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Asymmetric Total Synthesis of Dendrobatid Alkaloid 251F

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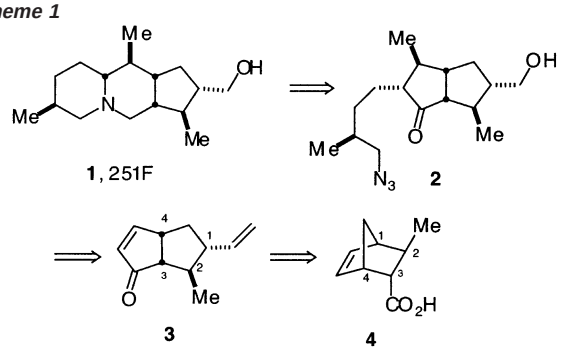
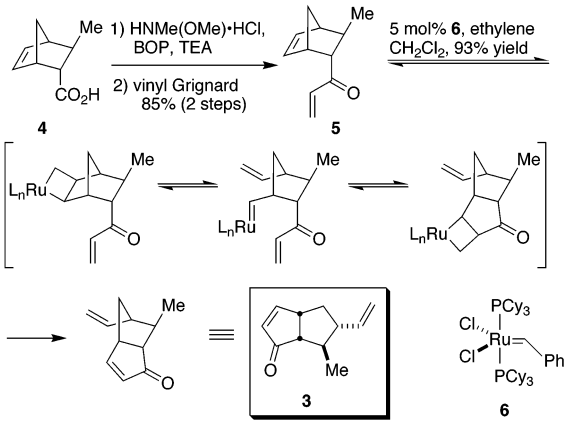
In 1992, Daly, Spande, and co-workers reported the isolation of a structurally unique tricyclic alkaloid, 251F, **1**, from the skin exudate of a Columbian dendrobatid poison frog, *Minyobates bombetes*.[1] As a class,[2] the dendrobatid alkaloids possess numerous kinds of biological activities; well-known examples include batrachotoxin[3] (agonist of voltage-dependent sodium channels) and epibatidine[4] (potent analgesic). However, the pharmacological profile of 251F remains unknown, not least because only 300 μg of the natural product was isolated from its amphibious source.[1] Matters of potential bioactivity aside, 251F constitutes an attractive synthetic target due to several challenging structural features, which include three fused rings and seven stereogenic centers (six of which are contiguous). To date, one synthesis of alkaloid 251F, by Taber and You, has been reported.[5] Herein, we describe a new total synthesis of 251F that features an intramolecular Schmidt reaction[6] (a process that has only recently been applied to problems in alkaloid synthesis[7]) as well as an unusually expedient route to a key chiral [3.3.0]bicyclooctane intermediate (Scheme 1). This strategy was particularly attractive because four of the seven stereocenters of 251F would directly arise in an asymmetric Diels–Alder reaction affording **4**. It was further expected that two additional centers would be susceptible to substrate control in reactions of the bicyclic enone.

Scheme 1



Scheme 2



Diels–Alder adduct **4** was prepared according to literature methods (we obtained material of 93% ee on a 1–2 g scale).[8] Our early work on the conversion of **4** to enones related to **3** utilized ozonolysis/aldol strategies.[9] However, a second-generation route featuring a tandem ring-opening/ring-closing metathesis (ROM/RCM) reaction ultimately proved most efficient in providing sufficient quantities of this key bicyclic intermediate.[10] Thus, conversion of acid **4** to the corresponding vinyl ketone (**5**) was carried out via the Weinreb amide[11] in 85% overall yield (Scheme 2). Treatment of **5** with Grubbs's catalyst **6** in methylene chloride saturated with ethylene afforded the bicyclic enone **3** in 93% yield. The ethylene atmosphere permits the recycling of alternative products (e.g., polymers or regioisomeric ring-opened products) into the pathway leading to **3**.

A 1,2-derivatization of the enone was necessary to prepare intramolecular Schmidt precursor **2** (Scheme 3). Thus, treatment of **3** with Me_2CuLi followed by quenching with aldehyde **7**[12] resulted in formation of enone **8**. Cuprate addition occurred from the exposed face of **3** and installed the methyl substituent with the desired exo stereochemistry. Dehydration of the initial aldol adduct occurred in situ and afforded the new enone as a single geometric isomer. Extensive 2D NMR analysis (COSY, HMQC, HMBC, NOESY) was used to assign *E* configuration to enone **8**; this presumably occurs to minimize steric interactions between the exocyclic olefin substituent and the nearby methyl group on the cyclopentyl ring. Treatment of compound **8** with Na/NH_3 effected both cleavage of the benzyl ether and reduction of the enone. This resulted in an approximately 4:1 mixture of inseparable diastereomers in 60% yield, in which the major isomer resulted from placement of the four-carbon side chain in the desired endo position. The side-chain stereochemistry could be explained on either thermodynamic (trans to the adjacent methyl group) or kinetic (exo protonation) grounds. The alcohol functionality could be converted into its azide derivative **9**, again isolated as a mixture of diastereomers in 50% yield from **8**, using an azide-modified Mitsunobu reaction.[13]

Standard conditions for carrying out the intramolecular Schmidt reaction, developed in these laboratories,[6] were then inflicted on **9**. However, treatment of **9** with either triflic acid (TfOH) or $TiCl_4$ yielded no lactam products, with only degradation products observed. To surmount this problem, **9** was converted to **2** via ozonolysis/DMS workup and careful reduction with $NaBH_4$. The two diastereomeric alcohols were separable at this stage using column chromatography. Satisfyingly, treatment of **2** with TfOH resulted in an intramolecular Schmidt reaction forming lactam **10** as a single diastereomer in 79% yield. X-ray analysis of lactam **10** established the relative stereochemistry of the molecule. The total synthesis of alkaloid 251F, **1**, was then completed by LAH reduction

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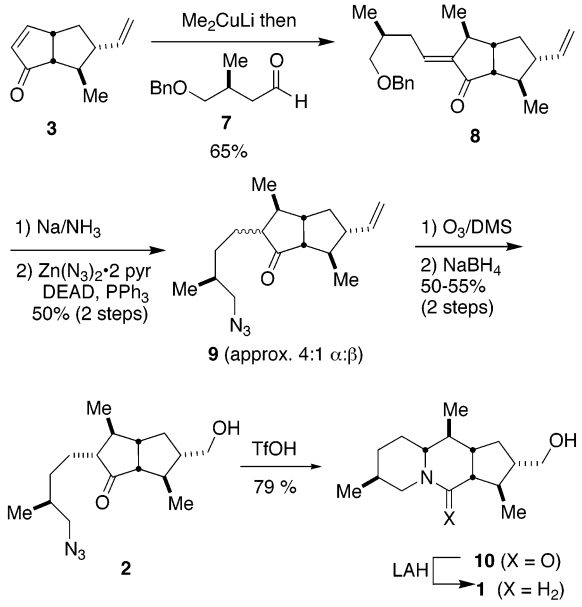
Scheme 3



of **10**, which proceeded in 86−100% yield. Spectral data (^{1}H, ^{13}C NMR, IR, and HRMS) were consistent with literature values,[1] and synthetic **1** had $[\alpha] = -11.1$ ($c = 0.960$), which is believed to correspond to material of ca. 93% ee.[14]

Noteworthy features of this synthesis (13 steps, 5−8% overall yield) include (1) the use of the very well-known Diels−Alder adduct **4** in total synthesis, (2) the use of ROM/RCM to effect an overall [2.2.1] → [3.3.0] ring system inversion (a process having considerable synthetic potential in a general sense), and (3) the use of an intramolecular Schmidt reaction to provide the ring system of 251F. Finally, we have prepared ca. 100 mg of 251F and are currently engaged in biological screening of this material and selected derivatives.

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

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(8) Preparation of **4**: (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256. For some recent examples of the use of acid **4** in total synthesis, see: (b) Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035−4043. (c) Krotz, A.; Helmchen, G. *Tetrahedron: Asymmetry* **1990**, *1*, 537−540. (d) Shimizu, I.; Matsuda, N.; Noguchi, Y.; Zako, Y.; Nagasawa, K. *Tetrahedron Lett.* **1990**, *31*, 4899−4902. (e) Krotz, A.; Helmchen, G. *Liebigs Ann. Chem.* **1994**, 601−609.

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(10) This reaction was inspired, if not literally preceded, by a reaction used in Grubbs's total synthesis of capnellene. (a) Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843−862. For other examples of this kind of "domino metathesis" process, see: (b) Stragies, R.; Blechert, S. *Synlett* **1998**, 169−170. (c) Arjona, O.; Csaky, A. G.; Medel, R.; Plumet, J. *J. Org. Chem.* **2002**, *67*, 1380−1383. (d) Professor Andrew Phillips at the University of Colorado has independently been exploring reactions such as this conversion in a synthetic program directed toward cylindramide and related natural products. Phillips, A., personal communication and Minger, T. L.; Phillips, A. J. *Tetrahedron Lett.* **2002**, *43*, 5357−5360.

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(12) Aldehyde **7** was prepared in 70% overall yield from (2*S*)-2-methyl-4-penten-1-ol (Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506−2526) via the following route: (a) NaH, BnBr, DMF; (b) cat. OsO_4, NMNO, $NaIO_4$, Et_2O/H_2O.

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(14) The specific rotation of 251F has not previously been reported (see refs 1 or 5). The enantiomeric purity and the absolute stereochemistry of the synthetic material are presumed to reflect those of acid **4** ($[\alpha]_D = -140$, $c = 3.6$, 95% EtOH): 93% ee (cf., ref 8a).

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