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Total Synthesis of Indolizidine (+)-223A

Mouloud Fellah,[a] Gérard Lhommet,[a] and Virginie Mouriès-Mansuy*[a]

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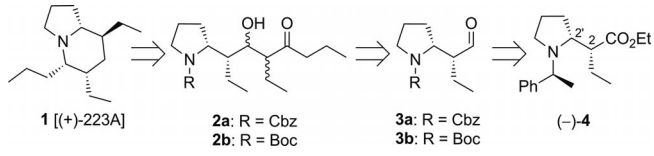
We described the diastereoselective total synthesis of indolizidine (+)-223A in 10 % overall yield over 14 steps starting from 6-chlorohex-2-ynoate. Our strategy involved chain elongation through aldolization, the formation of the indolizidine skeleton by cyclization, and stereocontrolled hydrogenation.

Introduction

Indolizidine and quinolizidine ring systems constitute the core of numerous structurally interesting alkaloids extracted from the skins of amphibians.[1] The small amounts isolated and the potent biological activities of these natural products make them attractive targets in organic synthesis. Among these alkaloids, indolizidine 223A, the first member of a new trisubstituted indolizidine class of amphibian alkaloids, was isolated by Daly and co-workers[2] from the skin extract of a Panamanian population of the frog *Dendrobates pumilio* Schmidt (Dendrobatidae). The first total synthesis of alkaloid 223A reported by the groups of Toyooka and Daly[3] allowed the determination of the correct structure. Recently, this natural product was shown to exhibit blocking effects on nicotinic acetylcholine receptors.[4]

To date, five syntheses of indolizidine 223A have been reported.[3,5] Most of them involve the elaboration of a chiral tetrasubstituted piperidine intermediate and its subsequent cyclization into the corresponding indolizidine. Recently, Aubé et al.[5d] performed a concise synthesis of alkaloid (–)-223A from norbornadiene through ring-opening-metathesis to form the indolizidine ring system.

Our goal was to develop a simple procedure providing easy access to alkaloid 223A in sufficient quantities from readily accessible compounds. In relation to our interest in the total synthesis of natural products using cyclic amino esters as versatile intermediates,[6] we report herein a highly stereoselective synthesis of indolizidine (+)-223A from a chiral pyrrolidine ester. Our strategy is outlined in Scheme 1. We envisioned that indolizidine (+)-223A could stem from pyrrolidine hydroxy ketone **2** by cyclization. Elaboration of the side chain of **2** could arise from aldehyde **3**, which could be obtained from (*R*)-ethyl 2-{(*R*)-1-[(*S*)-1-phenylethyl]pyrrolidin-2-yl}butanoate [(–)-**4**].[7]



Scheme 1. Retrosynthetic analysis for indolizidine (+)-223A.

Results and Discussion

Compound (–)-**4** was easily prepared as outlined in Scheme 2. Ethyl 6-chlorohex-2-ynoate (**5**, obtained from commercially available chloropentyne) was condensed with (*S*)-1-phenylethylamine to provide (*S*,*E*)-ethyl 2-[1-(1-phenylethyl)pyrrolidin-2-ylidene]acetate [(–)-**6**][8] in 96% isolated yield. Catalytic hydrogenation of this compound over PtO_2 afforded the expected amino ester as a 90:10 mixture of diastereomers in 96% isolated yield. Major diastereomer (–)-**7** was isolated in 60% yield after treatment of the mixture with picric acid, subsequent crystallization of the resulting salt, and conversion back to the free base. Compound (–)-**7** was alkylated by reaction with LDA followed by the addition of ethyl iodide to afford pyrrolidine (–)-**4** as a single diastereomer in 92% isolated yield. On the basis of previously obtained results, the absolute configuration of (–)-**4** was assigned to be (2*R*,2′*R*).[7]

For initial studies we focused our attention on the construction of a racemic pyrrolidine substituted by an appropriate functionalized side chain through an aldolization reaction, followed by intramolecular cyclization into an indolizidine. Required aldehyde **3**, N-protected by either a benzyl or a *tert*-butyl carbamate moiety, was prepared from pyrrolidine ester **8**.[9] The latter was subjected to alkylation to provide compound **9** in 98% isolated yield.[10] Reduction of the ester moiety of **9** with lithium aluminum hydride (LAH) led to alcohol **10** in 96% isolated yield. A debenz-

[a] UPMC Univ Paris 06, Sorbonne Universités,
Institut Parisien de Chimie Moléculaire (UMR CNRS 7201),
4 place Jussieu, C. 229, 75005 Paris, France
Fax: +33-1-44277360
E-mail: virginie.mansuy@upmc.fr

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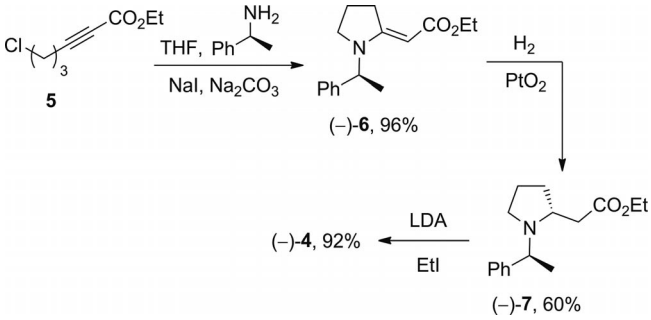
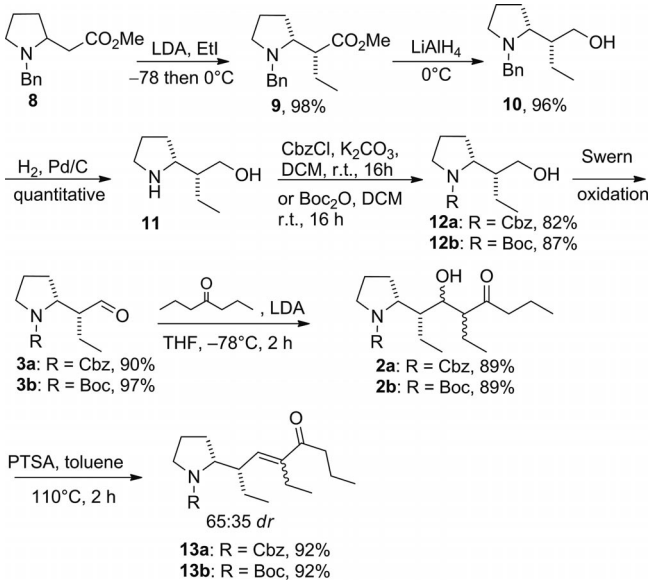


Scheme 2. Synthesis of (*R*)-ethyl 2-{(*R*)-1-[(*S*)-1-phenylethyl]pyrrolidin-2-yl}butanoate (**4**).

ylation/carbamation sequence gave either *N*-Cbz- (**12a**) or *N*-Boc-pyrrolidines (**12b**) in 82 and 87% isolated yield, respectively. Swern oxidation of these pyrrolidines provided corresponding aldehydes **3a** (90%) and **3b** (97%). These aldehydes were then subjected to aldolization with heptan-4-one. Expected aldol products **2a** and **2b** were thus obtained as mixtures of diastereomers in good yield. At this stage, we first envisaged to transform these compounds into the corresponding enones by dehydration in acidic medium [*para*-toluenesulfonic acid (PTSA) in refluxing toluene]. Pyrrolidines **13a** and **13b** were thus obtained in similar yields (92%) and in the same 65:35 ratio of *E*/*Z* diastereomers (Scheme 3).



Scheme 3.

With racemic, chain-extended pyrrolidines **13a** and **13b** in hand, we turned our attention to the construction of the indolizidine skeleton. We began our study by catalytic hydrogenation of *N*-Cbz-protected pyrrolidine **13a** over Pd/C. Reduction of the double bond with concomitant *N*-deprotection and intramolecular reductive amination afforded a 75:25 inseparable mixture of indolizidine diastereomers along with material that was not characterized. The configuration of 6-*epi*-indolizidine 223A (Figure 1) was ascribed to the major diastereomer through ^{13}C NMR spectroscopic analysis of the mixture (see the Supporting Information for spectroscopic data).[5d,11]

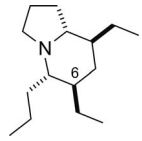
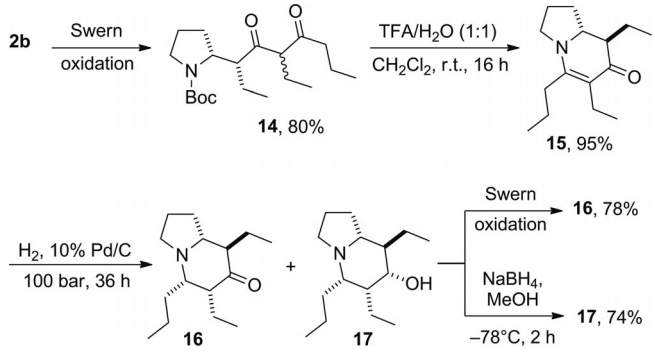


Figure 1. Structure of (±)-6-*epi*-indolizidine 223A.

To obtain the correct stereochemistry at C6 we thus decided to reduce the alkene moiety of **13** in a first step. We so examined the selective hydrogenation of the double bond of *N*-Boc-pyrrolidine **13b**. Numerous attempts did not produce the expected pyrrolidine. Catalytic hydrogenation (Pd/C, PtO_2, Pt/C), LAH, or metal-catalyzed silicon hydride reductions ($PdCl_2/Et_3SiH$,[12] IPr-CuCl-*t*BuONa-PMHS[13]) led only to the recovery or decomposition of the starting material.

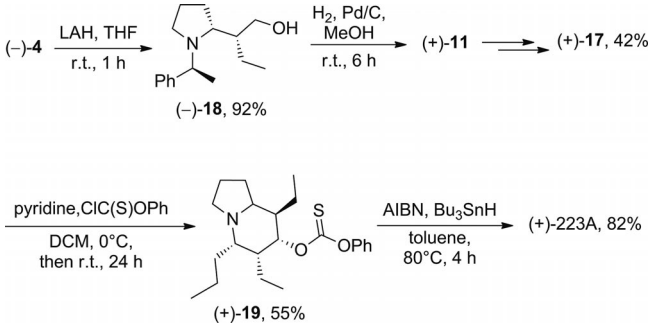
In view of these results, we decided to synthesize the indolizidine core by an alternative route involving the oxidation of the alcohol function before the cyclization step. Racemic pyrrolidine **2b** was therefore submitted to Swern oxidation providing pyrrolidine **14** as a complex mixture of diastereomers in 80% isolated yield. Acid-induced removal of the Boc protecting group and in situ cyclization afforded tetrahydroindolizinone **15** as a single diastereomer in 95% isolated yield. Treatment of **15** with various hydrides ($NaBH_4$, $NaBH_3CN$ under neutral or acidic conditions) only led to intractable mixtures. By contrast, catalytic hydrogenation[14] of **15** in the presence of Pd/C (10%) under 100 bar of H_2 led to a mixture of indolizidinone **16** and indolizidinol **17** in a 28:72 ratio. Swern oxidation of this crude mixture afforded **16** in 78% isolated yield, whereas reduction by sodium borohydride led to **17** in 74% isolated yield (Scheme 4). The *cis* hydrogenation of the double bond of **15** enabled the formation of the two last stereogenic centers on indolizidine 223A.



Scheme 4.

Compounds **16** and **17** were previously involved as intermediates in the synthesis of indolizidine (–)-223A described by Davis and co-workers.[5c] Therefore, this result allowed

us to envisage this route for the formal synthesis of indolizidine (+)-223A starting from chiral pyrrolidine **4**. Reduction of the ester function of pyrrolidine **4** with LAH afforded the corresponding pyrrolidine alcohol (–)-**18** in 92% isolated yield. Hydrogenolysis of (–)-**18** under a hydrogen atmosphere in the presence of 10% Pd/C delivered (+)-**11** in quantitative yield. According to the sequence previously described from racemic pyrrolidine **11**, chiral indolizidinol (+)-**17** was obtained from *N*-Boc-protected pyrrolidine (+)-**12b** as a single diastereomer (5*S*,6*R*, >98%*de*) in 42% overall yield in seven steps (as described in Schemes 3 and 4). The spectroscopic data of (+)-**17** corresponded to those described in the literature. Nevertheless, the sign of the optical rotation was identical to that reported by Davis and coworkers for its enantiomer.[15] To secure the absolute configuration of the stereogenic centers formed during our sequence, we decided to complete the synthesis of (+)-223A from (+)-**17** according to Davis' route for indolizidine (–)-223A. Conversion of alcohol (+)-**17** into the corresponding phenylthionocarbonate (+)-**19** (Scheme 5) followed by radical deoxygenation led to expected (+)-223A in 45% isolated yield.[16] The spectroscopic data and the positive optical rotation value of (+)-223A·DCl {$[\alpha]_D^{20}$ = +38.0 (*c* = 0.26, $CHCl_3$)} were in complete agreement with those reported in the literature for the opposite enantiomer[3,5] {$[\alpha]_D^{20}$ = –36.8 (*c* = 0.45, $CHCl_3$)}.[5c] This result confirmed our configurational assignments for compounds **16** and **17**.



Scheme 5.

Conclusions

In summary, we reported an efficient total formal synthesis of indolizidine (+)-223A, the opposite enantiomer of natural (–)-223A. Our strategy was based on three major steps: chain elongation by aldolization, formation of a bicyclic enone by cyclization, and stereocontrolled hydrogenation of the obtained tetrahydroindolizinone. To determinate the absolute configuration of the stereogenic centers created during our synthesis, we completed the synthesis of indolizidine (+)-223A following the Davis' route from alcohol (+)-**17**. Finally, expected indolizidine (+)-223A was obtained in 10% yield over 14 steps starting from readily available ethyl 6-chlorohex-2-ynoate (**5**). Application of this flexible route to the synthesis of more complex alkaloids is currently under investigation.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, copies of the NMR spectra.

Acknowledgments

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[9] Compound **8** was prepared in two steps from methyl 6-chlorohex-2-ynoate and benzylamine in 82% overall yield. Spectroscopic data of **8** corresponded to those reported: Y. J. Jeon, C.-P. Lee, P. S. Mariano, *J. Am. Chem. Soc.* **1991**, *113*, 8847–8863.
[10] Compound **9** was obtained from **8** in 98% isolated yield under the same conditions as those used for the obtention of **4** (Scheme 2).
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[14] This reaction was sluggish when it was performed under 1 bar of hydrogen and required an increase in the pressure up to 100 bar to force it to completion.
[15] **17** $[\alpha]_D^{20}$ = +59.1 (*c* = 0.69, $CHCl_3$), ref.[5c] $[\alpha]_D^{20}$ = +56.5 (*c* = 0.69, $CHCl_3$).
[16] To confirm our results, we performed the total synthesis of (+)-223A with a unique batch of compound (–)-**6**.

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