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Asymmetric Total Synthesis of Dendrobatid Alkaloids: Preparation of Indolizidine 251F and Its 3-Desmethyl Analogue Using an Intramolecular Schmidt Reaction Strategy

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Abstract: Total syntheses of alkaloid **251F** (**1**), a natural product detected from the skin extracts of the dendrobatid frog species *Minyobates bombetes*, and its racemic 3-desmethyl derivative (**2**) are reported. A Diels−Alder reaction initiated both syntheses and established four consecutive stereogenic centers. Important to the synthesis of **2** was a first-generation ozonolysis/olefination/aldol strategy to convert a [2.2.1] bicyclic acid to the [3.3.0]bicyclooctane diquinane **4b**. Further elaboration to an appropriate keto azide allowed for a key intramolecular Schmidt reaction to deliver the tricyclic core of the target molecule. In a second-generation approach, a tandem ring-opening/ring-closing metathesis reaction effected an overall [2.2.1] → [3.3.0] skeletal rearrangement to deliver diquinane **4a**. In similar fashion, **4a** was manipulated to an appropriate keto azide, and an intramolecular Schmidt reaction generated the core cyclic architecture of **251F**.

Introduction

For decades, amphibious sources have provided a rich array of natural product targets, particularly alkaloids, unprecedented in other biological systems.[1] Most likely used in chemical defense mechanisms, these alkaloids cover a wide spectrum of structural complexity and biological activity. Daly and co-workers have shown the dendrobatid family of frogs to be a highly prolific source of alkaloids.[1−3] To date, over 500 of these alkaloids have been detected in skin extracts of the dendrobatid frogs,[4] and nearly two dozen structural classes of alkaloids have been identified.[3] Some well-represented structural classes include the batrachotoxins (the class of alkaloids used as dart poisons), the histrionicotoxins and pumiliotoxin-A classes (a large family of bicyclic alkaloids), and the pyridine alkaloids (most notably, epibatidine).[1] Many of the individual dendrobatid alkaloids have been found in multiple frog species. Thus, a single alkaloid may be widely distributed among numerous species of dendrobatid frogs. The cyclopenta[*b*]quinolizidine alkaloids, however, have thus far been detected in only one species. Originally described as *Dendrobates bombetes*,[5] the taxonomic classification of this small, poisonous Colombian frog species was then changed to *Minyobates bombetes* (*M. bombetes*).[6] Alkaloid **251F** (**1**) was characterized as the major alkaloid of the skin extract of *M. bombetes*, and its structure was elucidated primarily via mass spectroscopy and NMR studies as reported by Daly and Spande in 1992.[7] The skin extract from *M. bombetes* caused severe locomotor difficulties, muscle spasms, and convulsions upon injection into mice.[3] It is quite possible the observed biological effects were due to other alkaloids present in the skin extract, so nothing is definitively known regarding the biological activity of **251F**.

With undetermined biological activity and a highly intriguing chemical structure including three fused rings and seven stereogenic centers (six on contiguous carbons), **251F** presents a distinct challenge for total synthesis. In 1995, Taber and You reported the first synthesis of **251F** utilizing a highly diastereoselective rhodium-catalyzed construction of a key cyclopentane intermediate.[8] For over a decade, our laboratory has investigated the intramolecular Schmidt reaction as a method for the construction of heterocycles bearing nitrogen at ring fusion positions.[9,10] However, this reaction has only recently been applied to the synthesis of complex alkaloids.[11−14]

Because of its structure and (as yet uncertain) potential biological activity, we identified alkaloid **251F** as a target for total synthesis.[15] Retrosynthetically, a key step would be the intramolecular Schmidt reaction that would entail the conversion of keto azides such as **3** to the lactam derivative of the target **1**

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(3) Daly, J. W.; Garraffo, H. M.; Spande, T. F. *The Alkaloids*; Academic Press: New York, 1993; pp 185−288.
(4) Daly, J. W. *J. Med. Chem.* **2003**, *46*, 445.
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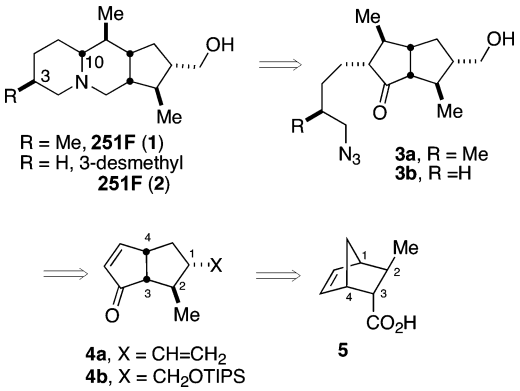
(14) Golden, J. E.; Aubé, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316−4318.
(15) Wrobleski, A.; Sahasrabudhe, K.; Aubé, J. *J. Am. Chem. Soc.* **2002**, *124*, 9974−9975.

10.1021/ja0320018 CCC: $27.50

Scheme 1



(Scheme 1). However, the complexity of ketones **3** would add another challenging element to the proposed synthesis. This paper fully discloses a set of studies of the problem of **251F** synthesis that not only provided advanced examples of the intramolecular Schmidt reaction but also established a new route to [3.3.0] bicyclic ketones related to **3**. In this work, two distinct total syntheses were carried out, one leading to (±)-desmethyl **251F 2** and the other affording **1** in enantiomerically enriched form.

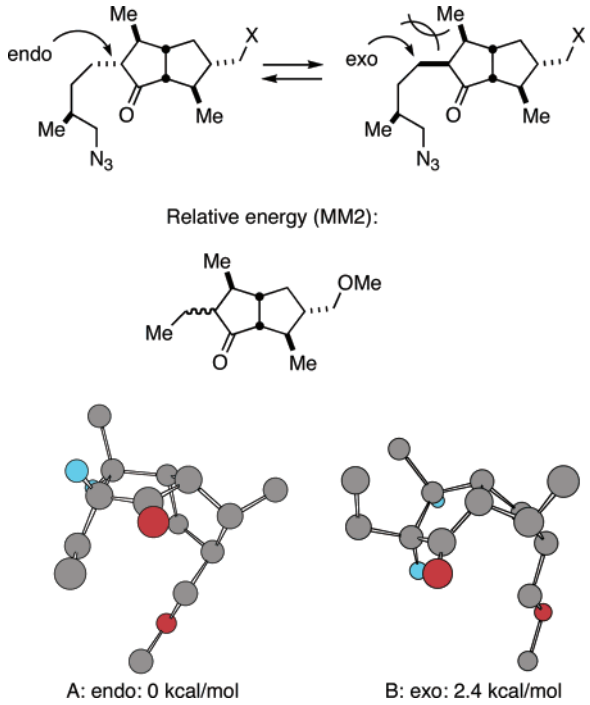
Retrosynthetic Analysis

As noted above, the targeted intramolecular Schmidt reaction required the intermediacy of keto azides **3a** and **3b**, respectively. These intermediates were proposed to result from the appropriate derivatization of a bicyclic enone **4a** or **4b** (X represents a hydroxymethylene equivalent). This sequence presents an important stereochemical issue in that the two groups being introduced onto the enone (an exo β methyl group and an endo α azido side chain) must occupy the indicated trans relationship relative to one another to complete the stereocontrolled installation of the six consecutive stereocenters. Plenty of precedent suggested that conjugate addition would result in exo methylation of the diquinane; however, the stereochemical outcome of installing the adjacent azidobutyl side chain was less secure. Although the desired product would result from placing this group trans to the adjacent methyl group, doing so would force it onto the endo face of the [3.3.0] bicyclooctane system (which is less favored relative to the exo orientation due to the cuplike ring system). To address this, MM2 calculations were performed on model substrates bearing substituents at the α and β centers with both cis and trans configurations (Scheme 2). Calculations indicated that the energy of isomer B with both groups exo and cis to one another was 2.4 kcal/mol greater than that of the desired epimer A. Minimally, this suggested that thermodynamics might work in our favor even if a kinetic addition of the desired group failed to afford the desired relative stereochemistry.

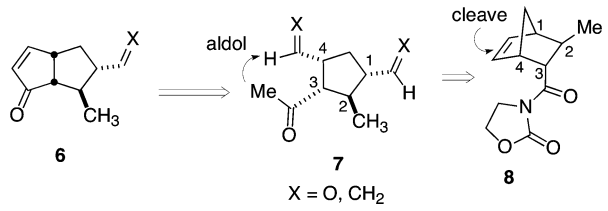
Stereoselective syntheses of diquinanes **4a**,**b** were required to realize the above strategy. An attractive solution toward this problem was suggested by the recognition that the four stereogenic centers in compounds **4** could be directly mapped onto **5** as shown (Scheme 3), coupled with the fact the latter should be readily generated from a garden variety Diels−Alder reaction of cyclopentadiene and a crotonic acid equivalent.

Key precedent for our approach to enone **6** was found in the literature of triquinane natural product synthesis. Thus, conversion of the acyloxazolidinone portion of **8** to the corresponding methyl ketone followed by oxidative cleavage (ozonolysis, for example) of the endocyclic olefin would generate dialdehyde **7**. An intramolecular aldol reaction of **7** could in principle provide bicyclic enone **6**. A variant of this ozonolysis/aldol strategy was previously explored by Sternbach et al. in an approach to hirsutene[16] and the total synthesis of silphinene[17] (Scheme 4).

Scheme 2



Scheme 3



In other work, Grubbs published a route for converting [2.2.1]-bicycloheptene ring systems to the corresponding [3.2.0]heptane enol ethers using titanocene alkylidene complexes (Scheme 4).[18,19] This served as a key reaction in a synthesis toward capnellene. These titanium-mediated transformations are clearly related to the now-common ruthenium alkylidene-catalyzed metathesis reactions. Several groups have utilized ring-opening/ring-closing versions of this latter transformation to carry out skeletal rearrangements of the type needed here.[20−27] We

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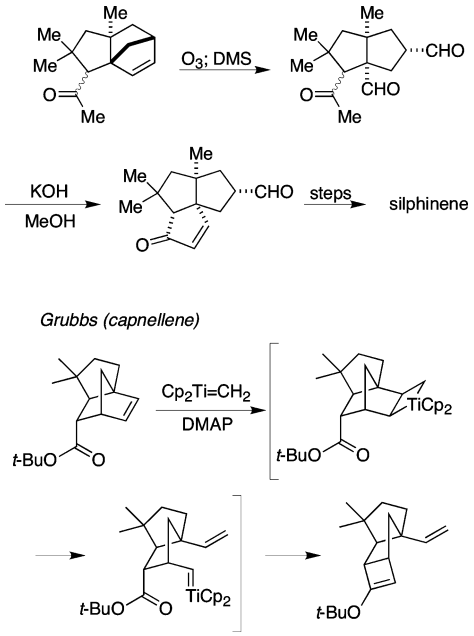
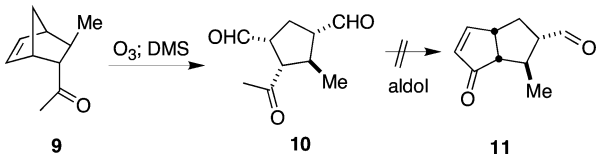
(17) Sternbach, D. D.; Hughes, J. W.; Burdi, D. F.; Banks, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 2149−2153.
(18) Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843−862.
(19) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855−856.
(20) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634−6640.
(21) Minger, T. L.; Phillips, A. J. *Tetrahedron Lett.* **2002**, *43*, 5357−5359.
(22) Stragies, R.; Blechert, S. *Synlett* **1998**, 169−170.
(23) Arjona, O.; Csaky, A. G.; Medel, R.; Plumet, J. *J. Org. Chem.* **2002**, *67*, 1380−1383.
(24) Hagiwara, H.; Katsumi, T.; Endou, S.; Hoshi, T.; Suzuki, T. *Tetrahedron* **2002**, *58*, 6651−6654.

Scheme 4



Scheme 5



investigated, and here compare, both aldol and metathesis approaches to the synthesis of the desired enones.

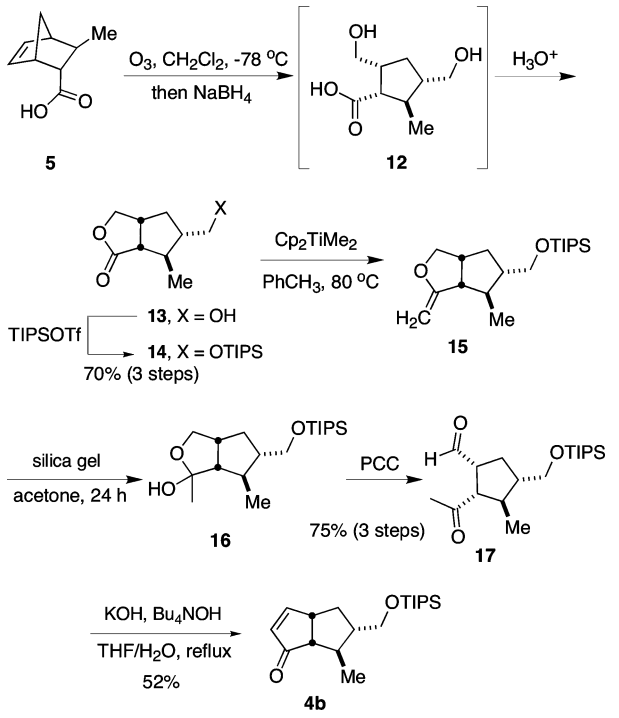
Synthesis of (±)-3-Desmethyl 251F (2)

To permit us to concentrate on the coupled problems of [3.3.0] bicyclooctane synthesis and relative stereocontrol about the ring system, we chose to first prepare (±)-3-desmethyl **251F** lacking the isolated methyl group. Since all the remaining stereocenters were destined to arrive from relative stereocontrol techniques, this allowed us to work in the racemic series at the outset.

Starting from a racemic derivative of **5**, an extremely direct intramolecular aldol route to **4b** was briefly investigated. Accordingly, olefin **9**[28] (Scheme 5) was ozonized to yield the corresponding dialdehyde **10**; however, under no conditions examined could an intramolecular aldol reaction be induced to afford **11**. It is likely that the abundance of acidic protons and subsequent retroaldol opportunities available in **10** rendered the desired aldol process ineffective. A variety of epimerization reactions may have also competed with the desired cyclization reaction.

Guided by the hypothesis that reduction of the extraneous aldehyde in **10** would eliminate some of the untoward pathways, a second attempt involved pursuing an aldol precursor via a lactone derivative of acid **5** (Scheme 6). Ozonolysis of olefin **5** followed by borohydride reduction gave diol **12**, which upon

Scheme 6



acidification spontaneously lactonized to alcohol **13**. This allowed for ready differentiation of the two alcohols. Subsequent protection yielded lactone **14** in 70% overall yield for the three-step sequence from **5**. Addition of varying methyl nucleophiles (MeLi, MeMgBr, etc.) gave complex mixtures of products, so an olefination of lactone **14** was planned to effect the homologation to the methyl ketone. Initial experiments focused on using the Tebbe reagent[29] to convert **14** to the analogous enol ether; however, no positive results were obtained via this avenue. Fortunately, Petasis' reagent[30] (Cp_2TiCl_2) in place of Tebbe's provided the desired enol ether **15**. After some experimentation, it was discovered that carrying out the olefination according to the procedure developed by Howell[31] proved most effective. The resulting enol ether was subsequently hydrolyzed to hemiacetal **16** and immediately oxidized with PCC to generate the aldol precursor **17**. A number of conditions were examined to carry out the intramolecular aldol conversion of **17** to **4b** but failed to produce the aldol adduct in acceptable yields. Eventually, reasonably efficient conditions were uncovered. Thus, KOH and Bu_4NOH in refluxing THF/water (THF, tetrahydrofuran) provided aldol adduct **4b** in 52% yield.

Though the route presented in Scheme 6 afforded quantities of **4b** in excess of 2 g, numerous drawbacks using this strategy soon became apparent. The Petasis olefination product **15** was obtained cleanly and could be used in subsequent transformations without purification (though some titanocene byproduct could be seen in the NMR spectrum of the crude product). However, only after the aldol step could product be purified chromatographically. The four-step sequence from **14** to **4b** was routinely carried out with crude reaction mixtures, analyzing

(25) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828−1829.
(26) Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291−4298.
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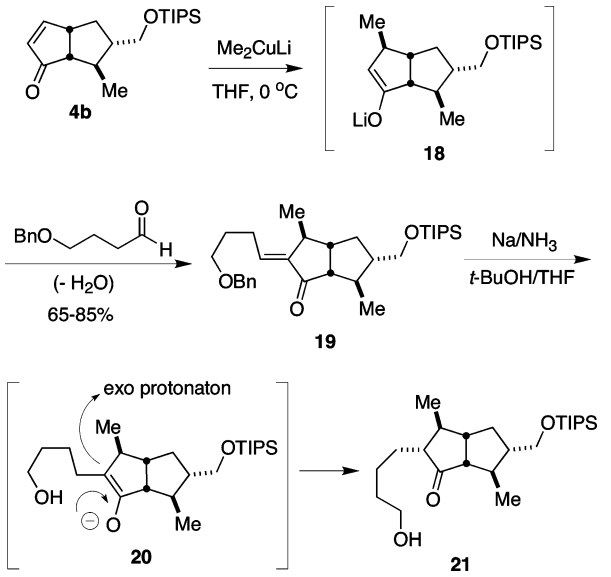
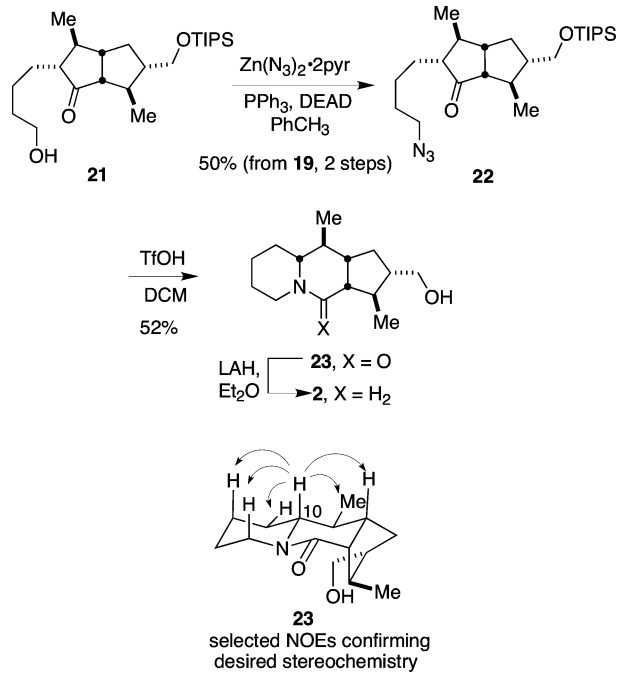
(28) Available in two steps (Weinreb amide formation then methyl Grignard addition) from acid **5**.
(29) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611−3613.
(30) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392−6394.
(31) Dollinger, L. M.; Ndakala, A. J.; Hashemzadeh, M.; Wang, G.; Wang, Y.; Martinez, I.; Arcari, J. T.; Galluzzo, D. J.; Howell, A. R. *J. Org. Chem.* **1999**, *64*, 7074−7080.

Scheme 7



Scheme 8



the intermediate products only with ^{1}H NMR to ensure complete reactant consumption. Overall, the seven-step sequence from **5** could be carried out in 27% overall yield. At seven steps, this sequence was sufficient for carrying out preliminary experiments; however, more efficient means would ultimately be sought to streamline the synthesis. The ozonolysis/olefination/aldol strategy was certainly lengthier than the initially proposed route, and we felt that a more rapid and efficient enone synthesis would help ensure a more attractive synthesis of **251F** in the end. Despite this, we decided to use enone **4b** obtained via this route to investigate the addition of the two remaining side chains and the following Schmidt reaction.

Considering the cup-shaped geometry of a cis-fused 5,5-bicyclic system, it was expected that methyl cuprate addition would occur from the desired exo position and that quenching the resultant enolate with an appropriate electrophile would stereoselectively install a precursor to the endo azido side chain (trans to the methyl group; see Scheme 2). However, conjugate addition of Me_2CuLi followed by quenching with 1-chloro-4-iodobutane resulted only in installation of a methyl group at the β position of the enone. Under a variety of conditions examined using even highly reactive alkyl halides such as iodomethane and allyl bromide as electrophiles, no successful instances of incorporation of α substituents were observed. Attempts at two-pot sequences in which the β-substituted ketone was treated with a variety of bases and subsequently treated with electrophiles resulted only in starting material.

Given these problems, we proposed that a one-pot conjugate addition/aldol strategy could serve as an effective means for introducing both substituents. Thus, to our delight, aldehydes proved to be efficient coupling partners (Scheme 7). Accordingly, conjugate addition of Me_2CuLi from the most exposed face of **4b** resulted in enolate **18**, which, when quenched with 4-benzyloxybutanal, led to a single olefinic isomer of **19**. Scheme 7 indicates the *E* stereochemistry for the aldol dehydration, but it was not until the asymmetric synthesis of **251F** was completed that the olefin geometry was rigorously proved (see below).

The in situ dehydration of the aldol adduct to exocyclic enone **19** precluded the direct formation of the sixth consecutive stereocenter. However, this point was muted as it was recognized that a dissolving metal reduction could serve two functions: (1) cleavage of the benzyl ether of **19** to the corresponding alcohol and (2) reduction of the enone moiety to the saturated analogue placing the azido side chain precursor in the desired endo position (Scheme 7). The observed side chain stereochemistry can be rationalized in two ways. On one hand, the calculations described above suggested that thermodynamic protonation of the intermediate enolate (**20**) would favor placing the side chain trans to the existing adjacent methyl group. Alternatively, kinetic protonation might favor quenching the enolate from the less hindered exo face. In practice, the dissolving metal reduction of **19** proceeded to yield a single diastereomer of **21**. However, the stereochemistry of this newly formed center was not verified until a later point in the synthesis due to the lack of diagnostic NMR evidence from **21** itself.

Progress toward the azido ketone Schmidt precursor was made via azidation of primary alcohol **21** under Mitsunobu conditions[32] to yield azide **22** in ca. 50% overall yield from **19** (2 steps, Scheme 8). With **22** in hand, the stage was set for carrying out the critical intramolecular Schmidt reaction. Thus, treatment of **22** with excess triflic acid (TfOH) smoothly converted the azido ketone to the ring-expanded lactam **23** while simultaneously removing the TIPS group to reveal the primary alcohol in 52% yield. At this time, extensive 2D NMR analysis was used to corroborate the stereochemistry of all six stereogenic centers. The most revealing piece of evidence came from the observation of an NOE between the C10 methine proton and the adjacent methyl group, indicating a cis orientation between the two or, alternatively, a trans relationship between the methyl group and side chain. Four other NOEs were observed and further corroborated that the Schmidt product had stereochemistry corresponding to that of the natural product (Scheme 8). Completion of the 3-desmethyl **251F** synthesis required only the reduction of the lactam to the corresponding tertiary amine.

(32) Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130−132.

Thus, treatment of **23** with LAH in ether afforded the desired amine **2** (confirmed from IR and MS data only due to isolation difficulties; Scheme 8).

Asymmetric Total Synthesis of 251F (1)

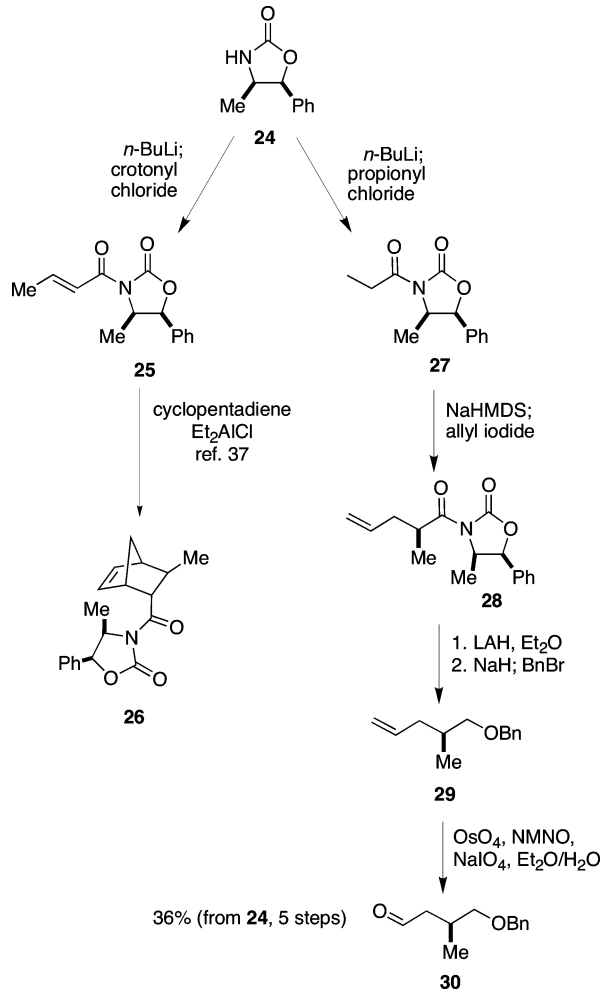
Although the model synthesis of **251F** helped develop a great deal of the chemistry needed to formulate a route toward the natural product, a number of issues remained unresolved. First, the issue of carrying out an asymmetric synthesis had to be considered. This issue was readily addressed as numerous efficient routes toward both enantiomers of acid **5** have been developed by other workers.[33−39] A more pressing task, however, was the desire to produce enone **4b**, or its equivalent, in a more direct route. This goal ultimately found its realization with the utilization of metathesis chemistry. In addition, the 3-methyl group had to be incorporated with the proper stereochemistry. Finally, a major goal of this synthesis was to produce meaningful (decigram) quantities of the dendrobatid natural product.

Two of the above issues were resolved via the dual utilization of a common chiral auxiliary to control the formation of five of the seven stereogenic centers of alkaloid **251F**. Thus, an asymmetric Diels−Alder reaction using **25** set the four consecutive stereocenters of acid **5** in both a relative and absolute sense (Scheme 9). In addition, the same auxiliary, (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone, can be used to control the outcome of an asymmetric alkylation reaction to set the C3 stereocenter (Scheme 9).

The synthesis of enantiopure aldehyde **30** commenced with conversion of auxiliary **24** to **27** via deprotonation (*n*-butyllithium, THF) and quenching with propionyl chloride. The enolate of **27** was generated with NaHMDS (sodium bis(trimethylsilyl)amide) and subsequently reacted with allyl iodide to provide allylated **28** as a white solid that could be recrystallized to ≥95% diastereomeric purity. Cleavage of the chiral auxiliary (LAH) afforded an enantiopure alcohol[40] which was immediately benzylated to ether **29**. Finally, oxidative cleavage of the olefin afforded the desired aldehyde **30** in 36% yield over the five-step sequence. Conversion of **25** to **26** was effected by treating a mixture of **25** and cyclopentadiene in methylene chloride at −100 °C with diethyl aluminum chloride. Diels−Alder adduct **26** was isolated in ca. 93−95% diastereomeric purity on a 2 g scale.[37]

With protocols in hand for the asymmetric synthesis of acid **5** and provisions met for the stereocontrolled installation of the 3-methyl group, attention was then directed at retooling the route toward the key bicyclic enone intermediate **4b**, previously prepared via an ozonolysis/aldol method. As noted earlier, it was felt that the use of metal alkylidene complexes (i.e., ruthenium-catalyzed ring-opening/ring-closing metathesis) could

Scheme 9



be utilized to catalyze the desired [2.2.1] → [3.3.0] skeletal rearrangement. To examine this strategy it was recognized that the acid portion of **5** would need to be converted to an olefinic derivative.

In building this substrate, Diels−Alder adduct **26** was cleaved to enantiomerically enriched acid **5** with $LiOH/H_2O_2$.[41] Thus, conversion of **5** to the Weinreb amide[42] followed by addition of vinyl Grignard afforded **31** in 85% yield for the 2-step sequence (Scheme 10). At this stage it became possible to explore the use of Grubbs's ruthenium catalysts to effect the desired ring-opening/ring-closing metathesis reactions. Early attempts using standard conditions[20] afforded the desired enone **4a**, albeit in poor yield. Examination of these results suggested that a good deal of the reaction products were oligomerized materials. Though only a 30% yield of metathesis product was isolated, it was felt that this yield could be increased with the identification of more fitting conditions.

Remarkable increases in reaction efficiencies were realized, however, when the tandem ring-opening/ring-closing metathesis was carried out in ethylene-saturated methylene chloride kept under an atmosphere of ethylene.[43,44] With a minimal amount

(33) Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035−4043.
(34) Fukuzawa, S.; Matsuzawa, H.; Metoki, K. *Synlett* **2001**, 709−711.
(35) Krotz, A.; Helmchen, G. *Tetrahedron: Asymmetry* **1990**, *1*, 537−540.
(36) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582−7594.
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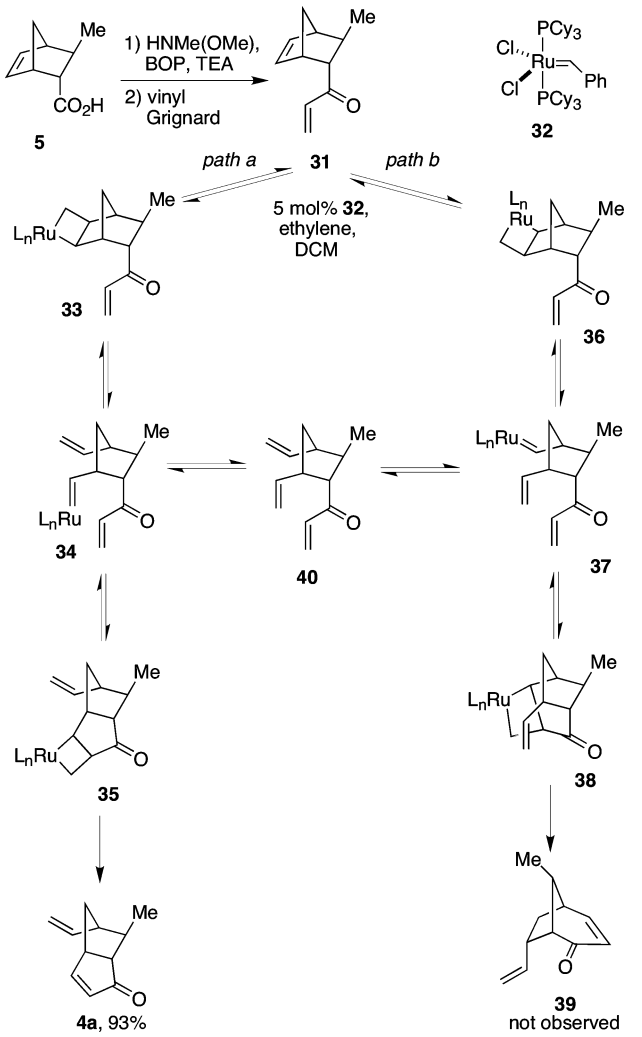
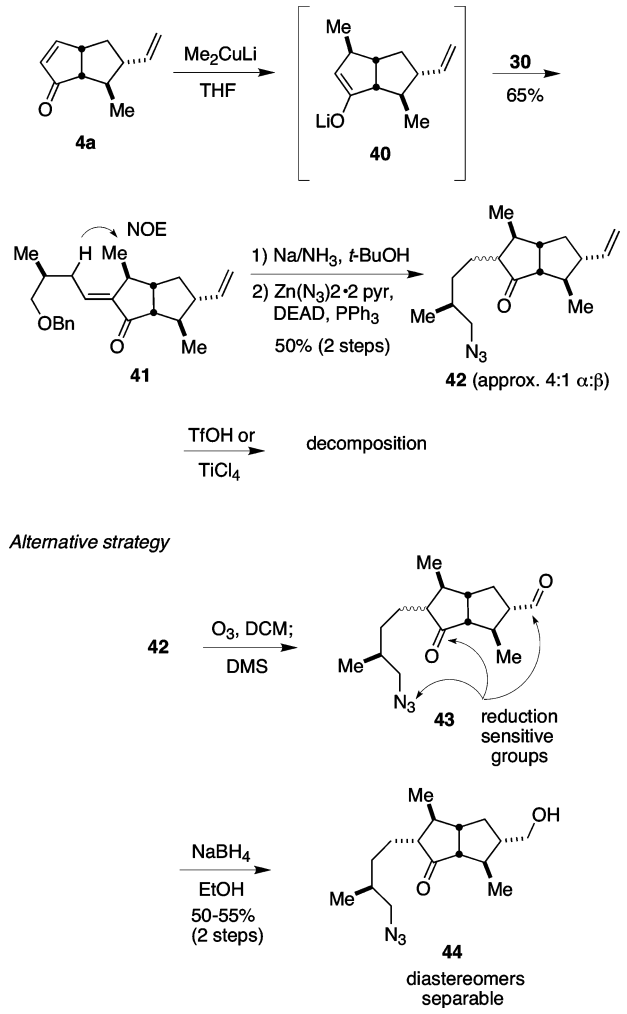
(44) Giessert, A. J.; Brazis, N. J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3819−3822.

Scheme 10



Scheme 11



of optimization, enone **4a** could be isolated in 93% yield using 5 mol % ruthenium catalyst **32** on multigram scale reactions.

Scheme 10 (path a) presents a possible blueprint for this reaction. Metallocycloaddition of **32** onto the endocyclic olefin of **31** generates metallocyclobutane **33**, which upon retro-cycloaddition provides alkylidene **34**. A second metallocycloaddition onto the enone olefin provides metallocyclobutane **35**, which again undergoes retro-cycloaddition to provide the targeted enone **4a**. The yield of **4a** is better than tripled when changing the saturation of the solvent and reaction atmosphere from argon to ethylene. Apparently having an excess of ethylene present in the reaction allows for the recycling of unproductive intermediates (i.e., those leading to polymers or other byproducts). Scheme 10 (path b) provides an example of one untoward possibility. In addition, dimeric or oligomeric materials can be reverted back to monomeric alkylidene intermediates capable of entering the pathway depicted in Scheme 10 en route to desired **4a**. This complex equilibrium of intermediates ultimately proceeds toward what is likely the most thermodynamically stable component, **4a**.

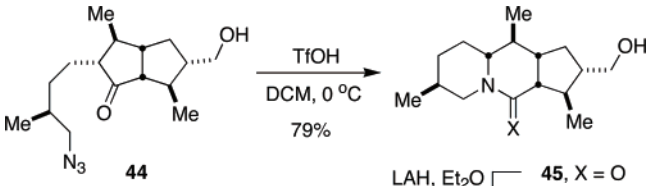
The successful incorporation of a tandem ring-opening/ring-closing metathesis in place of an ozonolysis/aldol route proved to increase the efficiency and ease of bicyclic enone synthesis tremendously. In only three steps, **5** was converted to **4a** in ca. 80% overall yield (compared to seven steps, 27% overall yield using the ozonolysis/aldol strategy). Multigram quantities of **4a** were readily produced with relative ease.

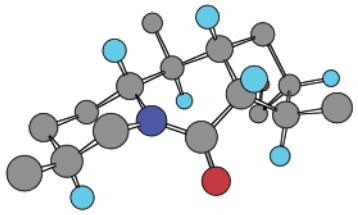
Completion of Indolizidine 251F Synthesis

As developed in the model study, it was envisioned that a one-pot conjugate addition/aldol reaction would install the exo methyl group and precursor to the azido side chain. However, the aldehyde component of the aldol reaction now had to incorporate the 3-methyl substituent with the proper stereochemistry. Thus, enone **4a** was reacted with Me_2CuLi to afford enolate **40**, which was quenched with chiral aldehyde **30** to provide dehydrated aldol adduct **41** (Scheme 11). The aldol adduct was isolated as a single olefinic isomer in 65% yield. The geometry of the newly formed olefin was investigated using 2D NMR techniques. With a NOESY experiment, it was found that an NOE existed between the newly installed exo methyl group and the allylic enone protons (Scheme 11). For these groups of protons to be within NOE proximity requires that the exocyclic enone olefin have the *E* configuration shown.

Following the protocol developed above, **41** was converted to the azido ketone Schmidt precursor **42** (Scheme 11). The multipurpose Na/NH_3 reduction converted **41** to the corresponding reduced alcohol (not shown) as a ca. 4:1 mixture of inseparable diastereomers epimeric at the α position. The major isomer was presumed to be that derived from exo protonation, placing the side chain in an endo orientation. A subsequent

Scheme 12





ball and stick depiction of the X-ray structure of lactam **45** showing selected protons

Mitsunobu reaction[32] transformed the primary alcohol to the corresponding azide **42** (50% yield, two steps), here obtained as an inseparable 4:1 mixture of diastereomers. With the necessary functional groups in place, the key intramolecular Schmidt reaction was then examined. Treating azido ketone **42** with either TfOH or $TiCl_4$ resulted only in apparent decomposition of the olefin functionality. None of the desired cyclized lactam product was detected.

Because the olefin was serving as a masked hydroxymethylene equivalent and given the earlier success in transforming an −OTIPS protected analogue into the lactam (Scheme 8), it was proposed that conversion to its oxidized analogue might be more consistent with a successful azido-Schmidt reaction. Toward this end, olefin **42** was reacted with ozone followed by dimethyl sulfide (DMS) to afford aldehyde **43** (ca. 70% yield). At this juncture, a few experiments were conducted on **43** to determine whether this substrate was a viable Schmidt substrate. Treatment of **43** with TfOH resulted in the detection of a lactam product (^{1}H and ^{13}C NMR); however, the reaction resulted in a variety of unidentified impurities, and attention was then directed at carrying out the Schmidt reaction on alcohol **44**. Caution was exercised with this reduction, though, as once **43** was produced, three functional groups capable of undergoing reduction were present. Reduction of either the azide or ketone eliminates one of the functional groups necessary for the Schmidt reaction. Fortunately, addition of 1 equiv of $NaBH_4$ chemoselectively reduced the aldehyde in the presence of both ketone and azide to afford alcohol **44** (50−55% yield for the two-step ozonolysis/reduction sequence). In addition, conversion of the 4:1 diastereomeric mixture of olefin **42** to alcohol **44** allowed for facile chromatographic separation of the diastereomers.

Once again, examination of the key intramolecular Schmidt reaction, this time with alcohol **44**, commenced. Treatment of **44** with excess TfOH proceeded smoothly and yielded the ring-expanded Schmidt product **45** in 79% yield (Scheme 12). Lactam **45** was crystallized, and X-ray analysis confirmed that the tricyclic structure and relative stereochemistry of this compound reflected those of **251F**.

Reduction of lactam **45** to the corresponding amine represented the final step of the synthetic sequence, and as expected, LAH reduction generated alkaloid **1** in 86−100% yield (Scheme 12). Synthetic 251F was identical in all respects to published spectra.[7,8]

Summary

In conclusion, a study ending in a racemic synthesis of 3-desmethyl **251F** allowed for the development of chemistry that ultimately culminated in an asymmetric total synthesis of alkaloid **251F**. Each synthesis was initiated with a stereoselective Diels−Alder reaction that established four consecutive stereogenic centers. Integral to both syntheses was the efficient construction of a key bicyclic enone intermediate. Preliminary studies focused on an ozonolysis/olefination/aldol method, and a more streamlined second-generation route was developed utilizing a tandem metathesis strategy. At seven steps and 27% overall yield, the ozonolysis/aldol strategy toward enone **4b** proved satisfactory. However, replacing this route with a domino metathesis strategy better than halved the number of steps (three total) and tripled the yield (80%) in route to the analogous enone **4a**. In general, this skeletal rearrangement reaction could prove to be a highly useful tool in the synthesis of substituted diquinane substrates from readily available [2.2.1] bicyclic systems. Key to both syntheses was the use of an intramolecular Schmidt reaction, which delivered the core tricyclic system, on advanced intermediates. Overall, the asymmetric total synthesis of **251F** proceeded in 13 steps with an overall yield of ca. 5−8%. Approximately 100 mg of the natural product was produced in this way—this amount is roughly equivalent to the amount that would have been isolated using current techniques from 30 000 frogs! Given this healthy supply of **251F**, the unknown biological properties of the alkaloid are currently under delineation.

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Supporting Information Available: Experimental procedures and compound characterizations (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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