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Synthesis of Alkaloid 223A and a Structural Revision

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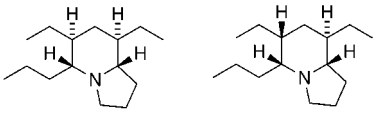
ABSTRACT



Synthesis of alkaloid 223A has been achieved by sequential use of our original conjugate addition reaction to enaminoesters as the key step. The proposed structure for natural 223A (A, absolute configuration unknown) was revised to B, and the relative stereostructure was determined to be 5*R,6*R**,8*R**,9*S** by the present synthesis.**

Amphibian skin has provided a wide range of biologically active alkaloids (over 20 structural classes and over 500 alkaloids) including pyrrolidines, piperidines, decahydroquinolines, pyrrolizidines, indolizidines, and quinolizidines.[1] The pharmacological activities associated with these alkaloids together with the small amounts isolated from skins have inspired many syntheses of these heterocycles.[2] The alkaloid **223A** (**A**), the first member of a new trialkyl-substituted indolizidine class of amphibian alkaloids, was isolated from a skin extract of a Panamanian population of the frog *Dendrobates pumilio* Schmidt (Dendrobatidae) in 1997 along with three higher homologues of **A**.[3] The structure of this alkaloid has been established to be **A** based upon GC-MS, GC-FTIR, and ^{1}H NMR spectral studies.[3] In this paper, we would like to report the first synthesis of alkaloid **223A** by sequential use of our original Michael-type of conjugate addition reaction to enaminoesters (**i**, **ii**) as the key step[4] (Figure 1). The proposed configuration at the 6-position of **223A** was found to be incorrect. The correct structure was proved by work reported here.

The synthesis began with (2*S*)-amide **1**,[5] which was converted to the cyclic enaminoester **2** using triflation of the intermediate imidourethane with Comins' reagent[6] followed by a palladium-catalyzed CO insertion reaction[7] of the

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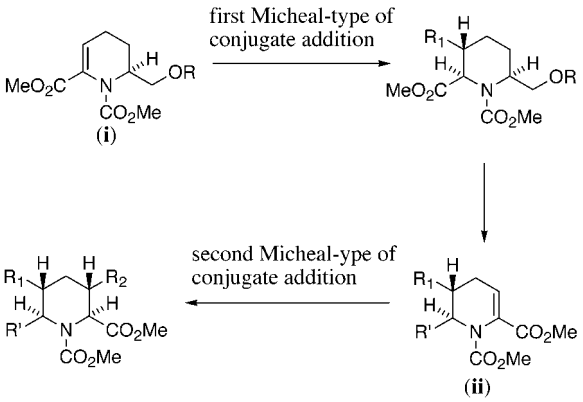
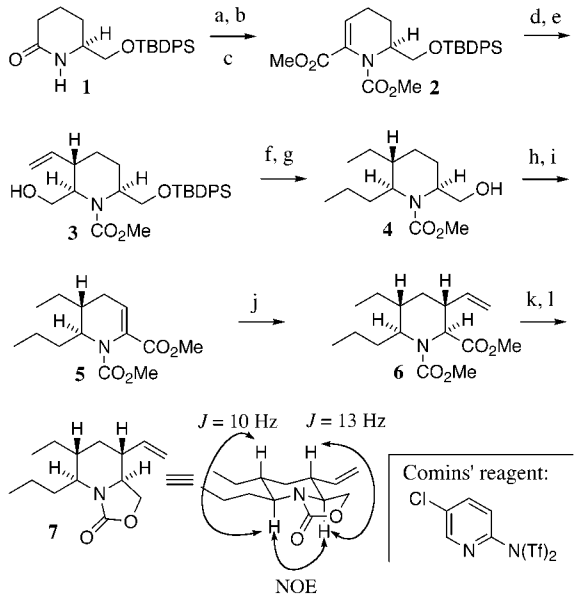


Figure 1. Basic strategy for the construction of the 2,3,5,6-tetrasubstituted piperidine ring system.

resulting enol triflate. The first Michael-type conjugate addition reaction of **2** proceeded smoothly giving the vinyl adduct as a single isomer,[4] which was transformed into the methyl urethane **4** via the alcohol **3**. The alcohol **4** was converted to the methyl ester, which was transformed into the cyclic enaminoester **5** using Rubio's protocol.[8] The second Michael-type conjugate addition of **5** proceeded to afford adduct **6**, again as a single isomer. The stereochemistry of **6** was determined by the coupling constants and NOE of the oxazolizinone derivative **7** as shown in Scheme 1.

Scheme 1[a]

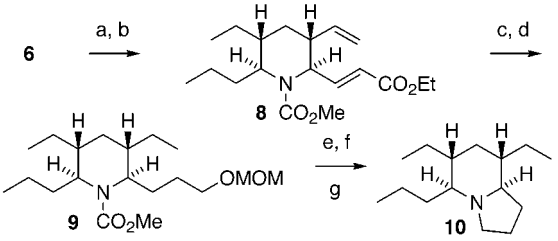


[a] Reagents and conditions: (a) *n*-BuLi, $ClCO_2Me$ (98%); (b) LiHMDS, Comins' reagent (96%); (c) CO, $Pd(Ph_3P)_4$, Et_3N, MeOH (88%); (d) $(vinyl)_2CuLi$ (96%); (e) Super-Hydride (96%); (f) Swern ox., then *n*-BuLi, $EtP^+Ph_3Br^-$ (79% 2 steps); (g) 5% Pd−C, H_2, then TBAF (77% 2 steps); (h) Swern oxidation, then $NaClO_2$,, NaH_2PO_4, and then CH_2N_2 (90% 3 steps); (i) LiHMDS, PhSeCl (77%); (j) $(vinyl)_2CuLi$ (90%); (k) Super-Hydride (99%); (l) NaH (84%). TBDPS = *tert*-butyldiphenylsilyl.

The stereoselectivity of the second and key Michael-type conjugate addition reaction can be rationalized as follows. The conformation of **5** will be restricted to **5-A** as a result of $A^{(1,3)}$ strain[9] between the *N*-methoxycarbonyl and *n*-propyl groups in **5-B**. Attack of the vinyl anion from the stereoelectronically favored α-axial direction provides the adduct **6** exclusively.

It is noteworthy that the stereochemical course of the above reaction is controlled by the stereoelectronic effect despite severe 1,3-diaxial steric repulsion between the axial ethyl group at the 5-position and the incoming vinyl anion. This remarkable stereoselectivity can be also explained by Cieplak's hypothesis.[10] On the preferred conformation **5-A**, the developing σ^* of the transition state is stabilized by the antiperiplanar donor σ_{C-H} at the C-4 position. Elaboration of the adduct **6** into the indolizidine **10**, previously proposed as the structure for natural **223A**,[3] is shown in Scheme 2.

Scheme 2[a]



[a] Reagents and conditions: (a) Super-Hydride (99%); (b) Swern oxidation, then NaH, $(EtO)_2P(O)CH_2CO_2Et$ (96% 2 steps); (c) 5% Pd−C, H_2 then Super-Hydride (89% 2 steps); (d) MOMCl, Hünig base (86%); (e) *n*-PrSLi, HMPA; (f) c. HCl, MeOH; (g) CBr_4, Ph_3P (52% 3 steps).

Reduction of **6** with Super-Hydride followed by Swern oxidation and Wittig−Horner reaction of the resulting aldehyde afforded the α,β-unsaturated ester **8**. Hydrogenation of **8** and reduction of the resulting saturated ester gave the corresponding alcohol, whose hydroxyl group was protected as the MOM ether **9**. Finally, deprotection[11] of the methoxycarbonyl group and cleavage of the MOM ether followed by indolizidine formation[12] furnished **10**. However the ^1H and ^{13}C NMR and IR spectra of **10** were not identical with those for the natural product, nor was the GC retention time.

The close similarity of the Bohlmann bands in the vapor phase FTIR spectra of **10** and natural **223A** indicated the same 5,9-Z configuration[3] for both compounds. On the basis of a detailed comparison of the ^1H and ^{13}C NMR spectra,[13] we concluded that natural **223A** differed from **10** only in the 6-position configuration. Therefore, we commenced the

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(12) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876−2882.
(13) H-5 in **10** and **223A** was a dt signal with *J* values of 11, 2.5 and 11, 4.7 Hz, respectively. Hindered rotation at C-5 in **223A** leads to an 11-Hz J_{5-10} coupling and does not reflect the J_{5-6} coupling as was erroneously proposed initially.[3]

synthesis of the diastereomeric indolizidine **11** from piperidone **12**.[14]

The piperidone **12** was converted to cyclic enaminoester **13** in the same manner as described in Scheme 1. Addition of divinylcuprate to **13** provided the adduct **14** as a single isomer in excellent yield. The indicated coupling constant and NOE experiments of oxazolizinone **16** derived from **14** via the alcohol **15** confirmed that the stereogenic centers of the key intermediate **14** were correct for the synthesis of the target indolizidine **11**. Stereoselectivity of this Michael reaction can again be explained by $A^{(1,3)}$ strain and a stereoelectronic effect as shown in Figure 2. The synthesis

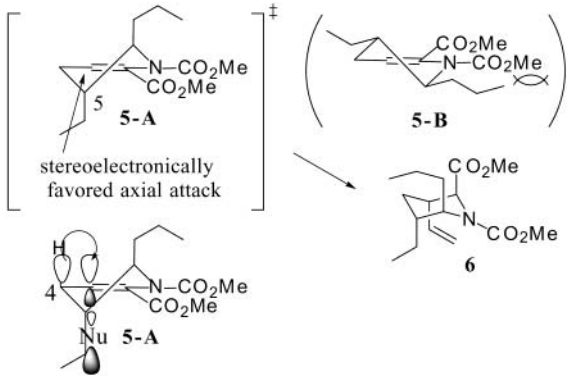


Figure 2. Stereochemical course of the key Michael-type conjugate addition reaction of **5**.

of **11** was accomplished via the alcohols **17** and **18** in the same manner as used in the synthesis of **10** in Scheme 2. The spectral data for **11** (^{1}H and ^{13}C NMR, GC-FTIR, GC-EIMS) were completely identical with those for the natural product. Thus the structure of natural **223A** is revised to **11**, and the relative stereostructure of this alkaloid was determined to be 5*R**,6*R**,8*R**,9*S**[15] by the present synthesis.

In summary, the first synthesis of alkaloid **223A** has been accomplished, the proposed structure has been revised, and the relative stereostructure of natural **223A** was determined. In the key Michael-type conjugate addition reaction, allylic 1,3-strain effectively restricts the addition to one conformation of the enaminoester, where a stereoelectronic effect

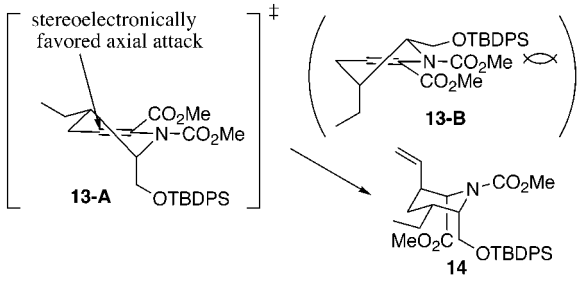
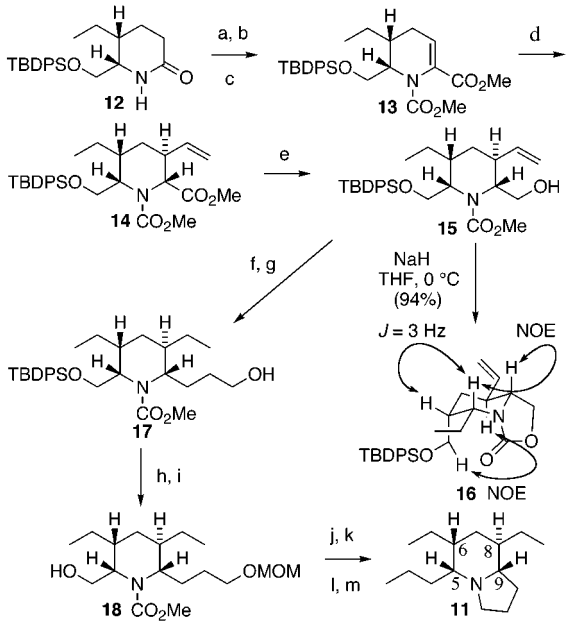


Figure 3. Stereochemical course of the key Michael-type conjugate addition reaction of **15**.

Scheme 3[a]



[a] Reagents and conditions: (a) *n*-BuLi, $ClCO_2Me$ (97%); (b) LiHMDS, Comins' reagent (97%); (c) CO, $Pd(Ph_3P)_4$, Et_3N, MeOH (75%); (d) $(vinyl)_2CuLi$ (95%); (e) Super-Hydride (96%); (f) Swern oxidation, then NaH, $(EtO)_2P(O)CH_2CO_2Et$ (92% 2 steps); (g) 5% Pd−C, H_2, then Super-Hydride (98% 2 steps); (h) MOMCl, Hünig base (89%); (i) TBAF (79%); (j) Swern oxidation, then *n*-BuLi, $EtP^+Ph_3Br^-$ (83% 2 steps); (k) 5% Pd−C, H_2; (l) *n*-PrSLi, HMPA; (m) c. HCl, MeOH, then CBr_4, Ph_3P (51% 4 steps)

confers selectivity to the addition. More importantly, any alkyl side chain could be introduced at the 3- and 5-positions by our strategy in a stereoselective manner. The carbon chain at the 2- and 6-positions can be elongated arbitrarily by appropriate modifications of oxygenated functional groups. This flexible route should be amenable to synthesis of other alkaloids such as three higher homologues of **223A** or unnatural congeners of dendrobatid alkaloids bearing highly substituted piperidine rings. Syntheses of the higher homologues of **223A**, such as **237L**, **251H**, and **267J**, are now under investigation.

Acknowledgment. We are grateful to Dr. Yoshihiko Hirose, Amano Pharmaceutical Co., Ltd., for the generous gift of lipase AK used in the synthesis of **12**.[14]

Supporting Information Available: Experimental procedures and characterization data for all new compounds and ^{1}H and ^{13}C NMR spectra of synthetic compounds **6**, **7**, **10**, **11**, **14**, **16**, and natural **223A**·DCl salt. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) This piperidone was synthesized from known (2*R*)-2-(hydroxymethyl)butyl acetate (Izquierdo, I.; Plaza, M. P.; Rodriguez, M.; Tamayo, J. *Tetrahedron: Asymmetry* **1999**, *10*, 449−455); see Supporting Information for the experimental details.

(15) The optical rotation of the DCl salt synthetic **11** was $[\alpha]^{26}_D$ −40.9 (*c* 0.25, $CHCl_3$). Although the small amount of natural 223A-DCl available was sufficient only to indicate a very small negative rotation (observed rotation −0.018° in $CHCl_3$), we suggest from this that our synthetic enantiomer **11** may have the natural absolute configuration. Additional work will have to confirm this.