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Asymmetric Total Synthesis of Alkaloids 223A and 6-*epi*-223A†

Partha Ghosh, Weston R. Judd, Timothy Ribelin, and Jeffrey Aubé*

Department of Medicinal Chemistry, 1251 Wescoe Hall Drive, Malott Hall, Room 4070, University of Kansas, Lawrence, Kansas 66045-7582

jaube@ku.edu

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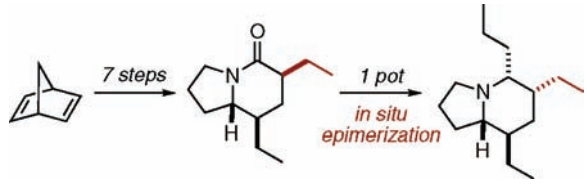
ABSTRACT



Concise and asymmetric total synthesis of the title compounds are described. The key ring system was constructed using an intramolecular Schmidt reaction on a norbornenone derivative, which was subsequently subjected to ring-opening metathesis followed by reduction. An unusual isomerization of the C-6 ethyl group afforded the desired stereochemistry of the natural product. The synthesis is readily adaptable to analogue production.

The skin glands of anurans are a major source of alkaloids used for chemical defense.[1] Recently, it has been reported that oribatid mites are the major dietary source for several of these alkaloids.[2] Many of these alkaloids containing the indolizidine ring system have exhibited promising biomedical relevance, such as inhibition of nicotinic acetylcholine receptors[3a] or binding affinity for the human δ-opioid receptor.[3b] In 1997, John Daly and co-workers reported the first trisubstituted indolizidine alkaloid **223A** along with three higher homologues, isolated from the Panamanian population of the frog *Dendrobates pumilio Schmidt*, and proposed the structure to be **2** (Figure 1).[4] Later, Toyooka et al., reporting the first total synthesis of this natural product, revised the structure of the natural product to **1** and assigned the originally proposed structure **2** to 6-*epi*-223A.[5]

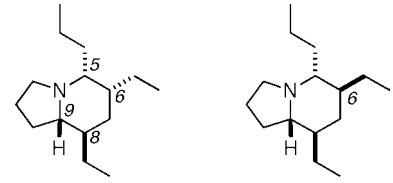


Figure 1. Indolizidine alkaloids **223A** and 6-*epi*-**223A**.

To date, four total syntheses of alkaloid **223A** (**1**)[5,6a−c] and two total syntheses of 6-*epi*-**223A** (**2**)[6a,7] have been reported. Each of these routes employed imaginative and modern synthetic procedures but nonetheless required ≥10 synthetic steps to prepare this seemingly simple natural product. Intrigued by the substitution pattern of **1** and challenged by the need for a route adaptable to the convenient preparation of analogues suitable for biological evaluation, we embarked on the development of a general synthesis of these trisubstituted natural products. Herein we communicate the successful realization of these objectives via a route that permits the ready

† Dedicated to the memory of John Daly.

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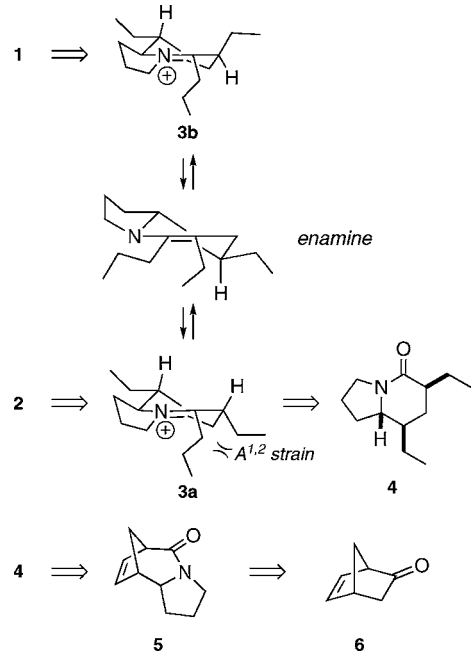
modification of all three alkyl groups; such analogues would be difficult to obtain from the natural product itself.

Our main synthetic strategy was to access **1** from the bicyclic amide **4**, which should be readily available from ketone **6** using an exo alkylation/ring expansion protocol similar to that previously employed in a total synthesis of (+)-sparteine.[8] Metathetic ring opening of the resulting lactam followed by hydrogenation would place the C-9 stereocenter relative to the *cis*-ethyl groups found in 6-*epi*-**223A** (**2**). In contrast, access to **1** would require the specific epimerization of the ethyl group at C-6. This strategy was risky insofar as the proposed epimerization step would move the 6-ethyl group into an axial orientation from a typically more stable equatorial position. However, propylation of the lactam in **4** followed by dehydration would initially lead to iminium ion **3a**, which suffers from $A^{1,2}$ strain between the 6-ethyl and *n*-propyl group (Scheme 1).[9] Should it be possible to effect

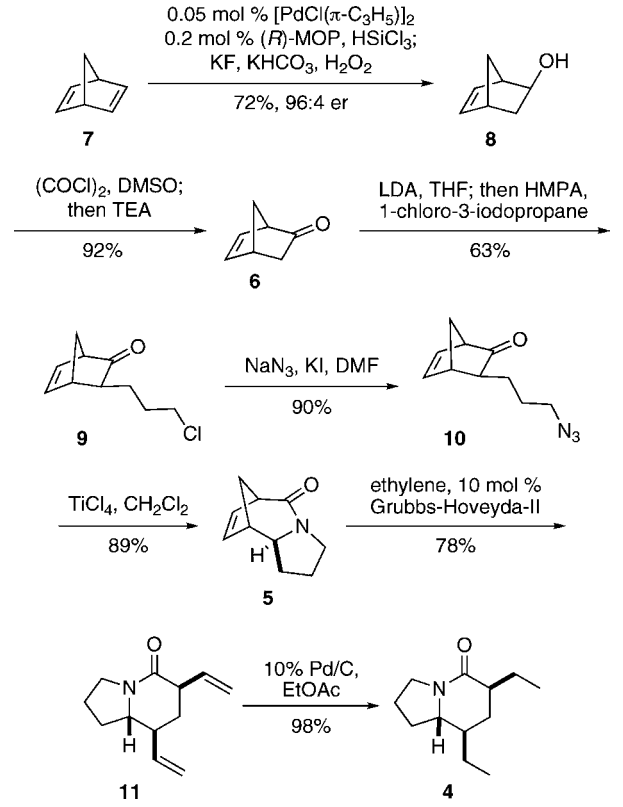
Scheme 1. Retrosynthetic Strategy



equilibration of **3a** at any stage following propylation, i.e., through the intermediacy of the enamine shown, a stereocontrolled and concise synthesis of **1** would be in hand.

Our synthesis began with the one-step enantioselective hydrosilylation/oxidation of norbornadiene **7** to afford the known alcohol **8** in 72% yield and 96:4 er (Scheme 2).[10,11] Swern oxidation of **8** provided the known norbornenone **6** in 92% yield.[12] α-Alkylation of **6** in 4:1 THF/HMPA with 1-chloro-3-iodopropane followed by azide substitution gave the desired ring expansion substrate.[13,14] Intramolecular Schmidt reaction of **10** in the presence of $TiCl_4$ resulted in the formation of lactam **5** in an excellent 89% yield.[15] Initial attempts at ring-opening metathesis (ROM) of **5** with ethylene were unsatisfactory. When ROM was performed in the presence of 10 mol % Grubbs-I catalyst, only 24% conversion to **11** was observed, which contrasted with previous reports on reactions carried out on similar ring systems but lacking amide functionality.[16] However, use of 10 mol % Grubbs−Hoveyda-II as catalyst resulted in an improved 78% yield of **11**.[17] Catalytic hydrogenation of both olefins in **11** gave **4** in excellent yield.

Scheme 2. Synthesis of Lactam **4**[a]



[a] (*R*)-MOP = (*R*)-(+)-2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl.

(5) Toyooka, N.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M.; Kaneko, T. *Org. Lett.* **2002**, *4*, 1715–1717.

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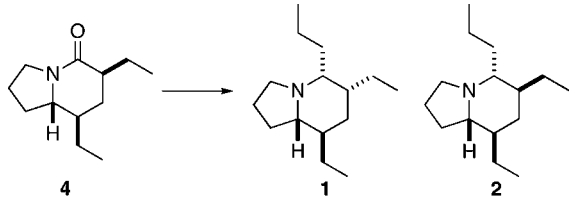
With the synthesis of **4** complete, the stage was set to execute our main strategic reaction.

Addition of *n*-propyllithium to lactam **4** led to an adduct that was not isolated. Acetic acid was added at 0 °C, and the reaction mixture was allowed to stir for 1 h. Upon addition of BH_3, both **1** and **2** were obtained in 32% and 44% yields, respectively (Scheme 3).[18] This result was encouraging as it

Scheme 3. Synthesis of **223A** and 6-*epi*-**223A**



	1	2
A	32%	44%
B	58%	16%
C	7%	65%

Conditions

A: 1.5 equiv *n*-PrLi, Et_2O, –10 °C to rt, 2 h; then 1.5 equiv HOAc, rt, 1 h, then BH_3, 0 °C to rt, 2 h.

B: 1.5 equiv *n*-PrLi, Et_2O, –10 °C to rt, 2 h; then 1.5 equiv HOAc, rt, 12 h, then BH_3, 0 °C to rt, 2 h.

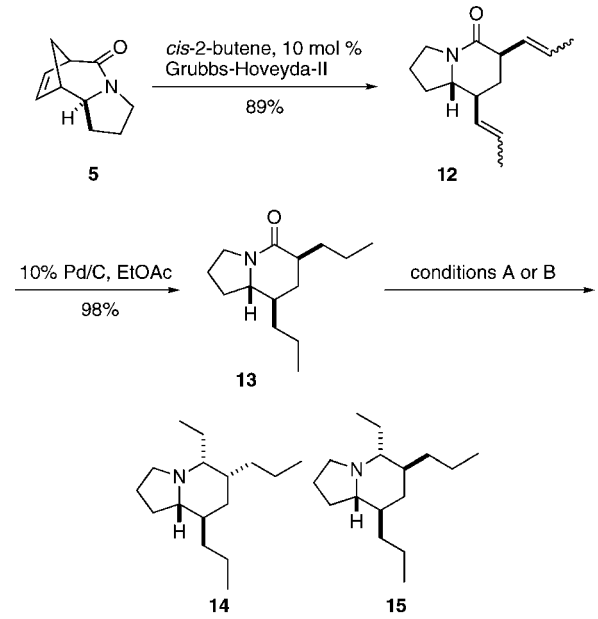
C: 1.5 equiv *n*-PrLi, Et_2O, –10 °C to rt, 2 h, then 1.5 equiv TFA, –40 °C, then BH_3, –40 °C to rt, 3 h.

suggested that the iminium intermediate **3a** had undergone partial epimerization under rather mild conditions. When the initial *n*-propyl adduct was allowed to equilibrate for 12 h in neutral conditions and subsequently reduced with BH_3, **1** was obtained as the major product with 58% yield together with **2** in 16% yield. Increasing the duration of epimerization to 24 h or changing the reaction medium from neutral to acidic (adding 3 equiv of acetic acid in quenching) gave **1** in reduced yield, without any significant improvement in selectivity over **2** (data not shown). However, when the reaction was quenched at −40 °C with trifluoroacetic acid, subsequent reduction with BH_3 generated **2** in 65% yield, accompanied by only 7% of **1**. Thus, in a single final step both the natural product 233A **1** and its best-known epimer **2** could be obtained from **4** in separate one-pot operations.

The flexibility of this route was demonstrated in a preliminary fashion by the synthesis of two epimeric analogues **13** and **14** (Scheme 4). Thus, ROM of lactam **5** with *cis*-butene followed by hydrogenation gave lactams **13** in 88% yield (two steps). When **13** was alkylated with ethyllithium and subsequently treated under conditions similar to those used for the syntheses of **1** and **2**, analogues **14** and **15** were obtained in 55% and 68% yields, respectively.

In conclusion, we have accomplished a concise, modular, and protecting group-free synthesis of alkaloid **223A** and

Scheme 4. Synthesis of Analogues



	14	15
A:	55%	19%
B:	6%	68%

Conditions

A: 1.5 equiv EtLi, Et_2O, –10 °C to rt, 2 h; then 1.5 equiv HOAc, rt, 12 h, then BH_3, 0 °C to rt, 2 h.

B: 1.5 equiv EtLi, Et_2O, –10 °C to rt, 2 h; then 1.5 equiv TFA, –40 °C, then BH_3, –40 °C to rt, 3 h.

the isomeric 6-*epi*-**223A**. The synthesis reported here is the shortest to date, requiring only six steps from known norbonenone **6** and eight steps from norbornadiene **7**. The natural product **1** was obtained in 14.8% overall yield from **7**. Finally, the use of an ROM step in this route opens to the door to analogues that would not be readily available from the naturally occurring alkaloid even if it were readily available. This instance of diverted total synthesis[19] has been preliminarily demonstrated by the preparation of isomeric analogues **14** and **15**. This work opens the door to both the systematic synthesis of analogues of this and related indolizidine alkaloids and their examination by high-throughput screening. This work is in progress and will be reported in due course.

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

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