new compounds
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-42-S1.doc]

Acknowledgments

We express appreciation to SCYNEXIS Chemistry & Automation, Inc. for financial support of this research. The NMR and mass spectra were obtained at NCSU instrumentation laboratories, which were established by grants from the North Carolina Biotechnology Center and the National Science Foundation (Grant CHE-0078253).

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Beilstein Journal of Organic Chemistry

Synthesis of densely functionalized enantiopure indolizidines by ring-closing metathesis (RCM) of hydroxylamines from carbohydrate-derived nitrones

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Full Research Paper

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Beilstein Journal of Organic Chemistry **2007**, 3, No. 44.
doi:10.1186/1860-5397-3-44

Received: 17 October 2007
Accepted: 12 December 2007
Published: 12 December 2007

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Abstract

Background

Indolizidine alkaloids widely occur in nature and display interesting biological activity. This is the reason for which their total synthesis as well as the synthesis of non-natural analogues still attracts the attention of many research groups. To establish new straightforward accesses to these molecules is therefore highly desirable.

Results

The ring closing metathesis (RCM) of enantiopure hydroxylamines bearing suitable unsaturated groups cleanly afforded piperidine derivatives in good yields. Further cyclization and deprotection of the hydroxy groups gave novel highly functionalized indolizidines. The synthesis of a pyrroloazepine analogue is also described.

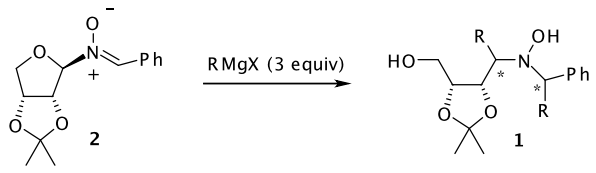
Conclusion

We have developed a new straightforward methodology for the synthesis of densely functionalized indolizidines and pyrroloazepine analogues in 6 steps and 30–60% overall yields from enantiopure hydroxylamines obtained straightforwardly from carbohydrate-derived nitrones.

Background

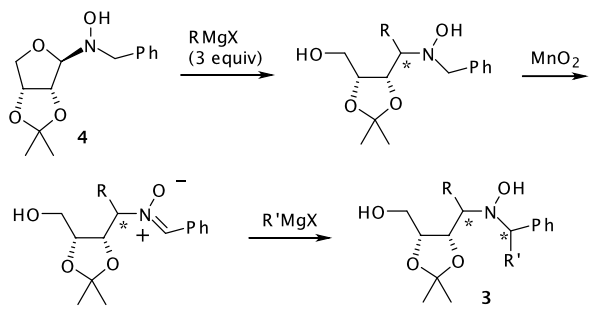
Indolizidine alkaloids have widespread occurrence in nature. They can be found in widely different organisms such as bacteria, fungi, higher plants, invertebrates and vertebrates.[1] For instance, the plant-derived polyhydroxylated indolizidines are well known as potent glycosidases inhibitors, and for this reason they are potential therapeutic agents. [2-4] A great deal of research is still devoted to the structural elucidation of these alkaloids as well as to their total syntheses. [5-18]

We accomplished the total syntheses of some indolizidine alkaloids and of several non-natural analogues employing chiral nitrones as key intermediates, either as dipolarophiles in 1,3-dipolar cycloaddition chemistry [19,20] or as electrophiles in the addition of organometallic reagents. [21,22] Recently, we developed a general protocol for the synthesis of α,α'-disubstituted enantiopure hydroxylamines **1** through the stereoselective double addition of an excess of a Grignard reagent to *C*-phenyl-*N*-erythrosylnitrone **2** (Scheme 1).[23] With this methodology, several symmetrically α,α'-disubstituted hydroxylamines **1** were afforded.



Scheme 1: Synthesis of symmetrically α,α'-disubstituted hydroxylamines **1**.

An alternative protocol for the synthesis of unsymmetrically α,α'-disubstituted hydroxylamines **3**, resulting from the sequential addition of two different Grignard reagents, was also developed in a stepwise process, based on an addition-oxidation-addition sequence starting from *N*-glycosylhydroxylamine **4** (Scheme 2).[24]



Scheme 2: Synthesis of unsymmetrically α,α'-disubstituted hydroxylamines **3**.

Addition of unsaturated Grignard reagents afforded synthetically useful hydroxylamine intermediates, which may serve as substrates for nitrogen ring forming reactions. We report in this article a straightforward access to indolizidine derivatives and a pyrroloazepine analogue through a key ring closing metathesis (RCM) of sugar derived hydroxylamines **1** and **3** bearing suitable unsaturated substituents at the α and α' positions.

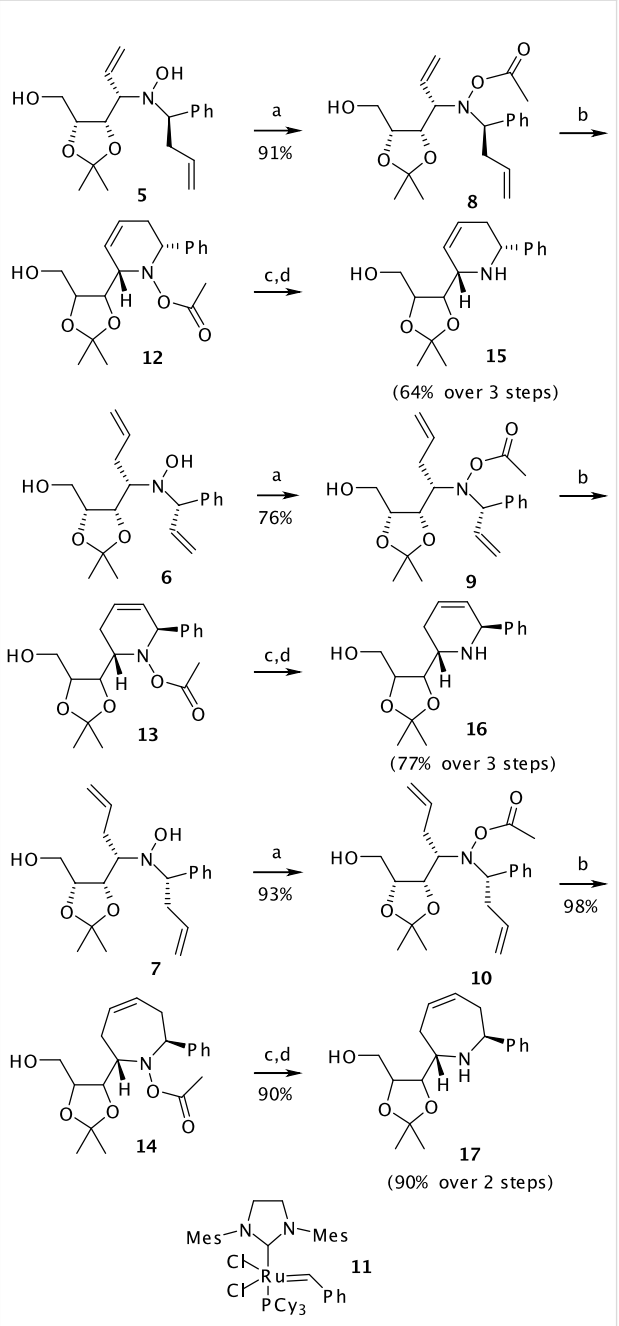
Results and discussion

Unsymetrically α,α'-disubstituted hydroxylamines **5** and **6** (Scheme 3) were synthesized according to our recently reported procedure based on the addition-oxidation-addition sequence starting from *N*-glycosylhydroxylamine **4** (Scheme 2),[24] while hydroxylamine **7** was obtained using an excess of allylmagnesium bromide in the addition to *C*-phenyl-*N*-erythrosylnitrone **2**.[23] It should be noted that the stepwise process furnishes configurationally diversified stereoisomers at the benzylic position (e. g. **5** and **6**), due to a high stereoselectivity in the first addition step but a poor one in the second.[24] Specifically, **5** was isolated as the major isomer from a ca 2:1 diastereomeric mixture, while **6** was obtained from an equimolecular mixture with its diastereoisomer.[24] Assignment of configuration has been secured by comparison with the double adducts of the one-pot process and by careful NMR studies of the final cyclic products after RCM. The scarce stereoselectivity of the second addition in the stepwise process, giving rise to two diastereoisomers, opens the way to the synthesis of diastereomeric indolizidines.

The RCM reaction has been successfully employed for the synthesis of polyfunctional indolizidines. [25-29] In order to accomplish successfully the key RCM reactions, preliminary protection of the hydroxylamine OH group was required. Selective acetylation of hydroxylamines **5–6** was achieved with acetic anhydride in THF at room temperature, while for hydroxylamine **7** it was necessary to heat the mixture at reflux. No acetylation of the primary alcohol was observed under these conditions.

Ring-closing metathesis (RCM) of *O*-acetylhydroxylamines **8–10** using the second generation Grubbs' catalyst **11** [30] in refluxing CH_2Cl_2 afforded compounds **12–14** in nearly quantitative yields (Scheme 3). However, compounds **12** and **13** suffered from low stability and for this reason the crude reaction mixtures were directly employed in the following steps.

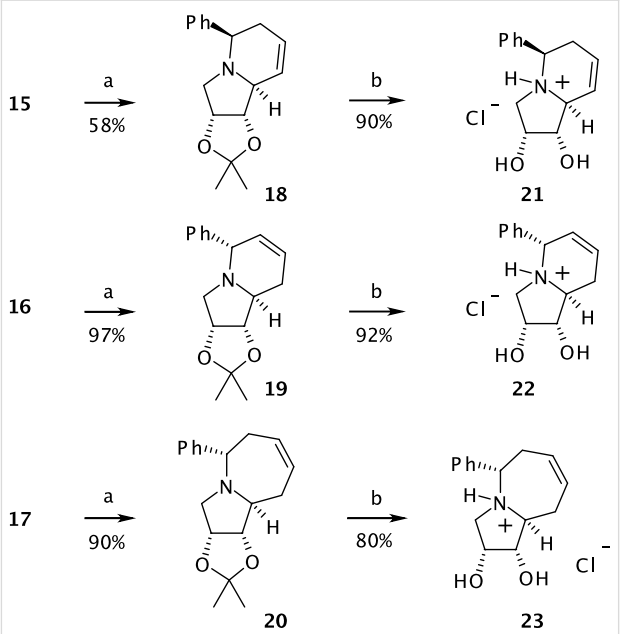
Identity of compounds **12** and **13** was firmly established after their transformation into the corresponding amines and further elaboration. After deacetylation with $KHCO_3$, *in situ* reduction of the N-O bond with zinc dust afforded tetrahydropyridines **15**



Scheme 3: Synthesis of piperidines **15–16** and azepine **17**. Reagents and conditions: a) Ac_2O, THF, 1 h, rt for **8** and **9**, reflux for **10**; b) 2nd generation Grubbs' catalyst **11** (5 mol%), CH_2Cl_2, reflux, 5.5 h; c) $KHCO_3$, MeOH, rt, 12 h; d) Zn, AcOH, rt, 2 h.

and **16** (Scheme 3). Analogously, deprotection of **14** and *in situ* reduction with zinc dust gave tetrahydroazepine **17** (Scheme 3).

Cyclization to give the fused 5-membered ring was achieved by treatment of compounds **15–17** with trifluoromethanesulfonic anhydride in pyridine at room temperature (Scheme 4). The structure of protected indolizidines **18–19** and of pyrroloazepine **20** (and therefore of compounds **12–14**) was unambiguously determined by spectral data, including 2D COSY and 1D NOESY experiments (See Experimental).



Scheme 4: Synthesis of indolizidines **21–22** and pyrroloazepine **23**. Reaction conditions: a) Tf_2O, Py, rt, 2 h; b) Conc. HCl, MeOH, rt, 2 h.

Final deprotection of **18–20** with an acidic solution of MeOH afforded protonated indolizidines **21–22** in good yields (Scheme 4). Analogously, deprotection of **20** gave pyrrolazepine **23**, which displayed good inhibition of α-glucosidase from yeast (90% at 1 mM).[23] Compounds **17** and **23**, containing an azepane moiety, might be of biological interest as shown recently. [31-35] Indolizidines **21–22** differ in the absolute configuration at C5 and in the position of the double bond, illustrating the structural diversity attainable with this strategy. It should be noted that similar dihydroxyhexahydroindolizines maintained glucosidase inhibition activity in analogy to the completely unsaturated compounds.[22] Moreover, it has been recently proved that dihydroxypyrrolidines bearing aromatic rings have interesting antitumor activities. [36,37] Work is underway to evaluate the biological activity of the newly synthesized compounds. In addition, the presence of a double bond should allow the introduction of additional hydroxy groups or other functionalities by appropriate elaboration.

Experimental

[See Supporting Information File 1 for full experimental data]

Supporting Information

Supporting Information File 1

Synthesis of densely functionalized enantiopure indolizidines by ring-closing metathesis (RCM) of hydroxylamines from carbohydrate-derived nitrones. Experimental Sections. Experimental procedures, characterization of new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-44-S1.pdf]

Acknowledgments

We thank Cassa di Risparmio di Firenze for granting a 400 MHz spectrometer. Maurizio Passaponti and Brunella Innocenti (Università di Firenze) are acknowledged for technical assistance. We thank INSTM for partially financing a research grant to one of us (MB)

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Desymmetrization of 7-azabicycloalkenes by tandem olefin metathesis for the preparation of natural product scaffolds

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Beilstein Journal of Organic Chemistry **2007,** *3,* No. 48.
doi:10.1186/1860-5397-3-48

Received: 22 October 2007
Accepted: 18 December 2007
Published: 18 December 2007

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Abstract

Background

Tandem olefin metathesis sequences are known to be versatile for the generation of natural product scaffolds and have also been used for ring opening of strained carbo- and heterocycles. In this paper we demonstrate the potential of these reactions for the desymmetrization of 7-azabicycloalkenes.

Results

We have established efficient protocols for the desymmetrization of different 7-azabicycloalkenes by intra- and intermolecular tandem metathesis sequences with ruthenium based catalysts.

Conclusion

Desymmetrization of 7-azabicycloalkenes by olefin metathesis is an efficient process for the preparation of common natural product scaffolds such as pyrrolidines, indolizidines and isoindoles.

Background

Azabicyclo [x.y.0]alkane scaffolds are ubiquitous structural elements in pharmaceutically important peptide mimetics [1-3] and several important classes of natural products such as indolizidine and quinolizidine alkaloids and azasugars. [4-6] In consequence, a number of groups have developed efficient syntheses of these bicyclic heterocycles. [7-9] Challenges for the synthesis of these structures are the introduction of chirality and of several functional groups into the scaffolds. In particular the latter point is often a problem, leading to multistep sequences.

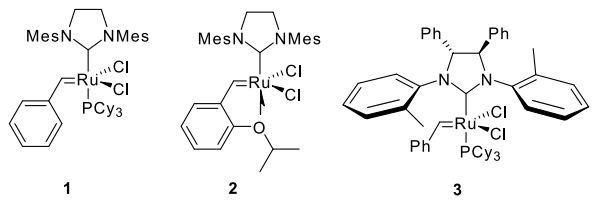
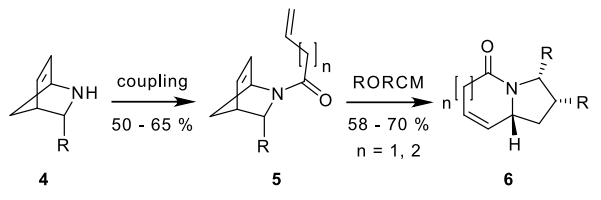


Figure 1: Ruthenium based precatalysts used in this study.

In this context, ring closing metathesis (RCM) and tandem metatheses [10-13] have been particularly successful strategies for the assembly of common natural product scaffolds. [14-22] A general advantage of these approaches is that ring closure and/or scaffold-rearrangements can be accomplished while generating a double bond as a valuable functional group for further manipulations. In addition, the common ruthenium (Figure 1) and molybdenum based catalysts for olefin metathesis are well known for their broad functional group tolerance.

The application of RCM to the synthesis of azabicycloalkane scaffolds was first described by Grubbs[23] for the synthesis of peptide mimetics and later extended by several other groups. [24-31] Key intermediates in these approaches are often alkenyl substituted pyrrolidines, which are *N*-acylated with an unsaturated carboxylic acid and submitted to a ring closing metathesis (RCM).

As a part of a general synthetic concept using azabicycloalkenes as masked analogs of functionalized pyrrolidines or piperidines [32-39] we have previously applied the concept of intramolecular ring-opening/ring-closing metathesis (RORCM) [40-54] to *N*-acylated 2-azabicycloalkenes **4** as precursors for azabicyclo [X.3.0]alkanes like **6** (Scheme 1).[55] Various other strained heterocycles have also been used for ring opening metathesis or other tandem metathesis sequences. [56-61]



Scheme 1: RORCM of 2-azabicycloalkenes **5** to bicyclic scaffolds **6**.

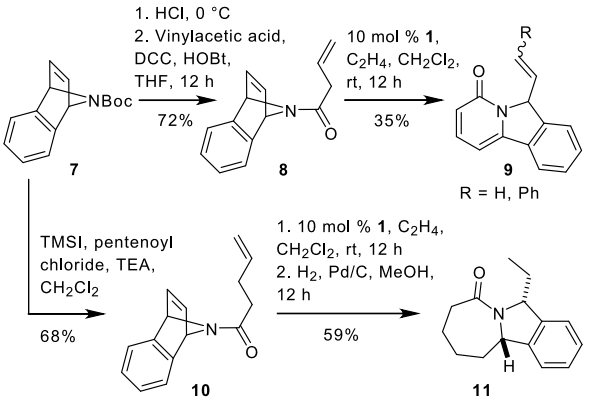
In this paper, we describe the extension of this work and show that desymmetrization of 7-azabicycloalkenes *via* RORCM leads to valuable natural product scaffolds. In this context, symmetrical derivatives of 7-azabicycloalkenes like **7** and **12** are extremely interesting substrates for RORCM conversions, because they may be desymmetrized either by diastereoselective or enantioselective metathesis.

Results and Discussion

In a first attempt to transfer the RORCM-strategy to 7-azabicycloalkenes, we chose **7** as a precursor for domino metathesis reactions. Our choice was due to the following two reasons: 1. Azabicycloalkene **7** is easy to synthesize *via* Diels-Alder reaction.[62] 2. It was assumed to be a good substrate for RORCM because it is strained and has been shown to be susceptible to other desymmetrizing ring opening reactions in the past.[63,64]

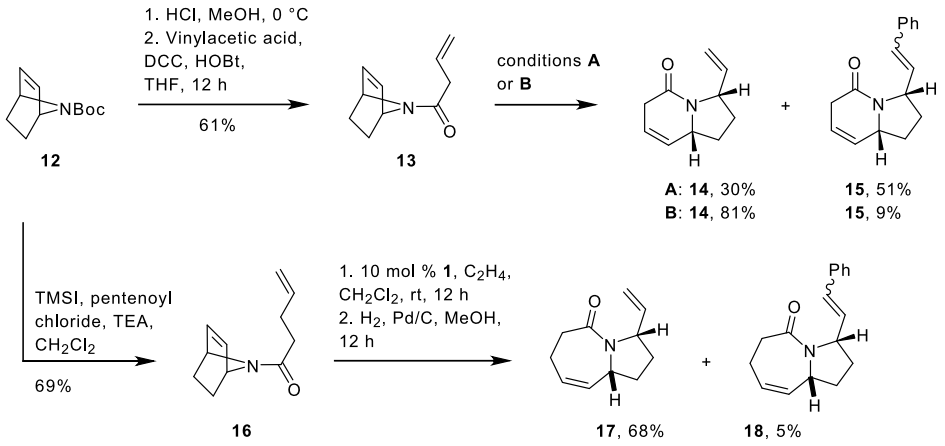
To generate appropriate precursors for the tandem conversions, **7** was deprotected and acylated with butenoic acid and pentenoyl chloride to give **8** and **10**. However, first attempts to convert the bis-olefin **8** *via* RORCM to the bicyclic target structure failed and only pyridone derivative **9** was isolated in small quantities along with large amounts of unreacted starting material. With turnover numbers of only three, the ruthenium based catalysts **1** and **2** were both quite ineffective in this metathesis reaction.

We assumed that the structure of the starting material **8** (location of the exocyclic double bond) and the following aromatization to **9** was the reason for the low catalytic efficiency of this conversion and tested this hypothesis with the conversion of the corresponding pentenoyl derivative **10** under RORCM conditions. As outline in Scheme 2, this reaction gave the expected metathesis product, which was hydrogenated to the isoindole derivative **11** in good yield, verifying our previous assumptions.



Scheme 2: RORCM of 7-azabicycloalkenes **8** and **10** to pyridone **9** and isoindole scaffold **11**.

As a general trend, it turned out that benzannelated azabicycloalkene derivatives like **8** and **10** give relatively unstable products. In consequence, products can only be isolated as



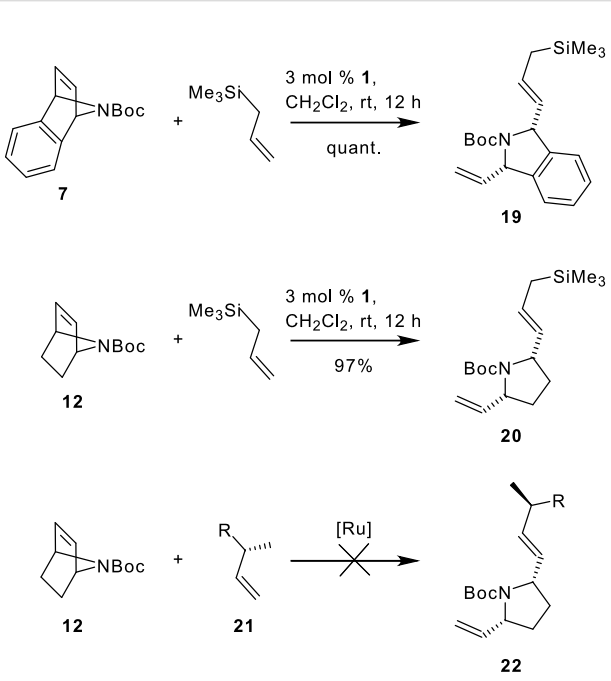
Scheme 3: RORCM of 7-azabicycloalkenes **13** and **16** to bicyclic scaffolds **14**, **15**, **17** and **18**. Conditions **A**: 10 mol % **1**, C_2H_4, 3 equiv styrene, CH_2Cl_2, rt, 12 h; **B**: 10 mol % **1**, C_2H_4, CH_2Cl_2, rt, 12 h.

pyridones **9**, derived from spontaneous aromatization or have to be hydrogenated to their saturated analogues **11**.

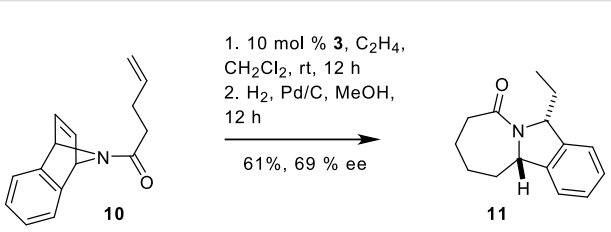
This unique reactivity of benzannelated metathesis precursors like **8** and **10** is not observed with other 7-azabicycloalkenes like **13** and **16** as depicted in Scheme 3. Starting from the known Boc-protected heterocycle **12**,[65,66] RORCM precursors **13** and **16** were generated after deprotection under standard acylation conditions in good yields. Treatment of these bis-olefins with Grubbs catalyst **1** gave the expected bicyclic compounds **14** and **17** in good yield along with some byproducts **15** and **18**, respectively. These byproducts are often observed, if the generated exocyclic double bond in the RORCM product is susceptible to olefin cross metathesis with the small amount of styrene that is derived from the precatalyst **1**. These types of products are favored, if additional olefins are added as CM partners. With addition of 3 equivalents styrene (condition **A** in Scheme 3), for example, the styrene adduct **15** becomes the main product.

Having established suitable protocols for conversions of 7-azabicycloalkenes to racemic products, we tried next to develop stereoselective variants and started our studies again with Boc-protected 7-azabicycloalkenes **7** and **12**. A sequence of ring opening and cross metathesis is extremely efficient for desymmetrization of **7** and **12** as depicted in Scheme 4 for the synthesis of isoindole **19** and the disubstituted pyrrolidine **20**. In these cases, catalyst loadings can be low and yields are excellent.

Unfortunately the ROCM of 7-azabicycloalkenes appeared to be quite sensitive with respect to the olefin cross metathesis partner [67] and we have not been able to transfer this reaction to α-substituted olefins like **21** yet.



Scheme 4: ROCM of 7-azabicycloalkenes **7** and **12** to isoindole and pyrrolidine scaffolds **19** and **20**.



Scheme 5: Catalytic enantioselective desymmetrization of 7-azabicycloalkene **10** to scaffold **23**.

A more successful attempt to introduce selectivity, was the enantioselective catalytic desymmetrization of bis-olefin **10** with the known chiral ruthenium catalyst **3**.[67] This reaction gave enantioenriched **11** in good yield (Scheme 5). However, the enantioselectivity of this reaction is only moderate compared to similar reactions using molybdenum based precatalysts and different azabicycloalkene starting materials that have been recently reported by Hoveyda and Schrock for the enantioselective preparation of piperidines.[68,69]

Conclusion

In this paper we have described efficient tandem metathesis protocols for the desymmetrization of 7-azabicycloalkenes. Desymmetrization is accomplished by intramolecular RORCM or intermolecular ROCM sequences to give a range of common natural product scaffolds such as pyrrolidines, indolizidines and isoindoles. The protocols use readily available starting materials, are simple and give densely functionalized metathesis products ready for further manipulations.

Supporting Information

Supporting Information File 1

Experimental. Experimental procedures for the synthesis of all compounds described, and characterization data for the synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-48-S1.doc]

Acknowledgments

We gratefully acknowledge support from the Deutsche Forschungsgemeinschaft (DFG, MA 2529/1) and from the Fonds der Chemischen Industrie.

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Beilstein Journal of Organic Chemistry

Synthesis of crispine A analogues *via* an intramolecular Schmidt reaction

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Full Research Paper

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Beilstein Journal of Organic Chemistry **2007**, 3, No. 49.
doi:10.1186/1860-5397-3-49

Received: 16 October 2007
Accepted: 19 December 2007
Published: 19 December 2007

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Abstract

An intramolecular Schmidt reaction strategy for the synthesis of various derivatives of crispine A using azido-ketone as a key intermediate is described.

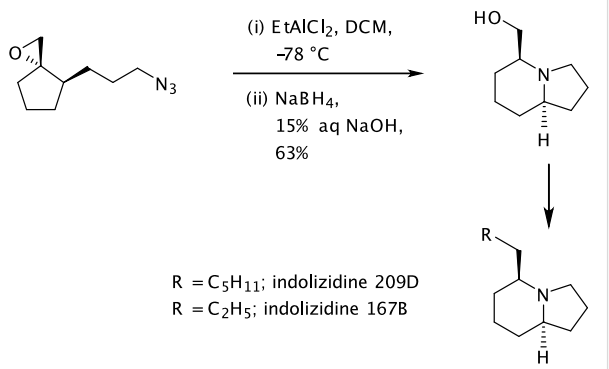
Background

The indolizidine skeleton is one of the most important structural subunits present in numerous biologically active molecules. [1-4] The polyhydroxylated indolizidines are potent inhibitors of carbohydrate processing enzymes and hence they are considered to be lead drug molecules in the treatment of metabolic diseases such as diabetes, cancer and HIV infection. [5-7] The alkyl indolizidine alkaloids, also called gephyrotoxins, are well-known for their ability to function as *non-competitive blockers of neuromuscular transmission* [2] by interacting with nAChRs. In addition, the indolizidine skeleton is also present in anticancer molecules such as lepadiformine,[8] antofine,[9] and tylophorine [9] as well as a immunosuppressive agent, FR901483.[10] The wide range of biological activities associated with the indolizidine alkaloids has elicited considerable interest in them as target molecules among synthetic organic chemists. As a result, numerous synthetic approaches have been developed for the synthesis of indolizidine alkaloids. [5-7] One of the most efficient methods for the construction of the indolizidine framework is based on the intramolecular Schmidt reaction of azides with carbonyl compounds.[11,12] Pearson and Aube have exploited the synthetic potential of the intramolecular Schmidt reaction in the synthesis of several indolizidine alkaloids. [11-15]

Recently, we reported a novel approach for the construction of the indolizidine skeleton using an epoxide initiated electrophilic cyclization of azide as a key step. This novel methodology has been efficiently applied in the stereo- and enantioselective synthesis of indolizidine 167B and 209D (Scheme 1). [16-18]

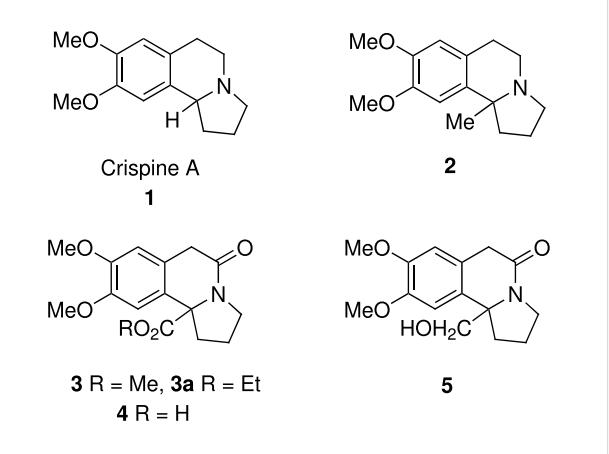
Results and discussion

In 2002, a new indolizidine alkaloid known as crispine A was isolated from *Carduus crispus*, a popular invasive plant occurring in Asia and Europe, which was found to exhibit superior antitumor activity against SKOV3, KB and HeLa human cancer lines.[19] As a result of its potent antitumor activity, various synthetic methods have been developed for the



Scheme 1: Epoxide initiated electrophilic cyclization of azide.

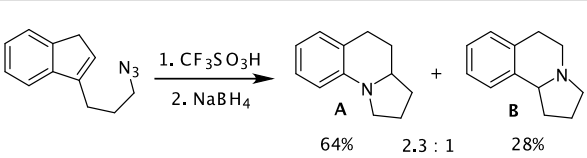
synthesis of crispine A. [20-28] Interestingly, Schell and Smith reported the first synthesis of crispine A, even before its isolation, using the *N*-chloramine rearrangement reaction as a key step.[25] In order to understand the structure activity relationship (SAR) as well as to improve the efficacy of this novel anticancer agent, a flexible approach for the synthesis of various derivatives of crispine A is in great demand (Scheme 2).



Scheme 2: Crispine A and its analogues.

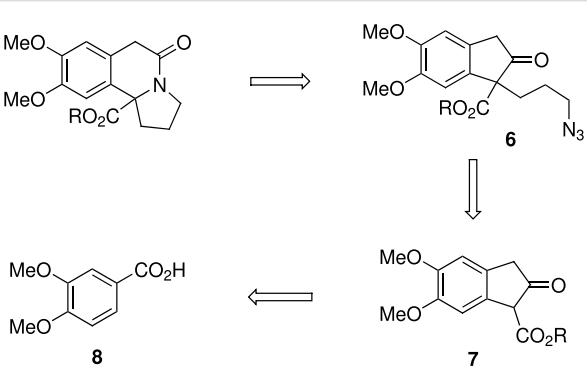
In 2000, Pearson reported the intramolecular Schmidt reaction based approach for the construction of benzo-fused indolizidine skeleton using azido-olefin as a key intermediate (Scheme 3). In this reaction, in addition to benzo[*e*]indolizidine **A**, a minor product **B** having the basic skeleton of crispine A was isolated in 28% yield. The intramolecular Schmidt reaction of azido-olefin in the presence of triflic acid proceeds with aryl migration rather than alkyl migration resulting in the formation of benzo[*e*]indolizidine [**A**] as a major product (Scheme 3).[29]

In this communication, we report the synthesis of crispine A analogues (**2**–**5**) using an intramolecular Schmidt reaction of azidoketone **6** as a key step. The azidoketone **6** can be readily



Scheme 3: Intramolecular Schmidt reaction of olefin azide.

prepared from the β-ketoester **7**, which in turn can be synthesized from the dimethoxybenzoic acid **8** as shown in Scheme 4.[30] 3,4-Dimethoxybenzoic acid (**8**) on treatment with paraformaldehyde in the presence of conc. H_2SO_4 followed by reduction with LAH gave the corresponding diol **9** as a white crystalline solid. Diol **9** on bromination followed by nucleophilic displacement with NaCN furnished the desired dicyano compound **10**.

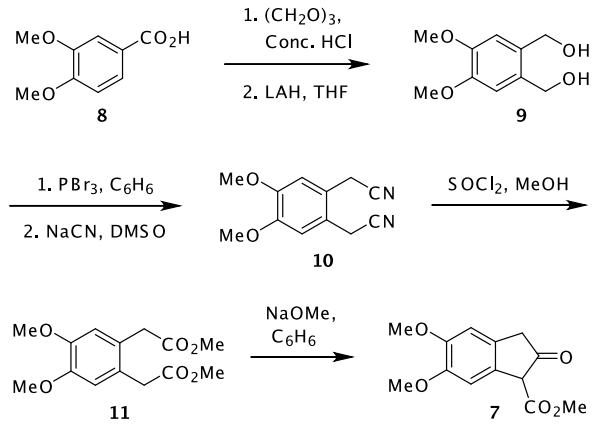


Scheme 4: Retrosynthetic approach for crispine A analogues.

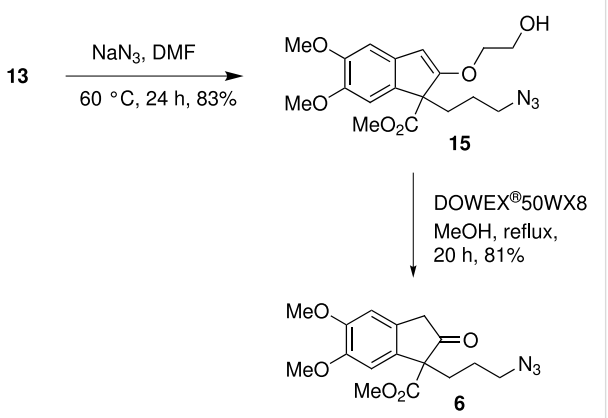
Treatment of dicyanide **10** with thionyl chloride in methanol gave the corresponding diester **11** as a colorless liquid in good yield. Compound **11** was then readily converted to the corresponding β-ketoester **7** *via* Dieckmann cyclization and the resultant product was purified by recrystallization using H_2O-EtOH solvent system (Scheme 5).

Our attempts towards the alkylation of β-ketoester **7** with 1-chloro-3-iodopropane under different reaction conditions were ineffective and resulted in poor yield. In order to improve the yield of the alkylation reaction, compound **7** was protected as the corresponding ethylene ketal **12** (Scheme 6).

Surprisingly, alkylation of ketal-ester **12** using NaH in dry DMF proceeded smoothly even at room temperature, however it resulted in an unusual cleavage of ethylene ketal under basic conditions, leading to hydroxy vinylether **13** in 70% yield. The formation of hydroxy vinylether **13** is evident from the spectroscopic data. The presence of a sharp singlet at δ_H 5.66 (s,1H) in ^{1}H NMR and signals corresponding to vinyl carbons (δ_c



Scheme 5: Synthesis of β-ketoester **7**.



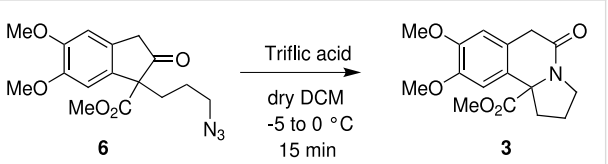
Scheme 7: Synthesis of azido-ketone **6**.

104.28, 164.39) in ^{13}C NMR, as well as an absorption at 3513 cm^{-1} in IR spectrum, clearly indicate the presence of a vinylether and a free hydroxyl group in compound **13**. Reaction of hydroxy vinylether **13** with acetic anhydride yielded readily the corresponding acetate derivative **14** which further supported the formation of hydroxy vinylether under basic conditions (Scheme 6).

Reaction of **13** with NaN_3 gave the corresponding azido derivative **15** which on further treatment with DOWEX®50WX8H^+ in methanol under reflux conditions afforded the corresponding azido-ketone **6** in 81% yield (Scheme 7).

Finally, the intramolecular Schmidt reaction of azido-ketone **6** was successfully achieved using TfOH at -5 to 0°C and the resultant cyclized product, indolizidine derivative **3**, was isolated in 54% yield (Scheme 8). Similarly, the indolizidine derivative **3a** was prepared from the dicyanide **10**.

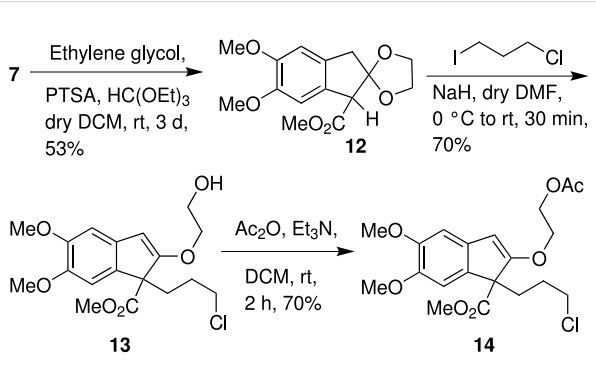
The structure of indolizidine derivative **3** was established by 1D and 2D NMR analyses which was unambiguously further



Scheme 8: The intramolecular Schmidt cyclization of azido-ketone **6**.

confirmed by single crystal X-ray analysis (Figure 1), on the corresponding acid derivative **4** (Scheme 9).

After achieving the construction of the indolizidine skeleton using the intramolecular Schmidt reaction, our next objective was to prepare various derivatives of the anti-cancer agent, crispine A, starting from the key intermediate **3**. Consequently, the ester functional group of the indolizidine derivative **3** was reduced with LAH in dry THF at 0°C to give the corresponding hydroxymethyl derivative **5**. Mesylation of **5** with mesyl



Scheme 6: Alkylation of ketal-ester **12**.

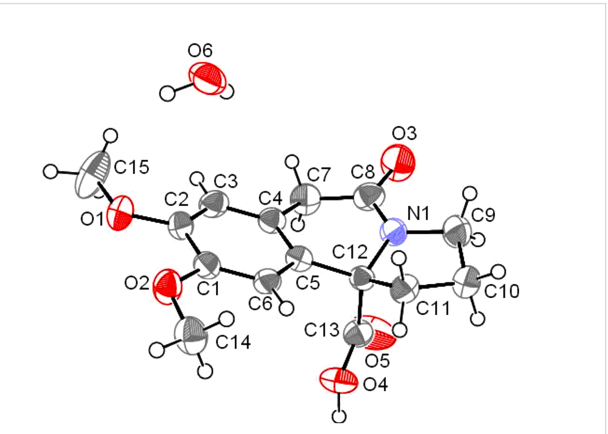
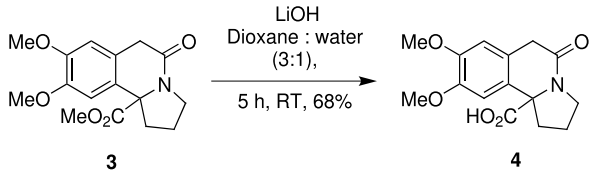
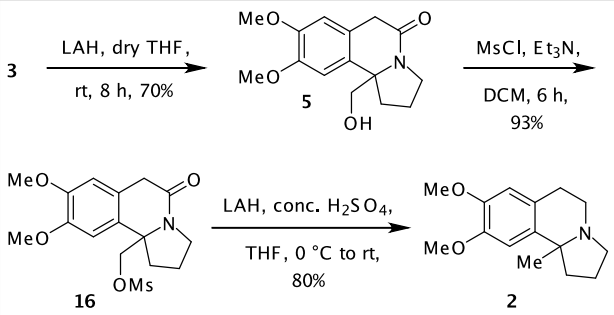


Figure 1: ORTEP diagram of the acid derivative **4**.



Scheme 9: Synthesis of acid analogue of crispine A.

chloride and triethylamine yielded the corresponding lactam **16** which on further exposure to LAH in the presence of conc. H_2SO_4 [20] gave the methyl analogue of crispine A (**2**) in 80% yield (Scheme 10). Spectral data of compound **2** were found to be in complete agreement with the reported values.[26] (See Supporting Information File 1 for full experimental data)



Scheme 10: Synthesis of methyl analogue of crispine A.

Conclusion

In conclusion, we have successfully achieved the synthesis of various derivatives of crispine A (**2**–**5**), starting from the azido ketone **6**, using the intramolecular Schmidt reaction as a key step. The structure of the cyclized indolizidine derivative **3** was unambiguously confirmed by single crystal X-ray analysis. Interestingly, an unusual cleavage of ethylene ketal to vinylether was observed during the alkylation of ketal-ester **12**. Since the compounds **5** and **16** are highly functionalized intermediates, they can be further exploited in the synthesis of a library of anti-cancer analogues. The structure activity relationships (SAR) and anti-cancer activities of our synthetic derivatives will be reported in due course of time.

Supporting Information

Supporting Information File 1

Experimental section. Experimental data, which includes experimental procedures and spectral data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-49-S1.pdf]

Acknowledgments

We thank DST (New Delhi) for financial support and the DST-FIST program for NMR facility. P.S.K (SRF) thanks CSIR (New Delhi) for a research fellowship.

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Beilstein Journal of Organic Chemistry

Synthesis of (–)-Indolizidine 167B based on domino hydroformylation/cyclization reactions

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Full Research Paper

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Beilstein Journal of Organic Chemistry **2008**, 4, No. 2.
doi:10.1186/1860-5397-4-2

Received: 27 September 2007
Accepted: 15 January 2008
Published: 15 January 2008

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Abstract

The synthesis of (–)-Indolizidine 167B has been achieved from optically active (*R*)-3-(pyrrol-1-yl)hex-1-ene. The key step is a highly regioselective hydroformylation reaction and a one-pot intramolecular cyclization providing a general approach to the indolizine nucleus.

Background

Indolizidine alkaloids are widely diffused in nature and have attracted considerable attention because of their varied range of pharmaceutical application. Indolizidine 167B (Figure 1), one of the simplest amphibian indolizidine alkaloids, was originally identified as (*5R,9R*)-octahydroindolizine from the skin secretions of a frog belonging to the genus Dendrobates [1,2], which acts as noncompetitive blocker of neuromuscular transmission. Although the structure has been questioned [3], this alkaloid remains a target compound for many research groups [4-6].

We recently reported the synthesis of Indolizidine 167B both in racemic and optically active form [7,8]; the crucial key was the cyclodehydration of 4-carboxyethyl-4-(pyrrol-1-yl)butanal, obtained *via* selective reduction of pyrrole masked glutamic acid diethyl ester hydrochloride [9], to the corresponding 5,6-dihydroindolizine bearing the carboxyethyl group in position five. Successively a series of ester group transformations to *n*-propyl group followed by final exhaustive hydrogenation gave the desired product. In the synthesis of Indolizidine 167B depicted here the construction of the bicyclic core still occurs via a pyrrolylbutanal; unlike the previous case, the aldehyde comes from rhodium-catalyzed hydroformylation of optically active (*R*)-3-(pyrrol-1-yl)hex-1-ene (**1**) (Scheme 1). The formed linear aldehyde **2a** (Scheme 2), bearing an *n*-propyl group in the required position, undergoes sequential intramolecular cyclization/dehydration/hydrogenation *in situ* to give 5-*n*-propyl-

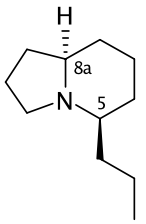


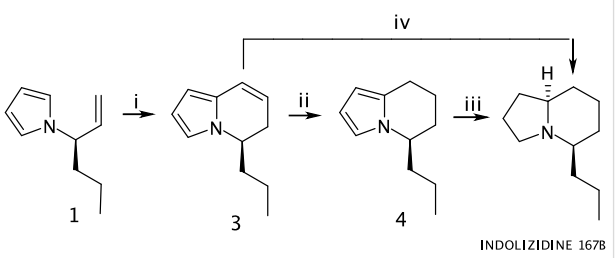
Figure 1: (–)-Indolizidine 167B.

5,6,7,8-tetrahydroindolizine (**4**), *via* 5-*n*-propyl-5,6-dihydroindolizine (**3**) having the same optical purity as the starting olefin; a successive enantioselective reduction gives the target compound (ee 92%) (Scheme 1).

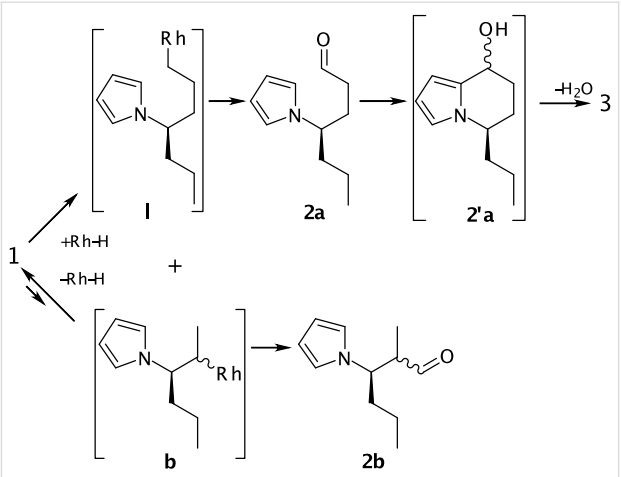
The rhodium-catalyzed hydroformylation of olefins is an important industrial tool for the production of aldehydes [10, 11]. During the last few years, the *oxo* process has been employed also in the synthesis of fine chemicals especially integrated in multi-step domino reaction sequences which are a very convenient approach to complex architectures in one simple, safe, environmentally acceptable and resource-effective operation [12-14]. The mechanistic as well as synthetic implications of the *oxo* reaction involving vinyl and allyl aromatic and heteroaromatic olefins has a topic of our research for many years [15-19]; now it is the first time that the rhodium catalyzed hydroformylation is employed by us in the total synthesis of a target compound and as a key reaction in a domino process with a high number of steps.

Results and Discussion

The optically active starting material **1** (ee 92%) was prepared from the corresponding amino acid D-norvaline as previously reported [20]. Then **1** was introduced in a 25 ml stainless steel autoclave, in the presence of $Rh_4(CO)_{12}$ as a catalyst precursor (Rh/substrate = 1/100), at 125 °C and 30 atm total pressure (CO/H_2 = 1:1), in toluene as solvent. After 25 min, the olefin



Scheme 1: Reagents: i $Rh_4(CO)_{12}$, 30 atm $CO:H_2$ = 1:1, 125 °C, toluene, 24 min, 76% yield; ii the same conditions as i 12 h under H_2 50 atm, after CO and H_2 removal, 80% yield; iii 10 atm H_2, Rh/C (5%), r.t. 45 min, 75% yield; iv H_2 10 atm, Rh/C (5%), r.t., 60 min, 64% yield.



Scheme 2: Stereospecific interconversion of the rhodium-alkyl intermediates as the key for regioselective formation of the linear aldehyde **2a.**

was completely absent and 5-*n*-propyl-5,6-dihydroindolizine (**3**) was the predominant product (Scheme 1). As far as the typical *oxo* products are concerned, i. e. the aldehyde isomers, the linear **2a** was present only in trace amounts in the reaction mixture while the branched one **2b** was in 13% (GC-MS control) with respect to the indolizine structure (Scheme 2). While at room temperature and high pressure the **2a**/**2b** ratio is largely favorable to the branched aldehyde (29/71) [21], under the above conditions (high temperature and low pressure) a highly regioselective hydroformylation into the linear aldehyde takes place; this is a consequence of the isomerization of the branched alkyl-rhodium intermediate **b**, precursor of **2b**, into the linear one **l**, precursor of **2a**, *via* a ß-elimination process with formation of olefin **1** (Scheme 2) [22]. This transformation is completely stereospecific and it does not involve the chiral center. An evaluation of the enantiomeric excess of both unconverted **1** and produced **3** was carried out in order to test the configurational stability of these structures under hydroformylation conditions. Interestingly **1** showed, at all conversions, practically the same ee, that is, the starting ee value (92%). A similar behaviour occurred for dihydroindolizine **3**, its ee value remaining the same as that of the corresponding olefin **1** (ee 92%) at all reaction times. The isomerization of **b** into **l** and the absence of racemization of starting substrate are the peculiar features of this process. Indeed, under the adopted experimental conditions, aldehyde **2a**, as it forms, reacts further in an *in situ* intramolecular electrophilic substitution on position two of the pyrrole nucleus giving dihydroindolizine **3**, likely *via* formation of the bicyclic alcohol **2'a** followed by dehydration (Scheme 2). Thus the cyclization of the linear aldehyde results much faster than hydroformylation while the same reaction does not occur for the branched one, which remains unaltered in the reaction mixture.

Compound **3** is stable enough to be handled easily at room temperature without any decomposition or change of enantiomeric excess. When, at complete conversion of **1**, the gas mixture was removed from the crude hydroformylation product and H_2 (50 atm) was added and the reaction vessel heated for a long time (12 h), **3** disappeared and the corresponding 5,6,7,8-tetrahydroindolizine **4** was obtained (Scheme 1; ii), together with the diastereoisomeric alcohols coming from the branched aldehyde: additional reduction of the pyrrole nucleus was never observed even by forcing the conditions (high pressure and high temperature). This goal was successfully reached by treating **4** (or **3**) with Rh on carbon 5% as catalyst precursor, under H_2 (10 atm), with the hydrogenation time varying from 60 min to 45 min respectively. In both cases only the diastereomer corresponding to indolizidine 167B, characterized by C5 and C9 chiral centers with the same absolute configuration, was obtained, the reaction being completely stereoselective as evidenced by comparison with literature data for the same isomer [23]. It is to remarkable that the global synthesis is completely stereospecific, with the final product having the same optical purity as the starting olefin (ee 92%).

Conclusions

We describe here a new synthesis of optically active (–)-Indolizidine 167B based on regioselective hydroformylation/intramolecular cyclization reactions which provides a general approach to the indolizine nucleus. It is a multi-step domino process which starts with the interconversion of the isomeric rhodium-alkyl intermediates and carries on with the intramolecular cyclodehydration of the formed linear aldehyde followed by hydrogenation. All steps occur with almost complete configurational stability and the final indolizine has the same optical purity as the starting material. The hydroformylation conditions are perfectly compatible with optically active pyrrolylolefins, and the *oxo* process is proposed as a convenient instrument for indolizine synthesis in general.

Supporting Information

Supporting Information File 1

Experimental data. This file contains all experimental methods and analytical data belonging to the compounds described in the article.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-2-S1.doc]

Acknowledgments

Financial support by MIUR-Programma di Ricerca Scientifica di Rilevante Interesse Nazionale-is gratefully acknowledged.

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Beilstein Journal of Organic Chemistry

Knorr-Rabe partial reduction of pyrroles: Application to the synthesis of indolizidine alkaloids

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Full Research Paper

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Beilstein Journal of Organic Chemistry **2008**, 4, No. 3.
doi:10.1186/1860-5397-4-3

Received: 08 October 2007
Accepted: 15 January 2008
Published: 15 January 2008

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Abstract

Background

The Birch reduction of electron rich pyrroles does not occur readily. However, dissolving metal reduction with zinc under acidic conditions gives 3-pyrrolines (2,5-dihydropyrroles) in reasonable yield. This dissolving metal reduction was first reported by Knorr and Rabe in 1901 but since then has only been reported for the reduction of electron rich pyrroles.

Results

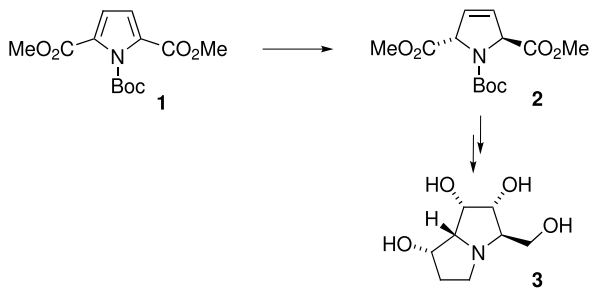
The partial reduction of bicyclic α-ketopyrrole derivatives has been performed under dissolving metal conditions with zinc and hydrochloric acid to give excellent yields of hexahydroindolizidines. This reduction method has been utilised for the diastereoselective synthesis of 5-alkylindolizidines and the stereoselectivity obtained is opposite to that of catalytic hydrogenation.

Conclusion

An efficient stereoselective synthesis of indolizidine alkaloids has been developed from α-ketopyrrole intermediates using a modified version of Knorr and Rabe's pyrrole reduction.

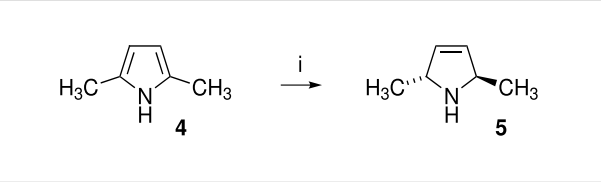
Background

The Birch reaction for the dearomatisation of aromatic substrates is an extremely practical and important tool for synthetic chemists and is used widely as a key step for the synthesis of natural products and molecules of biological interest [1]. However, the partial reduction of pyrrole is difficult as the high electron density of these aromatic heterocycles inhibits the addition of an electron, the first step of a Birch reaction [2]. Donohoe has shown that the partial reduction of pyrroles is possible but this process generally requires the presence of at least two electron withdrawing groups that reduce the electron density of the heterocycle such that reasonable yields of the 3-pyrrolines are obtained [3]. This method was recently exploited for the elegant synthesis of the pyrrolidine alkaloid (±)-1-epiaustraline (**3**) (Scheme 1) [4].



Scheme 1: Donohoe's approach to (±)-1-epiaustraline utilising a modified Birch reduction.

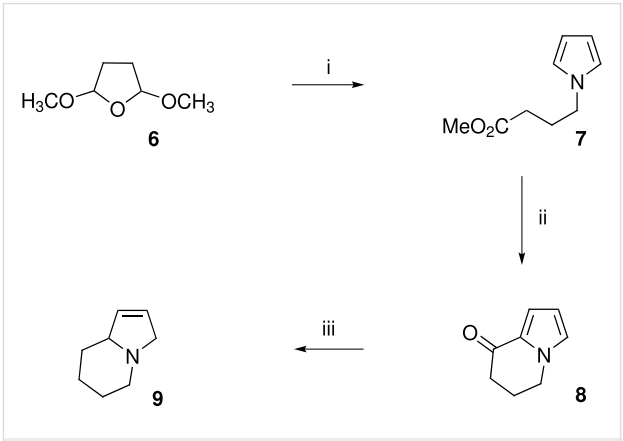
During our studies towards the synthesis of indolizidine alkaloids we required bicyclic 3-pyrrolines and chose to explore accessing these intermediates *via* partial reduction of the corresponding pyrrole derivatives. These substrates were far more electron rich than those of Donohoe and thus not amenable to Birch reduction methodology. Therefore, we turned to an underutilised reaction that was reported by Knorr and Rabe [5] in 1901 and has only been reported a handful of times since [6-9]. The method employs powdered zinc in an acid media to give 3-pyrrolines, presumably by protonation of the pyrrole to give an iminium ion which is then reduced. It has been shown that reaction of 2,5-dialkylpyrroles gives predominantly the *trans* 3-pyrroline isomer (Scheme 2) [7-9].



Scheme 2: Reaction conditions i) Zn, HCl (aq).

Results and Discussion

The synthetic plan that we adopted was to construct a bicyclic pyrrole derivative by exploiting the natural reactivity of pyrrole and then to partially reduce the heterocyclic core (Scheme 3). The synthesis started with formation of the γ-pyrrolic ester **7** in high yield using an improved Clauson-Kaas synthesis [10], followed by boron tribromide mediated cyclisation to give the known bicyclic ketone **8** [11]. Upon subjection of this α-ketopyrrole **8** to the modified conditions reported by Andrews and McElvain (slow addition of HCl to the substrate and Zn at 0–10 °C) [5,9] we observed no reaction and starting material was returned. However, when zinc and concentrated HCl were added in small portions to a hot solution of the α-ketopyrrole in methanol over ~10 minutes the starting material was consumed to give the hexahydroindolizidine **9** as the only observable product in ~80% yield. The chemoselectivity using these modified conditions is noteworthy while the carbonyl group is fully reduced the pyrrole group is selectively and partially reduced to the 3-pyrroline. This result was confirmed by comparison of the spectral data with that reported by Huxtable who prepared **9** as an intermediate in the synthesis of lentiginosine [12].

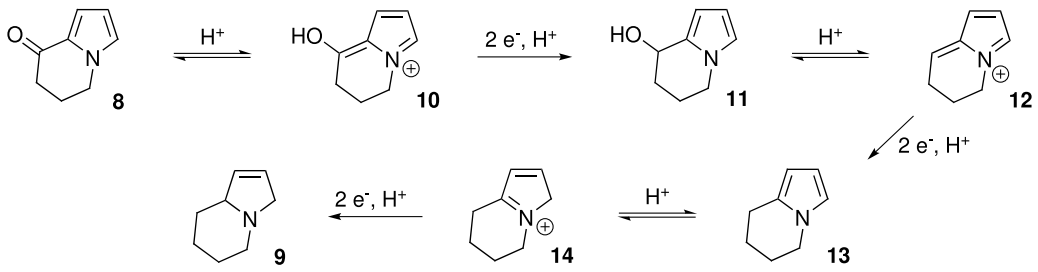


Scheme 3: Reaction conditions: i) ref. [10] ii) ref. [11] iii) Zn, conc. $HCl_{(aq)}$.

For the partial reduction of electron rich pyrroles reported previously, over reduction to give pyrrolidines is a problematic side-reaction. For example, Andrews and McElvain kept the reaction temperature below 10 °C to limit pyrrolidine formation. Under our conditions, starting with the α-ketopyrrole, there was no indication of pyrrolidine formation. The loss of the keto group means that the product is the same as that that would be obtained by reduction of the parent bicyclic pyrrole **13**. The reduction of the carbonyl group resembles that of a Clemmensen reduction; however, amalgamated zinc is required for Clemmensen reaction [13].

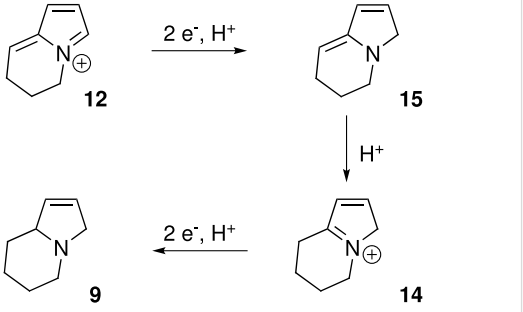
There are several possible mechanisms for this transformation, however, we propose the first step involves protonation of the carbonyl group to give a conjugated iminium ion **10** (Scheme 4). This species would undergo a two-electron reduction process, with associated protonation to give the α-hydroxy pyrrole **11**. Acid-promoted dehydration of **11** would afford a second iminium ion **12** which could undergo further reduction and protonation to give pyrrole **13**. The pyrrole could then be protonated to give a third iminium ion **14** and reduction would then give rise to the product **9**.

Our reaction conditions are much harsher than those previously reported, and yet we do not see pyrrolidine products and this suggests that an alternative pathway is in operation. One possibility is that the intermediate **12** could undergo reduction to give



Scheme 4: Potential mechanism for α-ketopyrrole reduction..

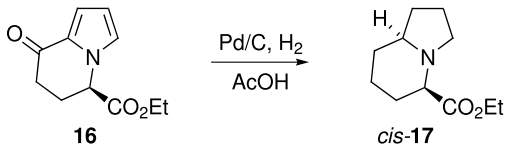
the final product directly without the formation of the pyrrole intermediate **13** (Scheme 5).



Scheme 5: Alternative reduction pathway.

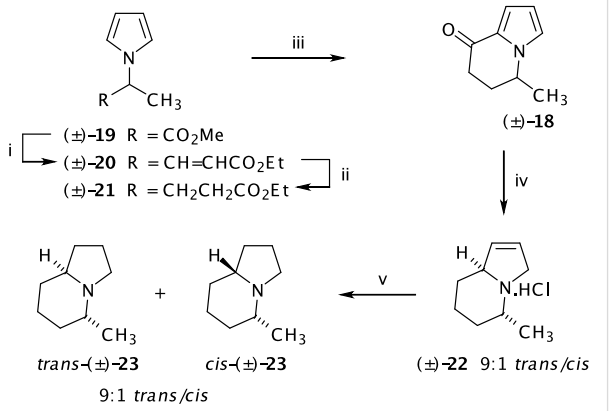
To test these hypotheses we reduced the ketone **8** with $NaBH_4$ to give the unstable α-hydroxy pyrrole **11** which was then immediately subjected to the reduction conditions. The same result was obtained giving the 3-pyrroline **9** which lends support to the suggestion that **11** is an intermediate in the reaction. When pyrrole **13** was reacted under the same conditions **9** was formed but the ^{1}H NMR spectrum also showed some starting material remained. The fact that the pyrrole **13** was not observed in the reduction products from α-ketopyrrole **8** lends the support to the suggestion of an alternative pathway. At the present time the intermediacy of **13** cannot be ruled out for the reduction of ketone **8** and alcohol **11**.

Due to the facile and rapid reaction of the α-ketopyrrole **8** we explored the potential tandem α-ketopyrrole reduction/catalytic hydrogenation as an alternative to catalytic hydrogenation. The catalytic hydrogenation of 5-substituted tetrahydroindolizidines proceeds with high diastereoselectivity [14,15] and has also been exploited for the synthesis of numerous indolizidine alkaloids [16,17]. The presence of a substituent at C-5 directs the hydrogenation at C-8a from the opposite, least hindered face, to give the *cis* derivative (Scheme 6).



Scheme 6: Catalytic hydrogenation.

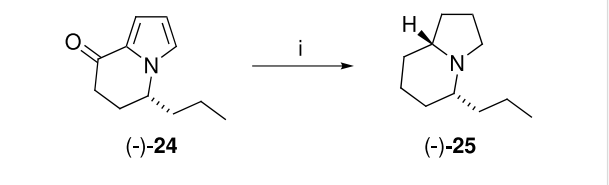
We were interested in the stereochemical outcome for C-8a using the modified Knorr-Rabe zinc reduction and synthesised the known 5-methyl derivative **18** (Scheme 7) as a model. The methyl ester of (±)-alanine was subjected to the modified Clauson-Kaas pyrrole synthesis to give an α-pyrrolic ester **19** which was subjected to two carbon homologation by ester reduction with DIBAl-H followed by an *in situ* Wadsworth-Emmons olefination [18]. The alkene **20** was then hydrogenated to the γ-pyrrolic ester **21** and cyclised to give α-ketopyrrole **18** in 67% overall yield from **19**. The modified Knorr-Rabe reduction of **18** gave the desired pyrroline **22** in near quantitative yield as a 9:1 mixture of diastereomers. The volatility of the compound meant that for practical purposes it was isolated as the hydrochloride salt by adding concentrated HCl to the organic extract before evaporation. Catalytic hydrogenation of the hydrochloride salt of the pyrroline gave a corresponding mixture of isomers of 5-methylindolizidine **23** but to our surprise the *trans* isomer was the major diastereomer. The stereochemical assignment of the major and minor isomers was confirmed by comparison of the ^{13}C NMR spectra with the reported spectra for both previously synthesised isomers [19]. The resonance of the carbon signals for C-8a, C-5 and C-3 are diagnostic with these carbons for the major isomer resonating 54.9, 50.2 and 49.1 ppm. This compares to 54.5, 50.0 and 49.2 ppm for the *trans* isomer and 64.8, 58.9 and 51.8 ppm for the *cis* isomer as reported in the literature [19]. This result indicates that the major product **22** from the modified Knorr-Rabe zinc reduction has the opposite C-5/C-8a stereochemistry to that typically obtained by catalytic hydrogenation.



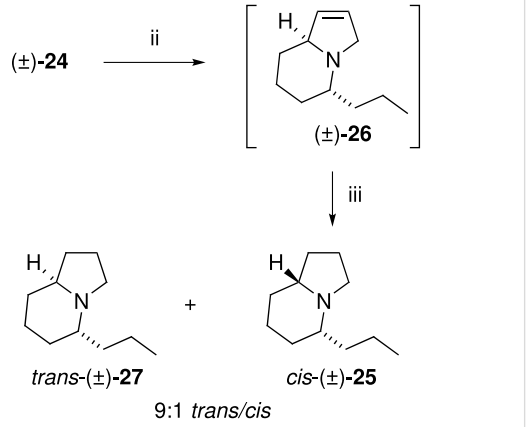
Scheme 7: Reaction conditions: i) DIBAL-H, CH_2Cl_2, -78 °C, 1 h then triethylphosphonoacetate, NaH, THF, −78 °C – rt ii) H_2 (40psi), Pd/C, EtOH iii) BBr_3, CH_2Cl_2, 0 °C, 10 min iv) Zn, conc. HCl(aq) v) H_2 (40 psi), Pd/C, EtOH, 2M HCl.

To explain this result we propose that the zinc complexation to the less hindered face of the indolizidine causes protonation to occur on the same side as the C-5 substituent, which results in the *trans* stereochemistry between C-5 and C-8a.

A beneficial outcome from these observations is that one can now reduce bicyclic intermediates like **18** stereoselectively to enter either diastereomeric series. Corvo has reported the synthesis of the proposed structure of indolizidine 167B by the catalytic hydrogenation of (−)-**24** (Scheme 8) [17], and herein we report the racemic synthesis of its epimer (Scheme 9). We have reported the synthesis of the bicyclic ketone (±)-**24** [18] and subjection of this α-ketopyrrole to the modified Knorr-Rabe reduction conditions gave the crude 3-pyrroline **26** which was immediately subjected to catalytic hydrogenation to yield a 9:1 mixture of (±)-*epi*-indolizidine 167B (*trans*-(±)-**27**) and (±)-indolizidine 167B (*cis*-(±)-**25**) in 91% overall yield from **24**. As for the 5-methyl derivative the spectral data of the *trans* isomer **27** was dramatically different to that of the *cis* isomer **25** and is consistent with that reported previously [20]. Therefore, this method extends the flexibility of bicyclic pyrroles as intermediates for the synthesis of indolizidine alkaloids, as diastereomeric targets can be accessed simply by the choice of reagent system for reduction of the pyrrole nucleus.



Scheme 8: i) ref. [17].



Scheme 9: i) CH_3OH, Zn, conc. HCl(aq) ii) H_2 (40 psi), Pd/C, EtOH, 2M HCl.

Conclusion

In conclusion, we have discovered a modified method for the Knorr-Rabe partial reduction of electron rich pyrroles which is effective for the reduction of bicyclic α-ketopyrroles to the corresponding 3-pyrroline or hexahydroindolizidine derivatives. The reduction occurs with high diastereoselectivity with 5-alkyl derivatives and gives the opposite diastereoselectivity to that of direct catalytic hydrogenation. This complementary method allows for the synthesis of both diastereomers of indolizidine 167B from a late-stage common intermediate.

Supporting Information

Supporting Information File 1

Experimental details which includes experimental procedures and spectroscopic data
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-3-S1.doc]

Acknowledgments

The authors thank the University of Tasmania and CSIRO for financial support. The authors would like to thank Peter P. Molesworth of UTAS for a sample of compound **13**. JHR thanks University of Tasmania for a Woolmers Lectureship. BSG is grateful for an Australian Postgraduate Award and a CSIRO Postgraduate Top-up Scholarship.

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Beilstein Journal of Organic Chemistry

Combining two-directional synthesis and tandem reactions, part 11: second generation syntheses of (±)-hippodamine and (±)-epi-hippodamine

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Full Research Paper

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Beilstein Journal of Organic Chemistry **2008**, 4, No. 4.
doi:10.1186/1860-5397-4-4

Received: 09 November 2007
Accepted: 17 January 2008
Published: 17 January 2008

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Abstract

Background

Hippodamine is a volatile defence alkaloid isolated from ladybird beetles which holds potential as an agrochemical agent and was the subject of a synthesis by our group in 2005.

Results

Two enhancements to our previous syntheses of (±)-hippodamine and (±)-epi-hippodamine are presented which are able to shorten the syntheses by up to two steps.

Conclusions

Key advances include a two-directional homologation by cross metathesis and a new tandem reductive amination / double intramolecular Michael addition which generates 6 new bonds, 2 stereogenic centres and two rings, giving a single diastereomer in 74% yield.

Background

Ladybird beetles (Coleoptera: Coccinellidae) are important predators contributing to the natural control of pest aphid populations and are therefore of considerable commercial interest. However, ladybirds themselves are attacked by a range of natural enemies. General predation on ladybirds by vertebrates such as birds is largely prevented by highly toxic defence alkal-

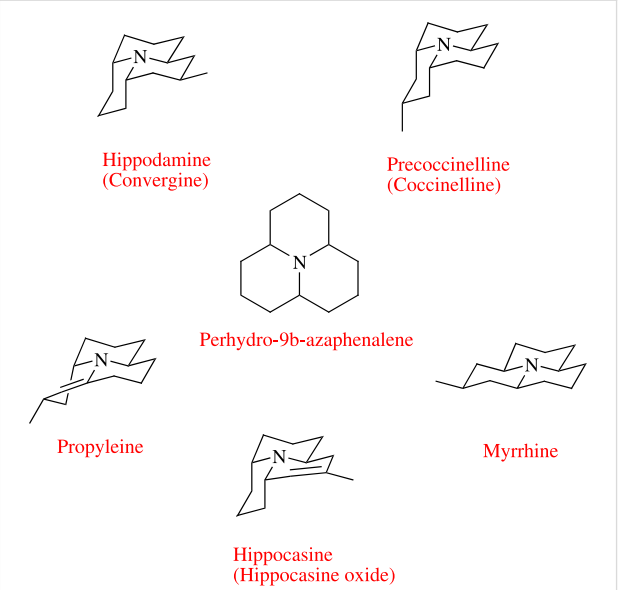
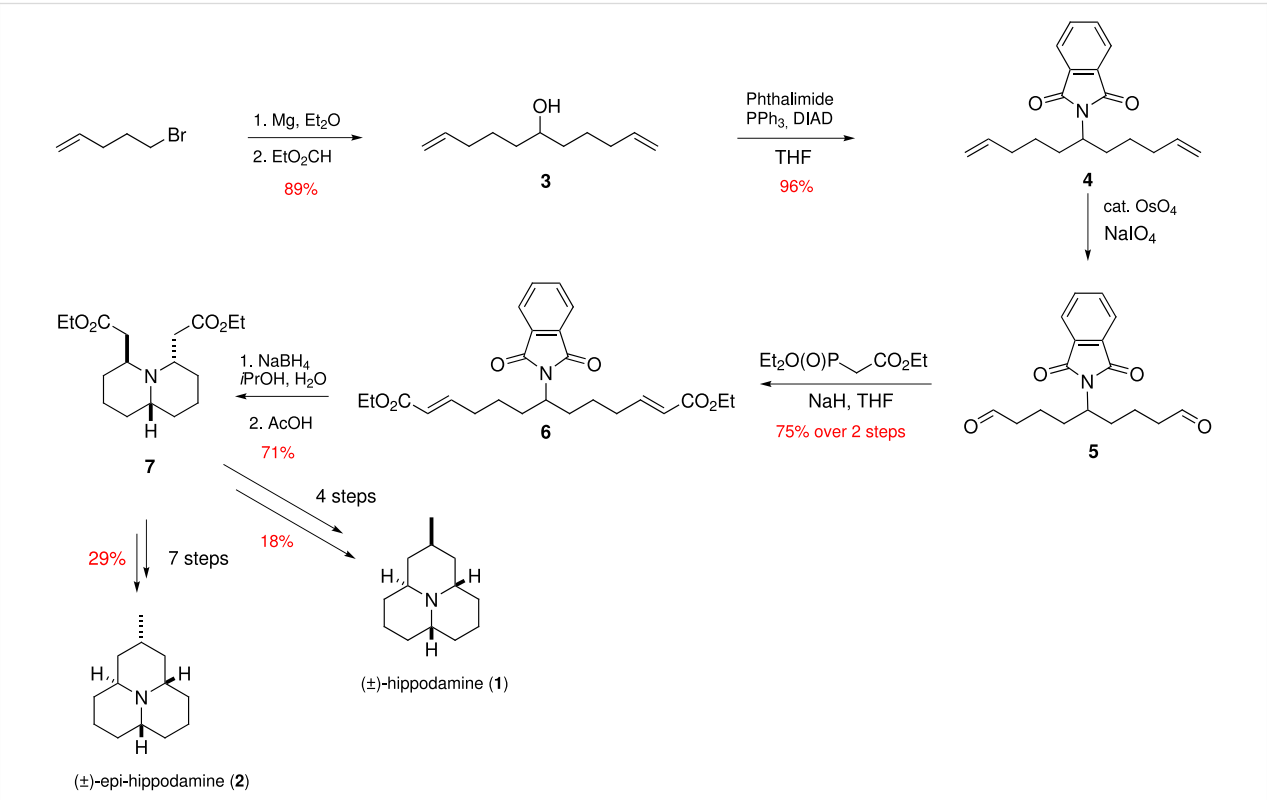


Figure 1: Structures of Coccinellid Alkaloids (*N*-Oxides and their names in brackets).

oids contained in a reflex bleed released when the ladybird is attacked. To date, eight alkaloids of this type have been isolated from coccinellid beetles [1], all of them being formally derivatives of perhydro-9b-azaphenalene (Figure 1). Another group of natural enemies, parasitic insects, can cause substantial reductions in populations of ladybird species. Recent research [2] has shown that the parasites locate the ladybirds through perception of certain defence alkaloids that they emit. If ladybirds are to be used effectively in insect pest control then their parasites must be controlled as well. The significant attraction of parasitic insects to the ladybird alkaloids suggests that there is potential for development of control strategies for this particular natural enemy. To further test this theory significant amounts of the defensive alkaloids will be needed. Coccinelid beetles seem to be the sole source of the defence alkaloids. Consequently much attention has been paid to developing syntheses of these compounds.

Hippodamine (**1**) is a naturally occurring alkaloid isolated from a ladybird beetle *Hippodamia convergens* by Tursch and co-workers in 1972 [3]. The structure of hippodamine (**1**) was established two years later by the same group [4] on the basis of a single-crystal X-ray diffraction experiment (Figure 1). Epi-hippodamine (**2**) is its unnatural isomer with an axial C-5 methyl group. Both hippodamine (**1**) [5-7] and epi-hippodamine (**2**) [8] have been synthesized previously, and we reported syntheses of these two compounds using a two-directional synthesis / tandem, reaction approach in 2005 [9]. Scheme 1 details the key aspects to our earlier work [10].



Scheme 1: Summary of our previous syntheses of hippodamine (**1**) and epi-hippodamine (**2**).

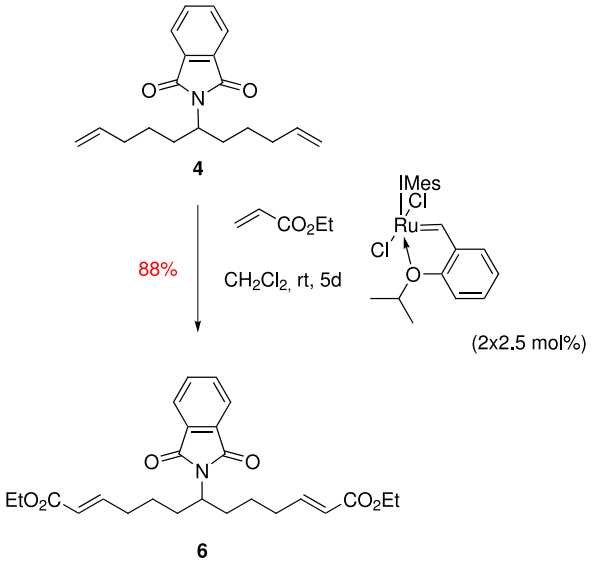
Table 1: Summary of our efforts to effect quinolizidine formation in a one-pot reaction.

Entry	Amine Source	Desiccant	Hydride reagent	Temp (°C)	Time (h)	% Yield
1	NH_4Cl and NEt_3	-	$NaBH_4$	75	48	-
2	NH_4Cl and NEt_3	-	$Na(BH_3CN)$	80	48	-
3	NH_3 in EtOH	4Å Sieves	$Na(BH_3CN)$	rt	96	-
4	NH_4OAc and NEt_3	4Å Sieves	$Na(BH_3CN)$	60	24	-
5	NH_4OAc and NEt_3	4Å Sieves	Hantzsch Ester	60	24	-
6	HCO_2NH_4 and NEt_3	4Å Sieves	$Na(BH_3CN)$	75	24	-
7	NH_3 in EtOH	$Ti(OEt)_4$	$NaBH_4$	75	48	74

Herein, we report two refinements to our earlier work which have allowed even more concise routes to azaphenalene alkaloids **1** and **2**.

Results and Discussion

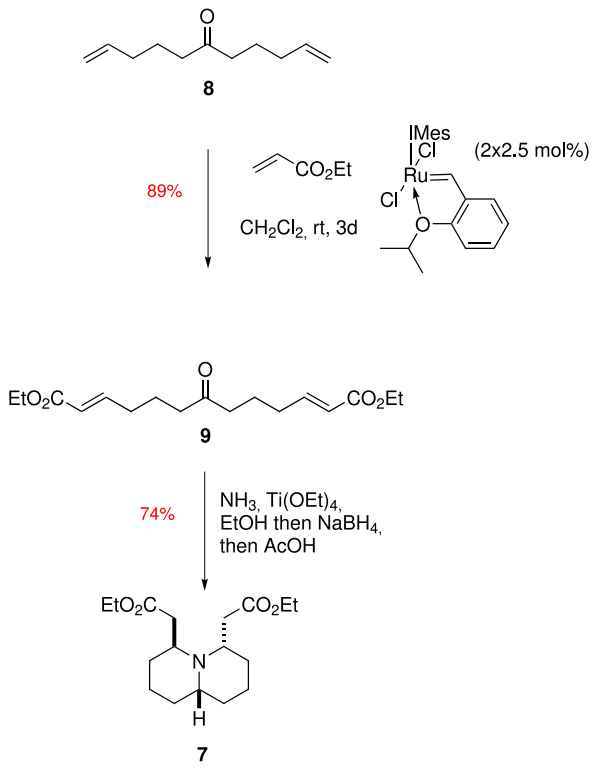
When we decided to take a second look at the syntheses of hippodamine and epi-hippodamine, we decided to focus on the synthesis of the key common intermediate **7** and try to realise an improvement over our earlier work. This paper discloses two such improvements. The first of these is the conversion of dialkene **4** into the diacrylate derivative **6** . Originally this was achieved by oxidative cleavage of the two alkene moieties of **4** to form the rather sensitive dialdehyde **5** . Whilst we were able to purify compound **5**, this resulted in a significant loss of material through degradation of the dialdehyde on the purification media, be it silica gel or neutral alumina. Thus, we found that use of the crude dialdehyde in the subsequent Horner-Wadsworth-Emmons reaction was preferable, and gave a good 75% yield of the doubly homologated compound **6** after purification by column chromatography. Whilst this process did allow us to produce multigram quantities of **6**, this sequence of reactions had the drawbacks that the olefination reaction needed to be carried out immediately after isolation of the dialdehyde **5** (this was found to decompose upon storage, even at low temperature), and also the oxidative cleavage reaction produced large amounts of toxic osmium waste. During our recent synthesis of histrionicotoxin [11], we found that two-directional homologation of a symmetrical dialkene similar to **4** using cross-metathesis with acrylonitrile was possible using the Hoveyda modification of Grubbs second generation catalyst [12] (Scheme 2). Thus, it seemed a logical extension of this thinking to see if we could carry out a direct double homologation of dialkene **4** with ethyl acrylate as the cross-metathesis coupling partner. In fact, due to the non-co-ordinating nature of ethyl acrylate (in comparison to acrylonitrile) and the inert phthalimide group, this reaction proved to be an outstanding success, delivering diester **6** in 88% yield over one step after a five day reaction in dichloromethane. This step therefore reduces the overall number of steps for the synthesis of hippodamine to eight, and increases the overall yield from 8 to 10%. Similarly it reduces our synthesis of epi-hippodamine to eleven steps and increases the yield from 13 to 16% overall. The two-directional cross-metathesis reaction is shown in Scheme 2.



Scheme 2: Improved synthesis of tandem reaction precursor **6**.

Having refined our synthesis of diester **7** by providing a shortened synthesis of its precursor, we decided to see if we could attain a synthesis of this common intermediate for the synthesis of both hippodamine and epi-hippodamine without the use of the phthalimide protecting group. This would render the entire synthesis of hippodamine free of protecting group chemistry – a distinct driving force for a compound which may find use as an agrochemical. Thus we postulated whether we would be able to transform keto-diester **9** into quinolizidine **7** by a tandem reductive amination / double intramolecular Michael addition. Our results are shown in Scheme 3.

Thus ketone **8** was formed by reaction of the commercially available hex-5-enylnitrile with 4-pentenylmagnesium bromide in 70% yield [13]. Double cross-metathesis was found to proceed smoothly in 89% yield using the Hoveyda-Grubbs



Scheme 3: Tandem reductive amination / double intramolecular Michael addition.

second generation catalyst in dichloromethane at room temperature for 3 days, giving ketodiester **9** [14]. We tried a range of reductive amination conditions for the formation of quinolizidine **7**. The ammonia equivalents tried were ammonium acetate, ammonium chloride and ammonium formate, along with sodium borohydride, sodium cyanoborohydride and Hantzsch ester in either ethanol or ethanol / acetic acid solvent systems. A summary of conditions tried is shown in Table 1. The ketodiester **9** was dissolved in ethanol and the ammonia source and desiccant were added and allowed to stir overnight to form the iminium species, before the hydride source was added and the reaction allowed to proceed for a further 24 h. The hydride source was quenched with acetone before excess glacial acetic acid was added and the reaction mixture was heated for the given time before quenching with brine. Entries 1–4 and entry 6 showed reduction of the ketone to the alcohol (by ^{1}H NMR), and entry 5 using the Hantzsch ester showed no reaction at all.

It was found that addition of ammonia in ethanol with titanium ethoxide [15] for 14 hours, followed by addition of sodium borohydride and stirring at room temperature for a further 8 hours, and finally the addition of acetone (to remove any remaining active hydride) and 30 equivalents of acetic acid followed by heating the reaction mixture at reflux for 48 hours gave a clean reaction as monitored by TLC to quinolizidine **7**, giving a 74% yield after purification by column chromatography over Brockmann Grade (III) neutral alumina. See Supporting Information File 1 for full experimental data. The tandem reductive amination / double intramolecular Michael addition generates 6 new bonds, 2 stereogenic centres and two rings, giving a single diastereomer.

In conclusion, we have increased the yield of our original hippodamine synthesis and reduced the number of steps required using a two-directional cross-metathesis of dialkene **4** with ethyl acrylate. We have also reported a new tandem reductive amination / double intramolecular Michael addition, which forms directly the quinolizidine core of hippodamine in a single step from a symmetrical keto-diester linear precursor. This new tandem reaction also reduces the number of steps for the synthesis of hippodamine to seven, and also removes any protecting group chemistry from the synthetic sequence and reduces waste whilst equalling the yield of the previous approach.

Supporting Information

Supporting Information File 1

Experimental. Experimental procedures for compounds **4**,**6**,**7**,**9**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-4-S1.doc]

Acknowledgments

The authors wish to thank Leverhulme Trust (MR), AstraZeneca (AFN, CASE award) and EPSRC (RAS, Advanced Research Fellowship) for funding and EPSRC Mass spectrometry service, Swansea for carrying out some of the high resolution mass-spectra.

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Beilstein Journal of Organic Chemistry

Analogues of amphibian alkaloids: total synthesis of (5*R*,8*S*,8a*S*)-(−)-8-methyl-5-pentyloctahydroindolizine (8-*epi*-indolizidine 209B) and [(1*S*,4*R*,9a*S*)-(−)-4-pentyloctahydro-2*H*-quinolizin-1-yl]methanol

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Full Research Paper

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Beilstein Journal of Organic Chemistry **2008**, 4, No. 5.
doi:10.1186/1860-5397-4-5

Received: 02 November 2007
Accepted: 18 January 2008
Published: 18 January 2008

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Abstract

Background

Prior work from these laboratories has centred on the development of enaminones as versatile intermediates for the synthesis of alkaloids and other nitrogen-containing heterocycles. In this paper we describe the enantioselective synthesis of indolizidine and quinolizidine analogues of bicyclic amphibian alkaloids *via* pyrrolidinylidene- and piperidinylidene-containing enaminones.

Results

Our previously reported synthesis of racemic 8-*epi*-indolizidine 209B has been extended to the laevorotatory enantiomer, (−)-**9**. Attempts to adapt the synthetic route in order to obtain quinolizidine analogues revealed that a key piperidinylidene-containing enaminone intermediate (+)-**28** was less tractable than its pyrrolidinylidene counterpart, thereby necessitating modifications that included timing changes and additional protection–deprotection steps. A successful synthesis of [(1*S*,4*R*,9a*S*)-4-pentyloctahydro-2*H*-quinolizin-1-yl]methanol (−)-**41** from the chiral amine *tert*-butyl (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}octanoate (+)-**14** was achieved in 14 steps and an overall yield of 20.4%.

Conclusion

The methodology reported in this article was successfully applied to the enantioselective synthesis of the title compounds. It paves the way for the total synthesis of a range of *cis*-5,8-disubstituted indolizidines and *cis*-1,4-disubstituted quinolizidines, as well as the naturally occurring *trans*-disubstituted alkaloids.

Background

The astonishingly diverse range of alkaloids isolated from the skins of amphibians includes numerous 1-azabicyclic systems belonging to the indolizidine (1-azabicyclo[4.3.0]nonane), quinolizidine (1-azabicyclo[4.4.0]decane) and lehmizidine (1-azabicyclo[5.3.0]decane) classes [1,2]. The first of these classes is by far the most populous, and has commanded enormous attention from organic chemists stimulated by the challenges of designing novel total syntheses [3]. The more recently discovered amphibian quinolizidines constitute a smaller group of alkaloids; they embrace homopumiliotoxins (*e.g.* (+)-homopumiliotoxin 223G **1**; Figure 1) and related systems, 4,6-disubstituted quinolizidines (*e.g. rel*-quinolizidine 195C **2**) and 1,4-disubstituted quinolizidines (*e.g.* (−)-quinolizidine 217A **3**). In the latter group, it appears that most of the well-characterised alkaloids have a 1,4-*trans* disposition of the substituents; the only alkaloid in which the substituents are unambiguously *cis* is (−)-quinolizidine 207I **4**. Comparatively few syntheses of quinolizidine 207I, 217A and related compounds have been reported [4-9].

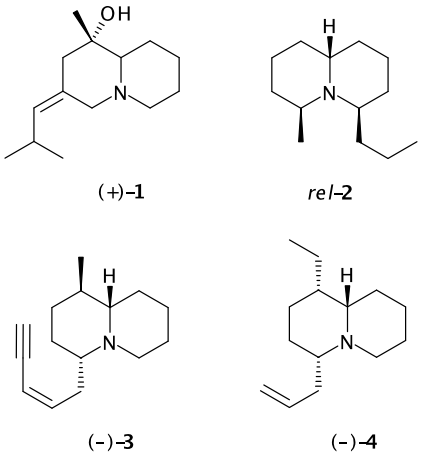


Figure 1: Representative quinolizidine alkaloids from amphibians.

As part of a long-standing investigation into the utility of pyrrolidinylidene- and piperidinylidene-containing enaminones (vinylogous urethanes) **5** and **6** as key intermediates in the synthesis of alkaloids and other nitrogen-containing heterocycles [10], we previously reported total syntheses of (−)-indolizidine 167B **7** [11,12], the 5,8-disubstituted indolizidine (−)-209B **8** and its racemic diastereomer (±)-**9** [13], and the 5,6,8-trisubstituted indolizidines (+)-**10** and (+)-**11** [14], among other similar compounds (Figure 2). While our attempts to prepare quinolizidines have been less successful, we have synthesised two simple lupin alkaloids, lupinine **12** and epilupinine **13**, in racemic form [15]. Although it might seem that reactions of the enaminones **5** and **6** should be directly comparable, we [15,16] and others [17,18] have previously found unexpected differences in the preparation and reactions of cyclic enaminones of different ring sizes. In this article we report our progress in preparing 1,4-disubstituted quinolizidine analogues of amphibian alkaloids by an extension of our approach to the synthesis of 5,8-disubstituted indolizidine alkaloids [19].

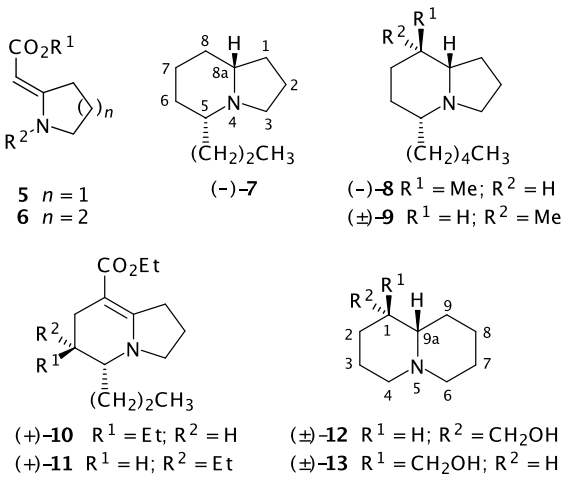
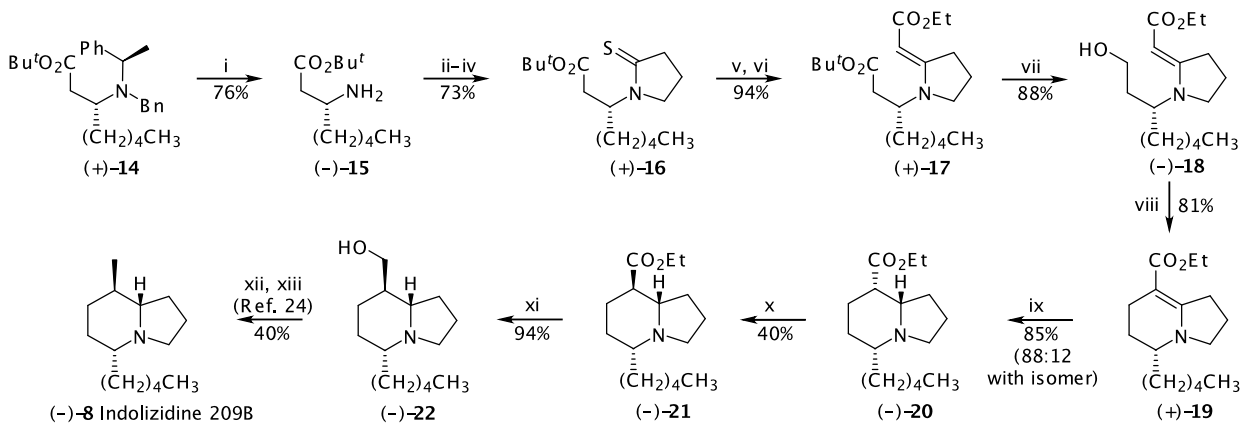


Figure 2: Indolizidines and quinolizidines prepared from enaminone precursors **5** and **6**. The conventional numbering scheme for both bicyclic systems is also shown.

Results and Discussion

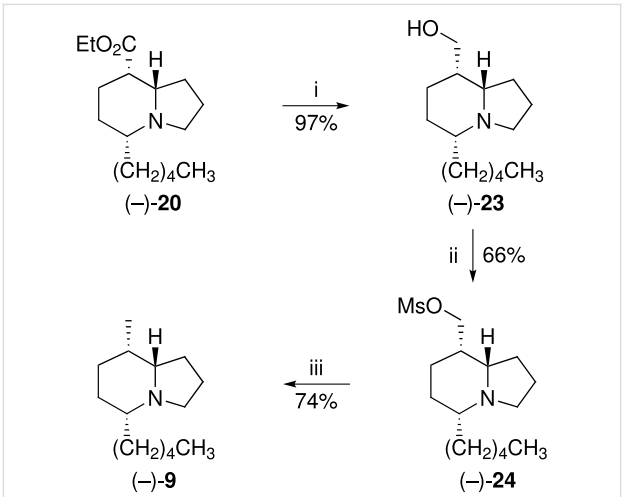
Steps in our reported total synthesis of (−)-indolizidine (−)-209B **8** [13] are shown in Scheme 1. Absolute stereocontrol resulted from use of the Davies protocol [20,21], whereby the homochiral amine (+)-**14** prepared from *tert*-butyl (*E*)-oct-2-enoate and (*R*)-*N*-benzyl-1-phenylethylamine, was converted into the primary amine (−)-**15** and thence in several steps into the thiolactam (+)-**16**. Eschenmoser sulfide contraction [22,23] with ethyl bromoacetate yielded the key enaminone intermediate (+)-**17**, chemoselective reduction of the saturated ester of which produced the alcohol (−)-**18**. The bicyclic core of the alkaloid was then constructed by a cycloalkylation that took advantage of the nucleophilic reactivity of the enaminone, following which a chemoselective and reasonably diastereoselective (88:12) reduction of the alkene bond of the bicyclic enaminone (+)-**19** set up the desired stereochemistry at C-8 and C-8a. Epimerisation of the ester in the reduced compound (−)-**20** produced (−)-**21**, reduction of which gave the alcohol (−)-**22**. Reduction of the corresponding methanesulfonate with lithium triethylborohydride, as described by Holmes *et al*. [24], completed the total synthesis of (−)-indolizidine 209B **8**.

As a postscript to the above synthesis, we have now completed an enantioselective synthesis (Scheme 2) of the indolizidine



Scheme 1: *Reagents:* (i) H_2 (7 atm), 10% Pd/C, AcOH, rt; (ii) $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$, reflux; (iii) $KOBu^t$, Bu^tOH, rt; (iv) Lawesson's reagent, PhMe, reflux; (v) $BrCH_2CO_2Et$, MeCN, rt; (vi) Ph_3P, Et_3N, MeCN, rt; (vii) $LiAlH_4$, THF, rt; (viii) I_2, imidazole, Ph_3P, PhMe, 110 °C; (ix) H_2 (1 atm), PtO_2, AcOH, rt; (x) NaOEt (cat.), EtOH, reflux; (xi) $LiAlH_4$, THF, 0 °C to rt; (xii) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C to rt; (xiii) $LiEt_3BH$, THF, 0 °C.

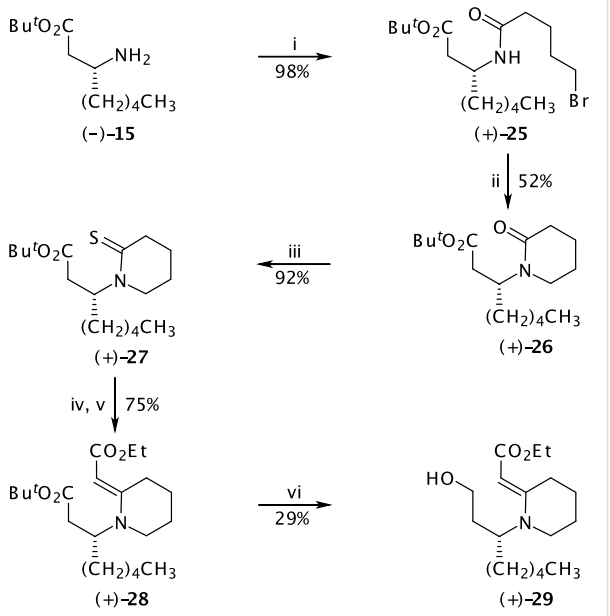
analogue of **8**, *viz*. (5*R*,8*S*,8a*S*)-8-*epi*-indolizidine 209B (−)-**9**, which we had previously made as a racemate [13]. Intermediate (−)-**20** was reduced with lithium aluminium hydride in diethyl ether to give the alcohol (−)-**23** in 97% yield (See Supporting Information File 1 for full experimental data). The corresponding methanesulfonate (−)-**24** (66%) was then defunctionalised by an improved procedure, which entailed treatment with freshly prepared Raney nickel [25] in boiling ethanol to give (−)-(5*R*,8*S*,8a*S*)-8-methyl-5-pentyloctahydroindolizine (8-*epi*-indolizidine 209B) **9** in 74% yield. The spectroscopic data for this product agreed with those reported for the racemate. Support for the *cis*-relationship of the hydrogen atoms at C-5 and C-8a in all of these compounds was provided by Bohlmann bands [26] at *ca*. 2790 cm^{-1} in the FTIR spectra, a feature that also implies a *trans*-disposition of the lone pair and 8a-H across the ring junction.



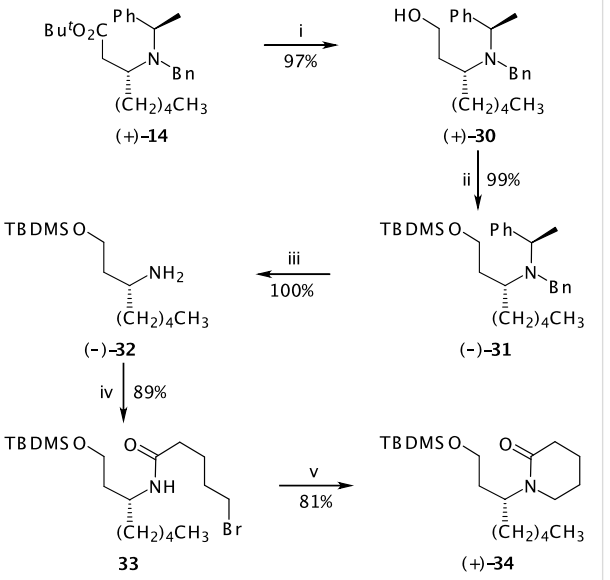
Scheme 2: *Reagents:* (i) $LiAlH_4$, THF, 0 °C to rt; (ii) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C to rt; (iii) Raney Ni, EtOH, reflux.

Extending the route illustrated in Scheme 1 to the synthesis of quinolizidine analogues required initial acylation of the chiral amine (−)-**15**, prepared as described in our prior work [13], with 5-bromopentanoyl chloride (obtained in two steps from δ-valerolactone) [27,28]. This afforded *tert*-butyl (3*R*)-[(5-bromopentanoyl)amino]octanoate (+)-**25** in 98% yield (Scheme 3). However, subsequent cyclisation to the lactam (+)-**26** was troublesome, giving at best a yield of 52% when performed with sodium hydride and tetrabutylammonium iodide in *N*,*N*-dimethylformamide. An effortless thionation of **26** with Lawesson's reagent in boiling toluene produced the thiolactam (+)-**27** in 92% yield. Eschenmoser sulfide contraction was then effected by first treating the thiolactam with ethyl bromoacetate, after which reaction of the resulting S-alkylated intermediate with triethyl phosphite and triethylamine in acetonitrile gave the vinylogous urethane (+)-**28** in 75% yield.

At this stage, however, our fears of the discrepant behaviour of five- and six-membered enaminones proved to be all too well founded. In the indolizidine series, the robust enaminone **17** survived reduction with lithium aluminium hydride, leaving only the saturated ester to be reduced. With the six-membered analogue **28**, the enaminone unit was far more susceptible to reduction, and despite many attempts to modify conditions, over-reduction led to a plethora of basic products that could neither be separated nor properly characterised. Although the desired alcohol (+)-**29** containing an intact enaminone system could be isolated on occasion, the best yield obtained was 29% when the reaction was not allowed to go to completion. Thus a change of strategy was required to produce **29**, the pivotal intermediate from which the quinolizidine nucleus needs to be constructed.



Scheme 3: *Reagents:* (i) $Br(CH_2)_4COCl$, $NaHCO_3$, $ClCH_2CH_2Cl$, rt; (ii) NaH, Bu_4NI, DMF, rt; (iii) Lawesson's reagent, PhMe, reflux; (iv) $BrCH_2CO_2Et$, MeCN, rt; (v) $P(OEt)_3$, Et_3N, MeCN, rt; (vi) $LiAlH_4$, THF, rt.

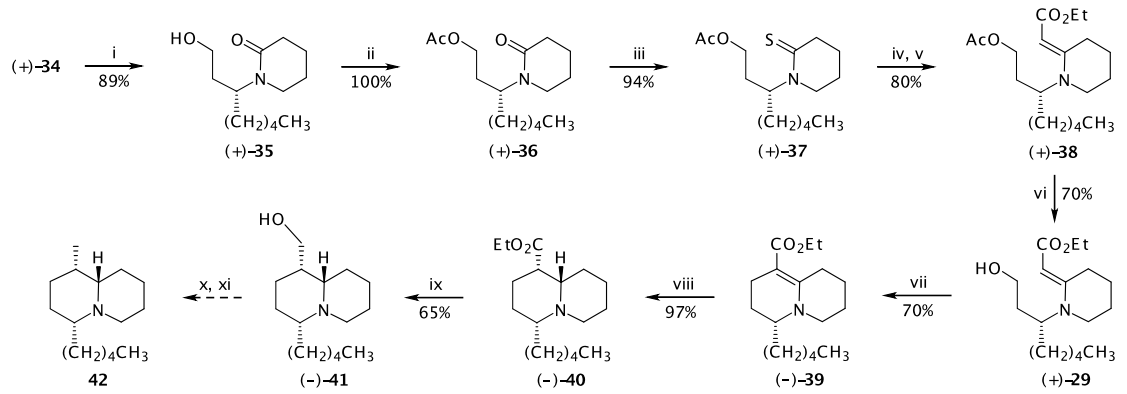


Scheme 4: *Reagents:* (i) $LiAlH_4$, Et_2O, 0 °C, then add (+)-**2** in Et_2O, rt; (ii) TBDMSCl, imidazole, DMF, rt; (iii) H_2 (5 atm), 20% $Pd(OH)_2$/C, AcOH, rt; (iv) $Br(CH_2)_4COCl$, $NaHCO_3$, $ClCH_2CH_2Cl$, rt; (v) *t*-BuOK, THF, rt, 25 min.

The reduction of the *tert*-butyl ester clearly needed to be performed at an early stage of the synthesis before the introduction of other incompatible functional groups (lactam, thiolactam, enaminone). The only feasible option was to go back to the chiral amine (+)-**14**, reduction of which with lithium aluminium hydride gave the unstable amino alcohol (+)-**30** in 97% yield as long as the amine was added slowly to a stirred suspension of the hydride in diethyl ether (Scheme 4). If the order of addition were reversed, the best yield obtained was 48%. The amino alcohol was protected as its *tert*-butyl(dimethyl)silyl ether (−)-**31** (99%) before hydrogenolysis of the benzyl groups over Pearlman's catalyst in glacial acetic acid gave the free amine (−)-**32** in quantitative yield. Treatment with 5-bromopentanoyl chloride as described above afforded the unstable bromoamide **33** as an orange oil in 89% yield. In this case, cyclisation of the crude intermediate to the lactam (+)-**34** was most successfully effected by adding potassium *tert*-butoxide to a solution of the bromoamide in dry tetrahydrofuran at room temperature, a yield of 81% being obtained by keeping the reaction time short (25 min). To our dismay, however, the attempted thionation of **34** with Lawesson's reagent under a variety of conditions was uniformly unsuccessful, apparently because the silyl ether failed to survive the reaction conditions.

Inelegant though it was, we were forced at this stage to change protecting groups on the alcohol. Fortunately, the drop in yield was not too serious when desilylation of **34** with aqueous hydrofluoric acid to give the free alcohol (+)-**35** was followed by acetylation with acetic anhydride in pyridine (Scheme 5). The lactam (+)-**36**, obtained in an overall yield of 89%, was then successfully thionated with Lawesson's reagent in boiling toluene to give the thiolactam (+)-**37** in 94% yield. Finally, reaction with ethyl bromoacetate followed by treatment with triphenylphosphine and triethylamine in acetonitrile give the vinylogous urethane (+)-**38** in 80% yield. Hydrolysis of the acetate with potassium carbonate in methanol then afforded the pivotal alcohol (+)-**29** (70%). The scene was now set for cyclisation to the quinolizidine system. Immediate conversion of the unstable free alcohol into the corresponding iodide with iodine, triphenylphosphine and imidazole in a mixture of toluene and acetonitrile [29] and heating the reaction mixture under reflux gave the desired 3,4,6,7,8,9-hexahydro-2*H*-quinolizine-1-carboxylate (−)-**39** in 70% yield.

In order to introduce the remaining stereogenic centres of the target system, the alkene bond of the bicyclic vinylogous urethane **39** needs to be reduced stereoselectively. Based on our previous success with the indolizidine analogue **19**, we opted for catalytic hydrogenation, which is expected to produce not only a *cis*-relationship between C-1 and C-9a, but also a *cis*-relationship between C-4 and C-9a. The developing chair conformation of the six-membered ring in the transition state should result in an equatorial preference for the pentyl side chain, which in turn should bias the approach of the reductant towards the more remote face of the double bond. Gratifyingly, hydrogenation of intermediate **39** over platinum oxide catalyst



Scheme 5: *Reagents:* (i) aq. HF (40%), MeOH, rt; (ii) Ac_2O, pyridine, 0 °C to rt; (iii) Lawesson's reagent, PhMe, reflux; (iv) $BrCH_2CO_2Et$, MeCN, rt; (v) Ph_3P, Et_3N, MeCN, rt; (vi) K_2CO_3, MeOH, rt; (vii) I_2, PPh_3, imidazole, MeCN-PhMe (2:1), reflux; (viii) H_2 (1 atm), PtO_2, AcOH, rt; (ix) $LiAlH_4$, THF, 0 °C to rt; (x) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C to rt; (xi) Raney Ni, EtOH, reflux.

in ethanol at a pressure of five atmospheres produced the quinolizidine (−)-**40** as a single diastereomer in 97% yield. The diastereoselectivity is manifestly better than in the indolizidine case. Support for the *cis*-relationship of the hydrogen atoms at positions C-4 and C-9a and the *trans*-ring junction in the product was once again provided by Bohlmann bands in the FTIR spectrum at *ca*. 2790 cm^{-1}. However, further confirmation of the relative stereochemistry by consideration of the ^1H NMR spectrum was not feasible because overlap of signals prevented the extraction of coupling constants for 1-H and 9a-H.

Finally, reduction of the ester to the primary alcohol (−)-**41** was accomplished in moderate yield (65%) with lithium aluminium hydride. Again, coupling constants could not be determined for 1-H and 9a-H. In this case, however, there is good precedent for assigning the relative stereochemistry of the hydroxymethyl substituent at C-1 on the basis of ^{13}C chemical shifts. For example, the chemical shift of C-1 in lupinine **12**, which possesses an axial hydroxymethyl substituent, is 38.8 ppm; whereas the corresponding chemical shift in epilupinine **13**, the equatorial hydroxymethyl epimer, is 43.8 ppm [30]. The chemical shift difference of about 5 ppm between the C-1 equatorial and axial hydroxymethyl epimers appears to be general for quinolizidines [31]. A similar effect has been reported for 8-hydroxymethylindolizidine epimers, for which the chemical shift difference is even larger (*ca* 10 ppm) [24]. In the present case, the observed chemical shift of 38.4 ppm for **41** is consistent with an axial disposition of the C-1 substituent, and thus with the expected *cis*-hydrogenation of **39**.

While it would have been desirable to conclude this investigation by preparing (1*S*,4*R*,9a*S*)-4-pentyloctahydro-2*H*-quinolizine **42**, the ring homologue of 8-*epi*-indolizidine 209B, this target eluded us. Attempts to reduce the corresponding methanesulfonate of **41** with Raney nickel in boiling ethanol gave ambiguous results no matter how we modified the reaction conditions.

Conclusion

Few approaches to 1,4-*cis*-disubstituted quinolizidines and 5,8-*cis*-disubstituted indolizidines of amphibian origin have been reported in the literature. Because the route we have devised proceeds through bicyclic enaminone intermediates in which the alkene bond is located between the bridgehead position and the adjacent site, we have a convenient and dependable method for introducing the correct relative stereochemistry at these two sites by means of catalytic hydrogenation. However, the differences in behaviour of pyrrolidinylidene- and piperidinylidene-containing enaminones that we have come to expect [15,16] was again apparent, necessitating several protection-deprotection steps that lengthened the route to the quinolizidine system. Nevertheless, our success in preparing the chiral alcohol **41** opens up a route to quinolizidine alkaloids containing C-1 methyl substituents (provided, of course, that we can find a better method for deoxygenation, probably by radical-mediated reaction). In addition, alkyl homologues at C-1 should be accessible; one could, for example, replace the alcohol by a leaving group that can be displaced by organometallic reagents (*e.g.* cuprates) of appropriate chain length. Substituents at C-4 can also be varied by choosing appropriate analogues of the chiral amine **14**, which should also be available in both enantiomeric forms by the Davies procedure [32]. Finally, since the pendent substituents in the indolizidine series can be induced to adopt a *trans*-orientation by base-catalysed epimerisation of a carbonyl substituent adjacent to the bridgehead position (*cf* Scheme 1), it should in principle be possible to effect a similar epimerisation in the quinolizidine series, thereby providing a route to most of the known 1,4-disubstituted amphibian quinolizidine alkaloids.

Supporting Information

Supporting Information File 1

Analogues of amphibian alkaloids - Full experimental details. The Supporting Information File contains detailed experimental procedures and full characterisation data for all new compounds prepared during the synthesis of the two title compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-5-S1.doc]

Acknowledgments

This work was supported by grants from the National Research Foundation, Pretoria (grant number 2053652) and the University of the Witwatersrand. We are grateful to Dr Tom Spande (NIH-NIDDK) for GC-FTIR and chiral GC analysis of (−)-8-*epi*-indolizidine 209B.

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The definitive version of this article is the electronic one which can be found at:
doi:10.1186/1860-5397-4-5

Beilstein Journal of Organic Chemistry

Facile synthesis of two diastereomeric indolizidines corresponding to the postulated structure of alkaloid 5,9*E*-259B from a Bufonid toad (*Melanophryniscus*)

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Full Research Paper

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Beilstein Journal of Organic Chemistry **2008**, 4, No. 6.
doi:10.1186/1860-5397-4-6

Received: 17 October 2007
Accepted: 21 January 2008
Published: 21 January 2008

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Abstract

A short synthesis of the postulated structure for indolizidine alkaloid **259B** with the hydrogens at C5 and C9 *entgegen* has been achieved with complete control of stereochemistry at C5. Both diastereoisomers at C8 were obtained, but neither proved to be the natural product. The comparison of the mass and FTIR spectral properties of the synthetic compounds to those of the natural material strongly suggest that the gross structure is correct and that the difference may be a branch in the C5 alkyl side-chain. The GC-retention times of the two synthetic compounds were markedly longer than that of the natural 5,9*E*-**259B**.

Background

Indolizidines are common in nature [1] and to date over eighty 5,8-disubstituted indolizidine alkaloids have been isolated from the skins of frogs [2]. Due to the scarcity of such indolizidine alkaloids from the natural sources, for the most part the biological properties of these materials have not been fully evaluated. However, synthetic 5,8-disubstituted indolizidine 5,9*Z*-**235B'** (Figure 1), has recently been shown to be a potent and selective non-competitive inhibitor of nicotinic acetylcholine receptors [3]. Earlier work had reported that indolizidines 5,9Z-**203A** and 5,9*Z*-**235B'** (Figure 1), and other 5,8-disubstituted indolizidines were non-competitive blockers of the ganglionic subtype of nicotinic receptors [4]. For most of the 5,8-disubstituted indolizidines the structures have been assigned by a combination of GC-mass spectrometry and GC-FTIR spectroscopy [2] and such structures must be considered tentative until NMR studies on isolated pure compounds can be obtained or until synthetic material is available for comparison. In the EI-mass spectrum of 5,8-disubstituted indolizidines loss of the C5 chain gives rise to the base peak, identifying the mass of the C5 substituent. The resulting

cation undergoes a retro Diels-Alder fragmentation losing an alkene thus identifying the mass of the C8 substituent. Once the gross structure has been assigned, analysis of the vapor-phase infrared spectrum, particularly the Bohlmann bands, allows assignment of the relative configuration of the chiral centres at C5 and C9. When the two hydrogens on C5 and C9 are both axial (*trans* anti-parallel to the *N* lone pair), designated as 5,9*Z* (Figure 1), the presence of a strong, sharp Bohlmann band at approximately 2789 cm^{-1} confirms this relative configuration. In the alternative diastereoisomer when one hydrogen is axial and the other equatorial, designated as 5,9*E*, the Bohlmann band is weak and is shifted to 2810 cm^{-1}. Most 5,8-disubstituted indolizidines detected in frog skin extracts have the 5,9*Z* relative configuration, with **259B** being very unusual in that it has the 5,9*E* relative configuration. Not surprisingly then, with the exception of the synthesis of two 5,9*E* diastereomers of the natural 5,9*Z*-**223V** [5], most of the synthetic effort has been directed towards the 5,9*Z* isomers and this has resulted in a large number of elegant approaches to these indolizidines [6-35].

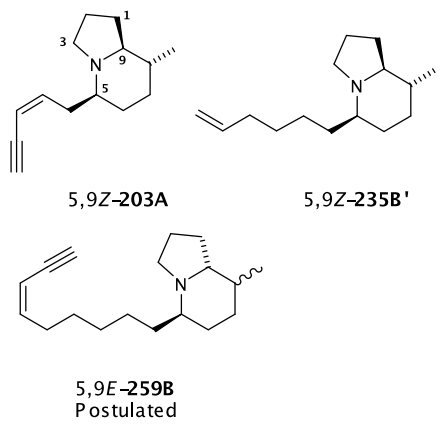
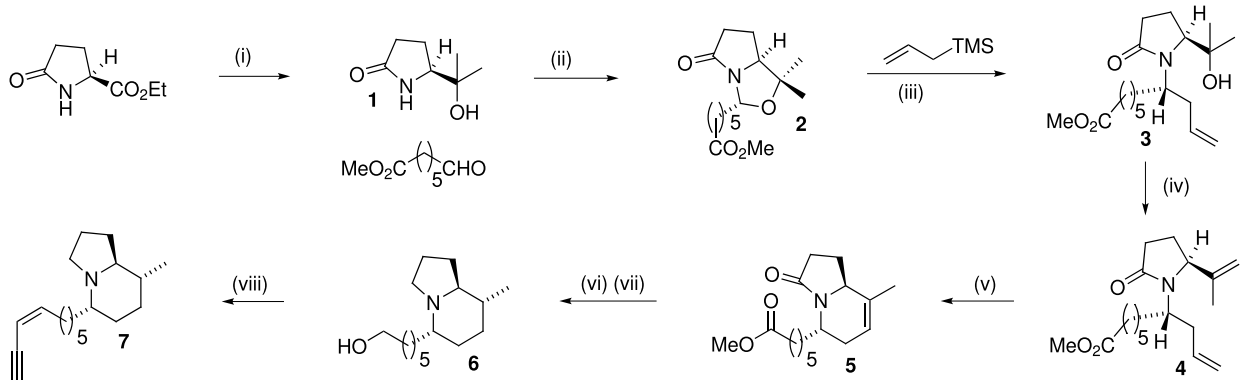


Figure 1: Subclasses of diastereoisomeric 5,8-disubstituted alkaloids. The absolute stereochemistry of 5,9*Z*-**203A** and 5,9*Z*-**235B'** are as shown, while the structure shown for 5,9*E*-**259B** is tentative as postulated based on mass and FTIR spectra [2]. Almost all of the 5,8-disubstituted indolizidines detected in frog skin extracts have proved to be the 5,9*Z* isomers [2].

Results and Discussion

The absolute configurations of 5,9*Z*-**203A** and 5,9*Z*-**235B'** (Figure 1) and several other such 5,9*Z* indolizidines are known [2]. Thus, in analogy to such 5,9*Z* indolizidines it might be anticipated that for the 5,9*E* indolizidines the stereochemistry at C9 will also be *R*. We now report an enantioselective synthesis of the tentative structure postulated for ent-indolizidine 5,9*E*-**259B**, which is outlined in Scheme 1 using (*S*)-pyroglutamic acid as the chiral starting material. The synthesis is extremely short, robust, does not utilise any protecting groups, appears to be completely diastereoselective at C5 and gives both diastereoisomers at C8.

Reaction of (*S*)-ethylpyroglutamate with an excess of methyl magnesium iodide gave the water soluble tertiary alcohol **1** in 96% yield. 7-Oxoheptanoic acid methyl ester was prepared by the literature procedure [36], by ozonolysis of 1-methoxycycloheptene, and then condensed with the amidoalcohol **1** with azeotropic removal of water to give the *N*,*O*-acetal **2** in 71% yield as a single diastereoisomer. It is likely that allylic strain of the lactam carbonyl group leads to the alkyl group preferentially occupying a pseudo-axial position [37-40]. Reaction of *N*,*O*-acetal **2** with trimethylallyl silane and titanium tetrachloride at room temperature for two days gave the product **3** in 68% yield. The alternate diastereoisomer could not be detected by NMR spectroscopy in the crude reaction mixture. Product **3** formally arises by attack of trimethylallyl silane from



Scheme 1: *Reagents:* (i) MeMgI. 96% (ii) PTSA 71%. (iii) $TiCl_4$ CH_2Cl_2 25 °C 3d 68%. (iv) MsCl, Et_3N, THF -40 °C, 74%. (v) Grubbs' catalyst, 25 °C CH_2Cl_2, 90%. (vi) H_2 MeOH Pt/C 79%. (vii) $LiAlH_4$, $AlCl_3$, 73%. (viii) (a) Dess Martin periodinane, 77%. (b) $Ph_3P^+CH_2I$ I^-, $NaN(SiMe_3)_2$ 51%. (c) TMS acetylene, CuI, $Pd(Ph_3P)_3$, Et_3N then K_2CO_3 MeOH, 69%.

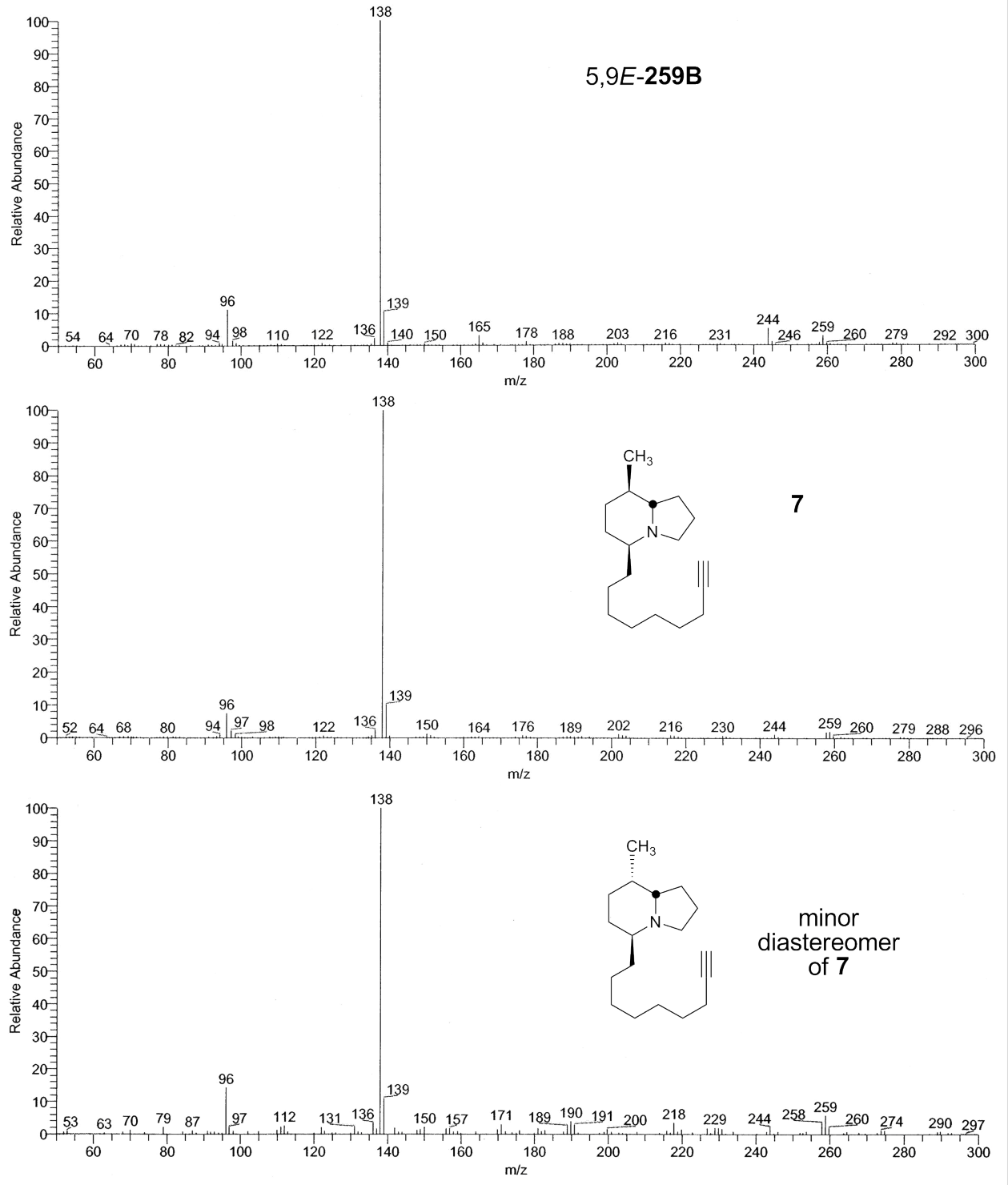


Figure 2: EIMS spectra of a) natural 5,9*E*-**259B**, b) synthetic **7**, and c) synthetic minor diastereomer of **7**. Structures are shown with relative configuration.

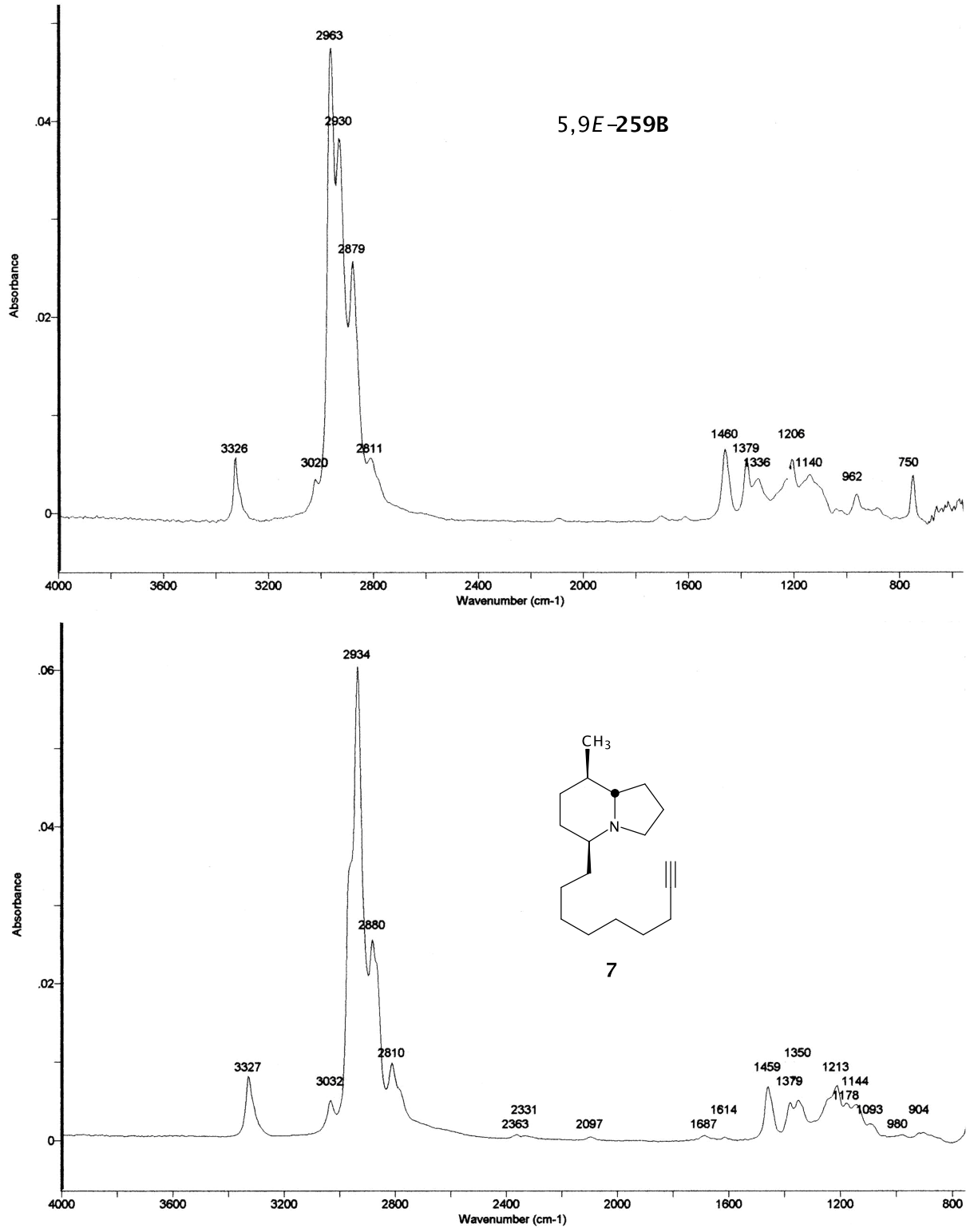


Figure 3: Vapor-phase FTIR spectra of a) natural 5,9*E*-**259B**, and b) synthetic **7**. Structure shown with relative configuration.

the least hindered face of the thermodynamically less stable *Z*-iminium ion and the mechanistic details of this intriguing transformation will be published elsewhere in due course. One-pot dehydration of the tertiary alcohol **3** was accomplished *via* the mesylate, and *in situ* elimination with triethylamine to give the diene **4** in 74% yield. Diene **4** smoothly underwent cyclisation to indolizidinone **5** when treated with Grubbs' first generation catalyst [41,42]. Analysis of the spectral properties of indolizidine **5** was considered convenient to confirm the stereochemistry at C5. It is known that in indolizidinones, with a carbonyl group at C3, the C5 hydrogen in the equatorial position will have an anomalously high chemical shift in NMR due to it lying in the deshielding cone of the lactam carbonyl group [5,37,38,43,44]. In the present case, the proton at C5 has a chemical shift at δ 4.24 ppm and the corresponding proton in similar indolizidinones with the 5,9*Z* relative configuration has a chemical shift at about δ 3.27 ppm. Reduction of the alkene **5** with hydrogen and a heterogeneous catalyst gave the product indolizidines as a mixture of C8 diastereoisomers. When platinum oxide was used as catalyst, a 1:1 mixture of diastereoisomers resulted, but when platinum-on-carbon was employed, a 4:1 mixture was produced with the isomer corresponding to **6** (Scheme 1) predominating. We have previously shown [45], and there is also good literature precedent [46,47], that in indolizidines with unsaturation at C7-C8 there is a tendency for the addition reactions to occur on the concave face, although this obviously will be influenced by the presence of other substituents. In the present case, there is an additional axial substituent at C5, which again would encourage reaction from the concave face. Although the mixture of isomers proved inseparable at this stage, the relative configuration at C8 in both diastereoisomers could be readily assigned by examining the multiplets for the hydrogen at C9. For the major diastereoisomer the coupling constant $J_{8\text{-}9}$ was 9.9 Hz, indicating a *trans* diaxial arrangement of these hydrogens and for the minor diastereoisomer the corresponding *J* value was 3.9 Hz. All that remained to complete the synthesis was the reduction of the lactam carbonyl group and the installation of the *cis*-enyne functionality. Simultaneous reduction of both the ester and the amide gave the alcohol **6**. Dess Martin oxidation [48] of the alcohol **6** gave an aldehyde, which on Stork Zhao reaction [49] gave the *Z*-vinyl iodide with a selectivity of 97:3. Finally, Sonogashira reaction [50] of the vinyl iodide with trimethylsilylacetylene followed by removal of the trimethylsilyl group gave synthetic **7**. At this stage the C8 diastereoisomers were separated by flash chromatography, though the minor component was contaminated with triphenyl phosphine / phosphine oxide residue from the Sonogashira reaction.

The two synthetic C8 diastereoisomers were compared to natural 5,9*E*-**259B** present in the alkaloid fraction obtained from a bufonid toad, *Melanophryniscus stelzneri* [51]. The GC mass spectra of the three compounds were very similar (Figure 2). However there was a greater loss of methyl for the natural alkaloid. The GC FTIR spectrum of the major synthetic diastereoisomer **7** differed from the natural 5,9*E*-**259B** in the finger-print region (Figure 3). In addition, the vinyl C-H stretching absorption band is at 3020 cm^{-1} rather than the expected 3032-3038 cm^{-1} for a conjugated CH=CH, as found in synthetic **7** and in the minor diastereomer. Finally, the intense C-H absorption band at 2963 cm^{-1} in natural 5,9*E*-**259B** suggests that two methyls rather than one are present. The corresponding band at 2961 cm^{-1} is merely a shoulder in the synthetic compounds that contain only one methyl. The GC FTIR spectrum of the minor synthetic isomer was very similar to that of the major isomer **7**, but due to a co-emerging contaminant the finger-print region could not be compared and the mixed FTIR is not shown. Remarkably, the GC retention time of the natural 5,9*E*-**259B** was markedly shorter than those of the two synthetic compounds as follows: Natural 5,9*E*-**259B:** 11.01 min; major synthetic isomer **7**: 13.01 min; minor synthetic isomer: 13.07 min. These retention times have been slightly adjusted to make them consistent with the retention times reported for the many frog skin alkaloids [2]. After hydrogenation the GC-retention times of the products (MW 265) were changed only slightly with the retention time of the perhydro-derivative of natural 5,9*E*-**259B** still markedly less than those of the perhydro-synthetics. This result proves that the carbon skeleton of **259B** is different to **7** and supports the proposal that there is a branch point in the C5 side-chain.

Clearly, a structural revision for 5,9*E*-**259B** is needed and it appears most likely that the point of difference is branching on the C5 side-chain. Isolation of 5,9*E*-**259B** for NMR spectral analysis will be required to establish the presence and nature of such branching. This hypothesis, if verified, is very significant because branching of the side-chains of 'izidine' alkaloids has been considered unlikely. The only documented case is the 5,6,8-trisubstituted indolizidine 5,9*E*-**249F**, isolated for NMR analysis from a dendrobatid frog, *Dendrobates auratus*, where there is an ethyl branch in the C5 substituent [51]. Further study will be needed to determine what other izidines detected in frog skin extracts have branch points in their side-chains. See Supporting Information File 1 for full experimental data.

Conclusion

An extremely short entry to the unusual 5,8-disubstituted 5,9*E*-indolizidine alkaloids has been developed giving a synthetic sample of two possible structures corresponding to the structure postulated for indolizidine alkaloid 5,9*E*-**259B**. The synthetic compounds had mass and FTIR spectra similar, but not identical to those of the natural product, but the GC-reten-

tion times of the two synthetic C8 diastereomers, which were quite similar, differed markedly from that of the natural 5,9*E*-**259B**. Thus, the postulated structure of **259B** is not correct and further study will be required, in particular as to whether and where the side-chain at C5 is branched.

Supporting Information

Supporting Information File 1

Experimental. Details of experimental procedures and data for characterisation of new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-6-S1.doc]

Acknowledgments

We would like to thank the Department of Education and Learning DEL for a studentship to Angela Nelson. The research at NIH was supported by the intramural funds of NIDDK.

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Beilstein Journal of Organic Chemistry

Total synthesis of the indolizidine alkaloid tashiromine

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Full Research Paper

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Beilstein Journal of Organic Chemistry **2008**, 4, No. 8.
doi:10.1186/1860-5397-4-8

Received: 18 October 2007
Accepted: 26 January 2008
Published: 26 January 2008

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Abstract

Background

Tashiromine (**1**) is a naturally occurring indolizidine alkaloid. It has been the subject of thirteen successful total syntheses to date. Our own approach centres on the stereoselective construction of the indolizidine core by capture of an electrophilic acyliminium species by a pendant allylsilane. The key cyclisation precursor is constructed using olefin cross-metathesis chemistry, which has the potential to facilitate both racemic and asymmetric approaches, depending upon the choice of the allylsilane metathesis partner.

Results

The use of the allyltrimethylsilane cross-metathesis approach enables the rapid construction of the key cyclisation precursor **3** (3 steps from commercial materials), which undergoes acid-induced cyclisation to give the desired bicyclic indolizidine skeleton as a 96:4 mixture of diastereomers. Simple functional group interconversions allowed the completion of the total synthesis of racemic tashiromine in six steps (19% overall yield). Three chiral α-alkoxyallylsilanes (**12**, **14** and **15**) were prepared in enantioenriched form and their cross-metathesis reactions studied as part of a putative asymmetric approach to tashiromine. In the event, α-hydroxysilane **12** underwent isomerisation under the reaction conditions to acylsilane **17**, while silanes **14** and **15** were unreactive towards metathesis.

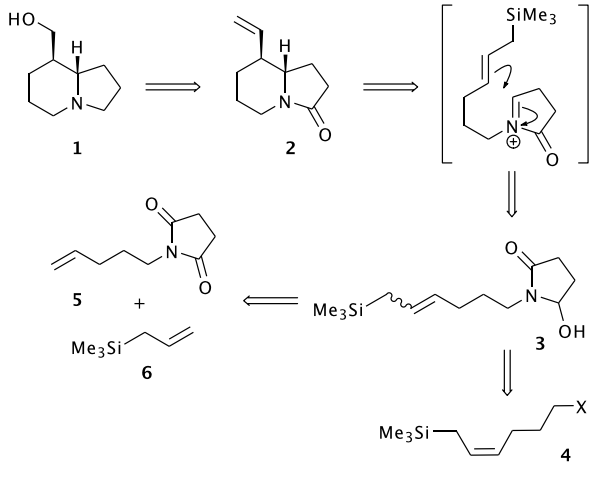
Conclusion

A concise, stereoselective total synthesis of racemic tashiromine has been developed. Attempts to translate this into an asymmetric synthesis have thus far been unsuccessful.

Background

Tashiromine (**1**) is a naturally occurring indolizidine, isolated from an Asian deciduous shrub *Maackia tashiroi* [1]. As one of the structurally simpler indolizidine alkaloids [2], tashiromine has been a popular target for synthetic chemists, and to date has succumbed to total synthesis on thirteen occasions [3-15]. A wide variety of reactions have been employed to assemble the

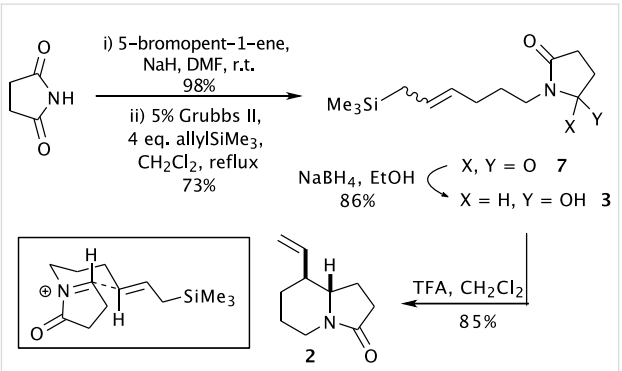
core indolizidine structure, including radical cyclisations [3]; nucleophilic addition to imines [5,14,15]; electrophilic alkylation of pyrroles [7,13]; alkylation of enamines [6], β-amino esters [8] and pyrrolidinyllithiums [12]; stereoselective reduction of enamines [4,9] and pyridinium salts [11]; and titanium-mediated reductive imide-olefin cyclisation [10]. Our own approach [14] utilises an intramolecular addition of an allylsilane to an *N*-acyliminium ion to deliver the [4.3.0]-azabicyclic (indolizidine) skeleton **2** (Scheme 1), wherein the pendant vinyl group acts as a handle to install the hydroxymethyl sidechain found in tashiromine. The synthesis of azabicyclic assemblies by intramolecular allylsilane/*N*-acyliminium cyclisations was first studied by Hiemstra and Speckamp [16], who prepared their functionalised allylsilane cyclisation precursors (such as **3**) by alkylation of cyclic imides with reagent **4** (X = OMs). This, in turn, was prepared in four steps by alkylation of an acetylide anion with commercially available iodomethyltrimethylsilane, followed by partial reduction of the alkyne. Alternative synthetic approaches to **4** (X = OMs, I) involve olefination of aldehydes using the Seyferth-Fleming phosphorane [17] or nickel-catalysed 1,2-metallate rearrangement of lithiated dihydropyran [18]. Our approach was informed by the prior work by our own group [19-24] and others [25-38] on the use of olefin metathesis to generate functionalised allylsilanes. Specifically, cross-metathesis of *N*-pentenylsuccinimide **5** with allyltrimethylsilane (**6**) [39] followed by chemoselective partial reduction of the imide would give the cyclisation precursor **3** in short order. Further, the use of chiral allylsilanes as cross-metathesis partners would potentially facilitate an asymmetric approach to the total synthesis of **1**. We report herein full details of the successful synthesis of racemic tashiromine **1** by this strategy [14], as well as our initial attempts towards an asymmetric variant.



Scheme 1: Retrosynthesis for tashiromine.

Results and Discussion

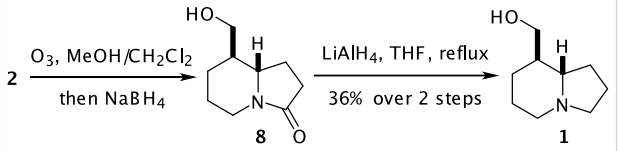
Metathesis precursor **5** was prepared by alkylation of the sodium salt of succinimide with 5-bromo-1-pentene in near quantitative yield (Scheme 2, see Supporting Information File 1 for full experimental data). The key cross-metathesis reaction of **5** was carried out using a fourfold excess of allyltrimethylsilane (**6**) and 5 mol% of Grubbs' second generation catalyst in refluxing dichloromethane. The desired product **7** was formed in 73% yield as an inseparable 3:1 mixture of *E*- and *Z*-isomers. Partial reduction with sodium borohydride generated the cyclisation precursor **3** in 86% yield, again as a 3:1 mixture of olefin isomers. Exposure of this mixture to trifluoroacetic acid in dichloromethane at room temperature gave the bicyclic amide **2** in 85% yield as a 96:4 mixture of diastereomers. The identity of the major diastereomer was confirmed by comparison of the spectral data with those of Hiemstra [16]: specifically, the signal for the (ring-fusion) proton at C6 for the major diastereomer appeared as a doublet of triplets with δ = 3.19 ppm, whereas the corresponding signal for the minor diastereomer appeared at δ = 3.67 ppm. The stereochemical outcome of this reaction was rationalised on the basis of the model shown in Scheme 2, whereby nucleophilic addition of the allylsilane to the *N*-acyliminium ion occurs through a chair-like transition state with the nascent alkene equatorially disposed.



Scheme 2: Stereoselective construction of the indolizidine core **2**.

All that remained to complete the synthesis of tashiromine **1** was to effect the oxidative cleavage of the C5 vinyl substituent, then carry out a global reduction of the resulting carbonyl function and the amide. In the event, attempts to form a C5 aldehyde using either ozonolytic or dihydroxylation/periodate alkene cleavage protocols were unsuccessful, with complex mixtures being obtained in both cases. We suspected that the problem lay in the potential for the desired aldehyde to undergo retro-Mannich fragmentation, and so elected to carry out a reductive work-up to the ozonolysis procedure (Scheme 3). The desired alcohol **8** was obtained in a crude form and immediately subjected to reduction with lithium aluminium hydride to

give our target tashiromine **1** in 36% yield over two steps. Our stereochemical assignment for the cyclisation of **3** was further corroborated by the agreement of the spectral data for **1** with those previously published in the literature [3-5,9-12]. Additionally, the spectral data for the diastereomeric *epi*-tashiromine have been reported and differ significantly from those recorded for **1** [10].



Scheme 3: Completion of the total synthesis of tashiromine **1**.

Having completed our target synthesis, our next goal was to investigate an asymmetric approach to tashiromine. Specifically, we envisaged that cyclisation precursors of type **9** ought to be readily available by cross-metathesis of **5** with an appropriate chiral allylsilane followed by chemoselective partial reduction by borohydride. Thereafter, exposure to acid would generate an *N*-acyliminium ion, which would cyclise through a chair-like transition state with the nascent alkenyl side-chain equatorially disposed, as in the racemic series (Figure 1). The absolute stereochemistry of the newly established asymmetric centres would be controlled by allylic strain arguments, assuming that the well-established precedent for *anti*-S_E2' attack of the iminium on the allylsilane was upheld here [40]. Thus, the predicted major stereoisomer **10** would have (5*S*,6*S*) stereochemistry and an *E*-configured side-chain, while cyclisation to the predicted minor (5*R*,6*R*) isomer **11** would be disfavoured by $A_{1,3}$-interactions between the R^1 group and vinylic proton (leading to the *Z*-configured side-chain). This would represent an immolative transfer of chirality approach to tashiromine, since the olefinic side-chains would be cleaved to install the hydroxymethyl side-chain required by the natural product.

Our approach centred on the readily availability of chiral α-hydroxysilane **12** in enantioenriched format [41]. Protection of the hydroxyl group, either before or after cross-metathesis, would allow access to chiral allylsilanes **9** with R^1 being an alkoxy or acyloxy group. Furthermore, this would generate products **10** and/or **11** with a readily oxidised enol-ether/ester side chain for progression to tashiromine. We were, of course, mindful that these functions could potentially act as nucleophiles themselves in the acidic medium of the electrophilic cyclisation, and the investigation of such chemoselectivity issues provided a further impetus for this study. Acylsilane **13** was therefore prepared from propargyl alcohol in four steps

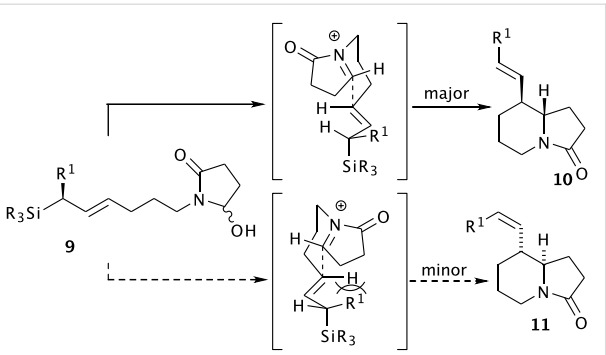
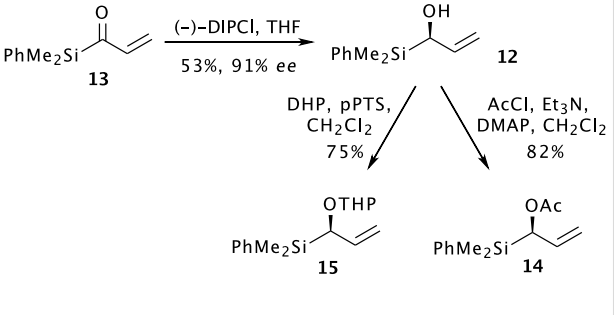


Figure 1: Rationale for stereoselective assembly of the indolizidine core using chiral allylsilanes.

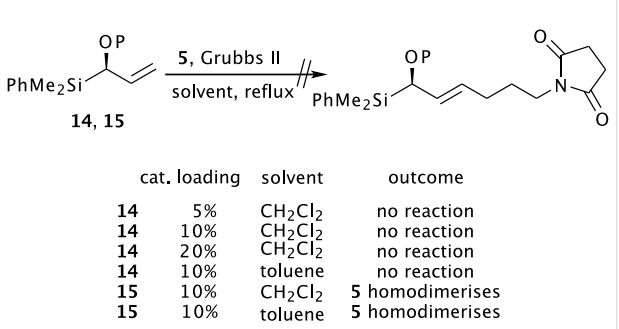
then subjected to asymmetric reduction with (−)-DIPCl according to Buynak *et al.* (Scheme 4) [41]. The desired hydroxysilane **12** was obtained in 53% yield and with 91% *ee* as determined by chiral HPLC analysis. Compound **12** was converted by standard methods to the acetate **14** and the tetrahydropyranyl ether **15**. The latter compound was formed as a 1.3:1 mixture of diastereomers which were partially separated by column chromatography — all subsequent reactions were carried out on diastereomerically pure material for ease of analysis.



Scheme 4: Asymmetric synthesis of chiral (alkoxy)allylsilanes.

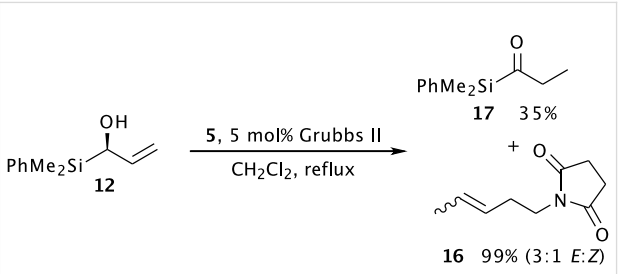
With the requisite enantioenriched allylsilanes in hand, we next investigated their behaviour in olefin cross-metathesis reactions. Unfortunately, neither **14** nor **15** reacted with **5** under the standard cross-metathesis conditions used for trimethylsilane **6**; the use of more forcing conditions (elevated temperature and higher catalyst loadings) did not effect the desired transformation, the only product observed being that of homodimerisation of **5** (Scheme 5).

Finally, we examined the behaviour of alcohol **12** under cross-metathesis conditions. In the event, two isomerised products were isolated from this reaction (Scheme 6): the internal alkene **16** (formed in 99% yield as a ca. 3:1 mixture of *E:Z* isomers)



Scheme 5: Attempted cross-metathesis of (alkoxy)allylsilanes.

and the acylsilane **17**. The formation of isomerised alkenes accompanying (or instead of) metathesis processes using ruthenium-based catalysts is well documented [42-63], as is the formation of carbonyl compounds by isomerisation of the corresponding allylic alcohols [64-68]. At this stage we therefore reluctantly abandoned our investigations into the asymmetric synthesis of tashiromine.



Scheme 6: Competing isomerisation processes in attempted cross-metathesis of (hydroxy)allylsilane **12**.

Conclusion

A concise, stereoselective total synthesis of racemic tashiromine has been developed (six steps from succinimide, 19% overall yield) in which the key steps are the preparation of a functionalised allylsilane by olefin cross-metathesis and the construction of the indolizidine core by intramolecular addition of the allylsilane to an *N*-acyliminium ion. Attempts to translate this into an asymmetric synthesis utilising cross-metathesis reactions of chiral α-alkoxysilanes have thus far been unsuccessful.

Experimental

Experimental protocols for the synthesis of tashiromine **1** and the preparation of silanes **12**, **14**, **15** and **17** available as Supporting Information File 1.

Supporting Information

Supporting Information File 1

Supporting Information. Full experimental details and compound characterisation data for all new compounds described.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-8-S1.pdf]

Acknowledgments

We thank the EPSRC for a studentship (ADM) and Pfizer and Merck for generous unrestricted research funding.

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