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A General, Convergent Strategy for the Construction of Indolizidine Alkaloids: Total Syntheses of (−)-Indolizidine 223AB and Alkaloid (−)-205B†

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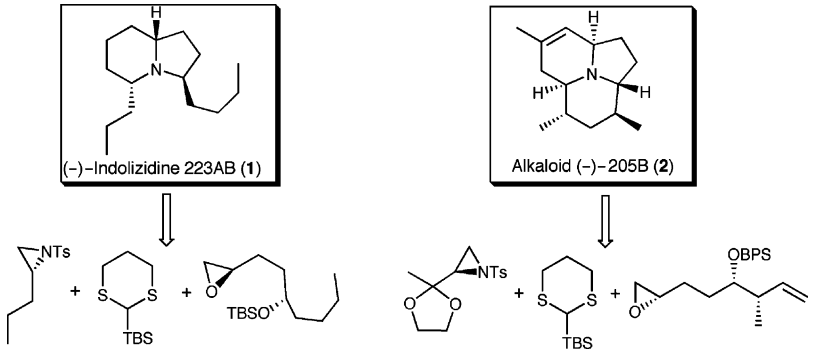

N-Toluenesulfonyl aziridines comprise effective second electrophiles in the solvent controlled three-component linchpin union of silyl dithianes for the stereocontrolled convergent elaboration of protected 1,5-amino alcohols. This tactic, in conjunction with a one-flask sequential cyclization, constitutes an effective general strategy for the construction of indolizidine and related alkaloids, illustrated here with the total syntheses of (−)-indolizidine 223AB (**1**) and alkaloid (−)-205B (**2**).

Introduction

In 1965, Corey and Seebach introduced the use of 1,3-dithianes as important umpolung linchpins in organic synthesis.[1] This tactic for over 40 years has become a mainstay for the union of both simple and complex fragments.[2] A wide range of electrophiles, including alkyl halides, aldehydes, and epoxides, react smoothly with the derived acylanion equivalents.[3] In 1997, on the basis of the precedent by Tietze,[4] we reported a variant of 1,3-dithiane chemistry, specifically the use of silyl 1,3-dithianes as a tactic for the one-flask multicomponent union of diverse epoxides, exploiting a solvent controlled Brook rearrangement,[5] to access differentially protected monosilyl 1,5-diol moieties with precise stereocontrol (Scheme 1). Initially

† This paper is dedicated to the memory of professor Kenji Koga (Tokyo University), scholar, gentleman, and friend.

(1) (a) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075. (b) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

(2) Reviews: (a) Seebach, D. *Synthesis* **1969**, 17. (b) Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357. (c) Page, P. C. B.; Van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643. (d) Kolb, M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 5, p 2983. (e) Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147.

(3) (a) Smith, A. B., III; Condon, S. M.; McCauley, J. A. *Acc. Chem. Res.* **1998**, *31*, 35 and references therein. (b) Smith, A. B., III; Lodise, S. A. *Org. Lett.* **1999**, *1*, 1249. (c) Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 191. (d) Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 196. (e) Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *J. Am. Chem. Soc.* **2003**, *125*, 350. (f) Smith, A. B., III; Zhu, W.; Shirakami, S.; Sfouggatakis, C.; Doughty, V. A.; Bennett, C. S.; Sakamoto, Y. *Org. Lett.* **2003**, *5*, 761. (g) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365.

(4) Tietze, L. F.; Geissler, H.; Gewert, J. A.; Jakobi, U. *Synlett* **1994**, 511.

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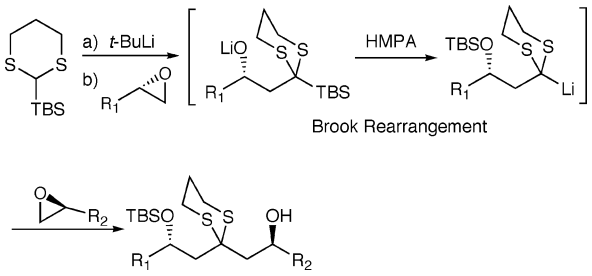
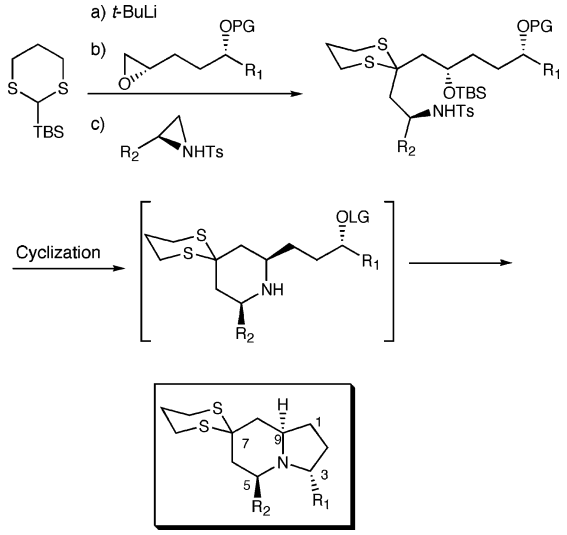
SCHEME 1



designed for the construction of the spiroketal segments of the highly potent antitumor spongistatins, this multicomponent coupling tactic has been employed for the gram-scale synthesis of a number of valuable advanced synthetic intermediates in several completed and ongoing synthetic ventures in our laboratory.[6]

To advance further the utility of this chemistry, we recently explored the use of nitrogen containing electrophiles, such as *N*-Ts aziridines,[7] as the second electrophile to access protected 1,5-amino alcohols (Scheme 2).[8] We reasoned that the resulting 1,5-amino alcohols could be exploited as advanced intermediates for the construction of 3,5-disubstituted indolizidine rings, via subsequent intramolecular alkylation of the 1,5-amino alcohols, wherein the nitrogen would act as a nucleophile, attacking electrophilic carbons bearing activated oxygen substituents. The dithiane moiety would also play a significant role in the subsequent construction of the bicyclic indolizidine system by inducing a conformation that would accelerate the cyclization (i.e., Thorpe−Ingold effect).[9] From the synthetic perspective, this convergent synthetic strategy should hold considerable promise, given the flexibility of both the structure and/or absolute configurations of the epoxide and aziridine coupling partners, thereby permitting the stereoselective synthesis of all possible diastereomers, as well as numerous analogues of this alkaloid class. Functionalization at C(6), C(7), or C(8) of the indolizidine system would also be possible by employing the reinstated C(7) carbonyl upon removal of the dithiane. This strategy would thus take full advantage of the versatility of the 1,3-dithiane group: first, as a linchpin in the bisalkylation step; second, as an auxiliary augmenting the cyclization step; and third, as a carbonyl protecting group.

SCHEME 2



Indolizidine alkaloids, disubstituted at the C(3) and C(5) positions, comprise the first in class to have been discovered, principally as components in the skin extracts of neotropical frogs.[10] Possessing a multitude of interesting biological activities such as blocking nicotinic receptor-channels, many alkaloids in this class have become attractive synthetic targets. Among these, (−)-indolizidine 223AB (**1**, Figure 1) has been constructed 10 times, and as such it serves as an excellent test case for any new synthetic strategy.[11]

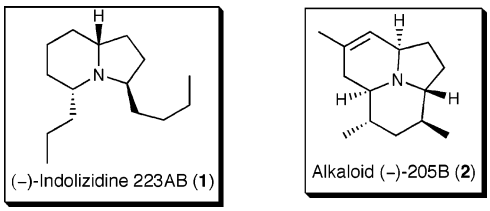


FIGURE 1. Structures of (−)-indolizidine 223AB (**1**) and alkaloid (−)-205B (**2**).

Alkaloid (−)-205B (**2**), a structurally more complex alkaloid, also isolated from the skin of a neotropical frog (*Dendrobates pumilo*) endemic to Panama, possesses an unusual tricyclic 8b-azaacenaphthylene ring system,[12] which embodies a similar 3,5-

(5) (a) Smith, A. B., III; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925. Also see: (b) Smith, A. B., III; Pitram, S. M.; Boldi, A. M.; Gaunt, M. J.; Sfouggatakis, C.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 14435.

(6) (a) Smith, A. B., III; Zhuang, L.; Brook, C. S.; Boldi, A. M.; McBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; Verhoest, P. R.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667. (b) Smith, A. B., III; Zhuang, L.; Brook, C. S.; Lin, Q.; Moser, W. H.; Trout, R. E. L.; Boldi, A. M. *Tetrahedron Lett.* **1997**, *38*, 8671. (c) Smith, A. B., III; Lin, Q.; Nakayama, K.; Boldi, A. M.; Brook, C. S.; McBriar, M. D.; Moser, W. H.; Sobukawa, M.; Zhuang, L. *Tetrahedron Lett.* **1997**, *38*, 8675. (d) Smith, A. B., III; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001. (e) Smith, A. B., III; Doughty V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783. (f) Smith, A. B., III; Pitram, S. M.; Fuertes, M. J. *Org. Lett.* **2003**, *5*, 2751.

(7) For early examples of *N*-Ts aziridine ring opening reactions by lithiated dithiane anions, see: (a) Bates, G. S. *J. Chem. Soc. Chem. Commun.* **1979**, 161. (b) Howson, W.; Osborn, H. M. I.; Sweeney, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2439. (c) Mao, H.; Joly, G. J.; Peeters, K.; Hoornaert, G. J.; Compernolle, F. *Tetrahedron* **2001**, *57*, 6955. (d) Reich, H. J.; Sanders, A. W.; Fiedler, A. T.; Bevan, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 13386.

(8) Prior to the work reported here, there was one report of an intramolecular linchpin reaction between bis(methylthio)trimethylsilylmethane and 1,4-biselectrophile, 1,2-epimino-3,4-epoxy-(*N*-Ts)butane, in which the aziridine moiety played the role as the second electrophile: Harms, G.; Schaumann, E.; Adiwidjaja, G. *Synthesis* **2001**, 577.

(9) (a) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224. (b) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. (c) Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305.

(10) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspective*; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol. 13, p 1.

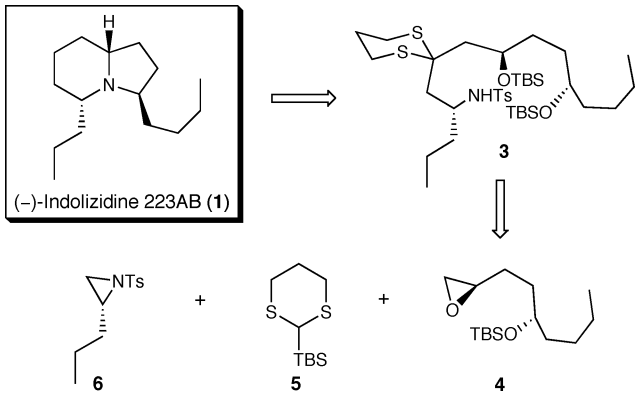
(11) (a) Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M. M.; Meyers, C. W. *Taxicon* **1978**, *16*, 163. (b) Tokuyama, T.; Nishimori, N.; Karle, I. K.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986**, *42*, 3453. For the synthesis of (−)-indolizidine 223AB, see: (c) Royer, J.; Husson, H. P. *Tetrahedron Lett.* **1985**, *26*, 1515. (d) Taber, D. F.; Deker, P. B.; Silverberg, L. J. *J. Org. Chem.* **1992**, *57*, 5990. (e) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 5178. (f) Fleurant, A.; Célérier, J. P.; Lhommet, G. *Tetrahedron: Asymmetry* **1993**, *4*, 1429. (g) Muraoka, O.; Okumura, K.; Maeda, T.; Tanabe, G.; Momose, T. *Tetrahedron: Asymmetry* **1994**, *5*, 317. (h) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717. (i) Takahat, H.; Bandoh, H.; Momose, T. *Heterocycles* **1995**, *41*, 1797. (j) Momose, T.; Toshima, M.; Koike, Y.; Toyooka, N.; Hirai, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, *9*, 1315. (k) Célimène, C.; Dhimane, H.; Lhommet, G. *Tetrahedron* **1998**, *54*, 10457. (l) Lee, E.; Jeong, E. J.; Min, S. J.; Hong, S.; Lim, J.; Kim, S. K.; Kim, H. J.; Choi, B. G.; Koo, K. C. *Org. Lett.* **2000**, *2*, 2169.

disubstituted indolizidine system encased within the skeleton. To date, only one report on the synthesis of this more complex alkaloid has appeared. Toyooka and co-workers in 2003 disclosed the synthesis of (+)-205B, the un-natural antipode, thereby establishing the absolute configuration.[13] A central feature of the Toyooka synthesis involved a series of Michael-type additions to enaminoesters; the longest linear sequence required 30 steps from known (*S*)-6-(*tert*-butyldiphenylsilyloxymethyl)-piperidin-2-one. Although the biological properties of the naturally occurring congener of 205B remain unknown, presumably due to lack of material, the unnatural (+)-antipode was reported recently to be a potent antagonist of the α7 nicotinic receptor.[14] In this, a full account, we present the total syntheses of both (−)-indolizidine 223AB (**1**) and alkaloid (−)-205B (**2**).[15]

Results and Discussions

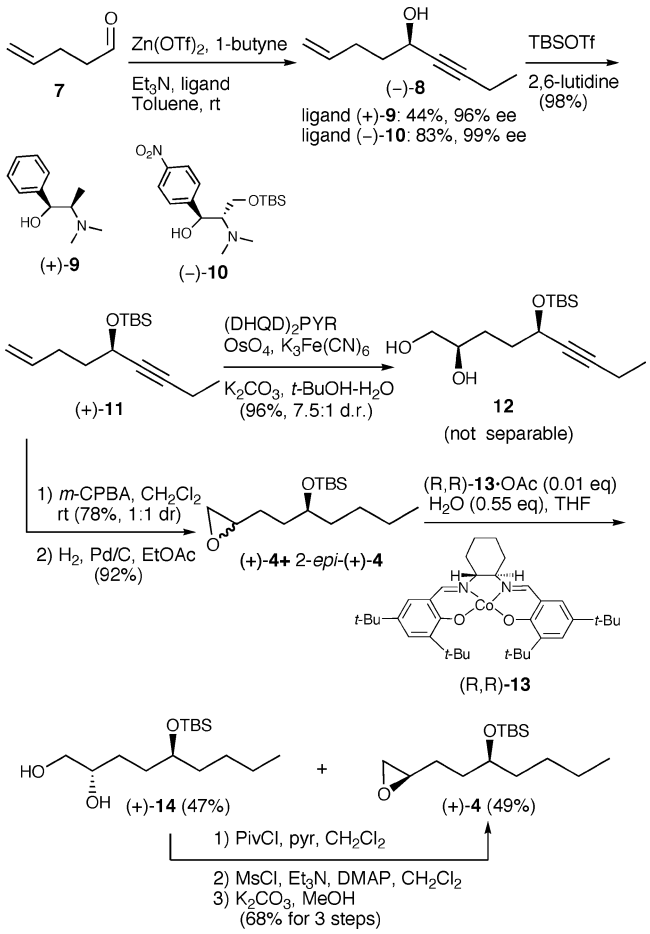
Total Synthesis of (−)-Indolizidine 223AB: Retrosynthetic Analysis. Our synthetic approach for the prototype 3,5-disubstituted indolizidine alkaloid 223AB (**1**) calls for the construction of protected amino alcohol **3**, via a solvent controlled, three-component linchpin coupling of silyl dithiane **5** with epoxide **4** and known aziridine **6**,[16] followed by sequential conversion to the indolizidine alkaloid (Scheme 3).

SCHEME 3



Epoxide 4. We began this venture with the construction of epoxide **4** (Scheme 4). Toward this end, propargylic alcohol (−)-**8**[17] was prepared from commercially available 4-pentenal **7** via the Carreira protocol.[18] Using (+)-*N*-methylephedrine (**9**) as a chiral ligand, we obtained (−)-**8** in 44% isolated yield and 96% ee (chiral HPLC). Better results were obtained by employing the Jiang chiral ligand (−)-**10**.[19] In this case, (−)-**8** was obtained in 83% yield and 99% ee. Protection of the hydroxyl

SCHEME 4



functionality as the TBS ether, followed by Sharpless asymmetric dihydoxylation,[20] furnished diol **12** as a diastereomeric mixture (ca. 7.5:1), which proved quite difficult to separate, either at this stage or at the stage of the corresponding epoxide. We therefore turned to the Jacobsen hydrolytic kinetic resolution (HKR)[21] to obtain pure epoxide (+)-**4** for the coupling protocol. Epoxidation of (+)-**11** without stereocontrol employing *m*-CPBA, followed by complete hydrogenation of the triple bond, furnished (+)-**4** and 2-*epi*-(+)-**4**, as a diastereomeric mixture (ca. 1:1). Jacobsen-HKR employing (*R*,*R*)-**13**·OAc as the catalyst readily led to the desired epoxide (+)-**4**, along with diol (+)-**14**, both diastereomerically pure (e.g., ^{1}H and ^{13}C NMR).[22] After separation by flash chromatography, diol (+)-**14** was transformed to (+)-**4** by chemoselective pivaloylation, followed in turn by mesylation of the secondary alcohol and ring closure employing potassium carbonate.

The Solvent Controlled, Three-Component Linchpin Union. With epoxide (+)-**4** and known aziridine (−)-**6** available, the latter readily prepared from (*D*)-norvaline in 2 steps,[16a] we

(12) (a) Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643. (b) Tokuyama, T.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *An. Asoc. Quim. Argent.* **1998**, *86*, 291.

(13) (a) Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3808. (b) Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Tetrahedron* **2004**, *60*, 6197.

(14) Tsuneki, H.; You, Y.; Toyooka, N.; Kagawa, S.; Kobayashi, S.; Sasaoka, T.; Nemoto, H.; Kimura, I.; Dani, J. A. *Mol. Pharmacol.* **2004**, *66*, 1061.

(15) For our initial disclosure on this work, see: Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2004**, *6*, 1493; **2005**, *7*, 3247.

(16) (a) Oppolzer, W.; Flaskamp, E.; Bieber, L. W. *Helv. Chim. Acta* **2001**, *84*, 141. (b) Oka, T.; Yasusa, T.; Ando, T.; Watanabe, M.; Yoneda, F.; Ishida, T.; Knoll, J. *Bioorg. Med. Chem.* **2001**, *9*, 1213.

(17) The absolute configuration was established by Kakisawa analysis of the Mosher esters of (−)-**8**: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(18) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.

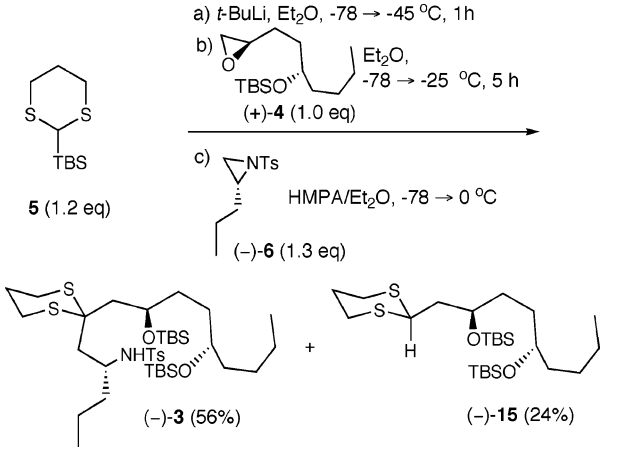
(19) (a) Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* **2002**, 1524. For preparation of (−)-**10**, see: (b) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451.

(20) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(21) (a) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147. (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776. (c) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.

(22) The relative and absolute configurations were confirmed by Kakisawa analysis of the Mosher esters of diol (+)-**14**; see ref 17.

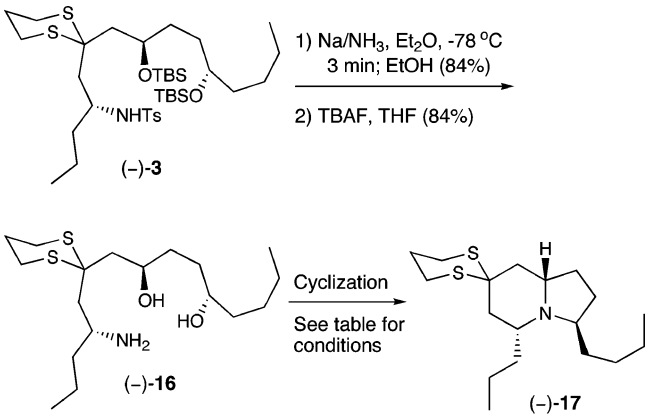
SCHEME 5



proceeded with the multicomponent union. Pleasingly, lithiation of dithiane **5** in Et_2O (−78 °C), followed in turn by addition of epoxide (+)-**4**, warming to −25 °C over a period of 1 h, stirring for an additional 4 h at −25 °C, and then addition of aziridine (−)-**6** in Et_2O containing HMPA (0.65 equiv) to effect the solvent controlled Brook rearrangement furnished (−)-**3** in 56% isolated yield, accompanied by dithiane (−)-**15** (24%), the latter not having undergone reaction with aziridine (−)-**6** (Scheme 5). Best results were obtained employing rapid warming to 0 °C after addition of aziridine (−)-**6**. Slower warming over 1−2 h resulted in capricious behavior (ca. 30−50%), in conjunction with formation of large amounts of (−)-**15**. The structure of (−)-**3** was secured by ^1H and ^{13}C NMR analysis.

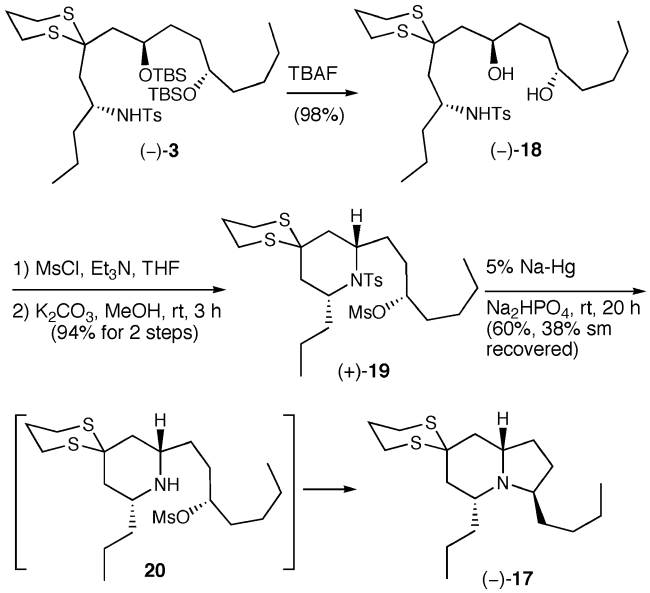
Development of a One-Flask Sequential Construction of the 3,5-Disubstituted Indolizidine Skeleton. Having achieved elaboration of the carbon backbone of (−)-indolizidine 223AB (**1**), we now faced the task of generating the bicyclic indolizidine ring. Toward this end, aminodiol (−)-**16**, obtained after removal of the Ts group (Na/NH_3) and the TBS groups (TBAF), was subjected to Mitsunobu or related protocols (Scheme 6).[23] Unfortunately, all attempts to convert (−)-**16** directly to

SCHEME 6



Entry	Conditions	Yield of (–)-**17**
1	CCl_4, PPh_3, Et_3N CH_3CN, rt	12%
2	DEAD, PPh_3 THF, rt	13%
3	I_2, PPh_3, Imidazole Toluene, reflux	0%

SCHEME 7

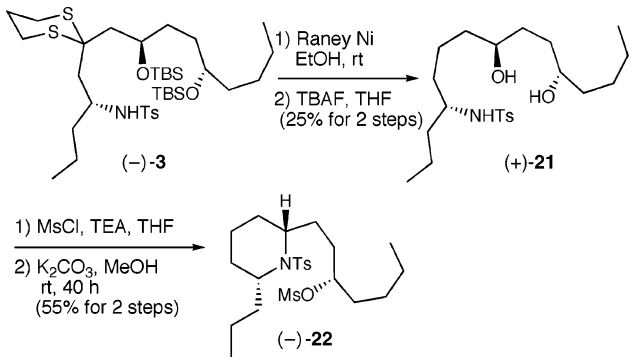


indolizidine (−)-**17** however proved ineffective; at best (−)-**17** was isolated in 13% yield. Removal of the dithiane prior to cyclization did not improve this transformation.

Our initial failure to achieve an effective one-flask cyclization led us to explore a stepwise scenario (Scheme 7). Pleasingly, monocycle (+)-**19** could be obtained in excellent yield (94%) upon removal of the TBS groups and in turn bismesylation and treatment of the resultant bismesylate with potassium carbonate in MeOH. Equally encouraging, treatment of (+)-**19** with 5% Na−Hg led selectively to removal of the *N*-Ts group in the presence of both the dithiane and *O*-mesylate moiety to furnish **20**, which in turn underwent the requisite second cyclization to furnish indolizidine (−)-**17** in 60% yield.

Crucial for efficient cyclization was the dithiane moiety (i.e., Thorpe−Ingold effect).[9] Without the dithiane, cyclization of (+)-**21** proved extremely slow (40 h), furnishing (−)-**22** at best in 55% yield (Scheme 8), compared to the similar two step sequence of (−)-**18** to (+)-**19** (Scheme 7), which proceeded in 94% yield.

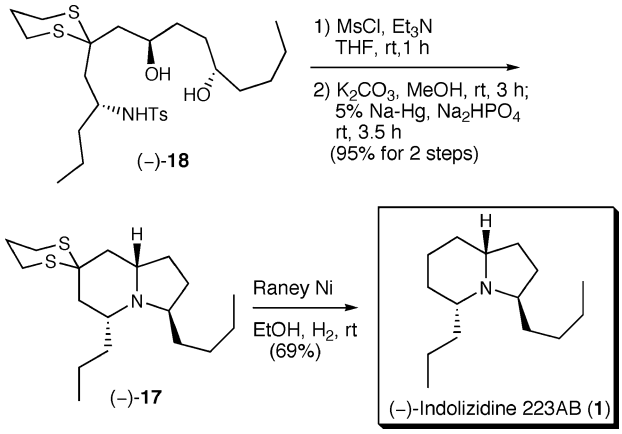
SCHEME 8



Careful additional experimentation revealed that sequential cyclization sequence could be conducted in a highly efficient manner in a single flask (Scheme 9). For example, bismesylation

(23) (a) Stoilvoa, V.; Trifonov, L. S.; Orahovats, A. S. *Synthesis* **1979**, 105. (b) Mereyala, H. B.; Gaddam, B. R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2187. (c) Bernotas, R. C.; Cube, R. V. *Tetrahedron Lett.* **1991**, *32*, 161.

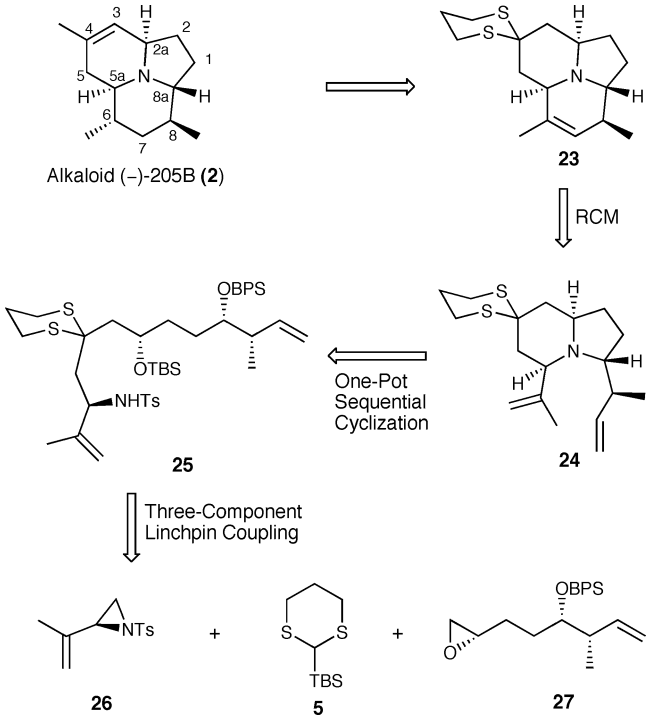
SCHEME 9



followed in turn without purification by treatment with potassium carbonate in MeOH for 3 h, and then addition of excess sodium amalgam (5%) directly to the reaction mixture furnished (−)-**17** in excellent yield (95%). Reductive removal of the dithiane with Raney Ni completed the synthesis of (−)-indolizidine 223AB (**1**), identical in all respects (e.g., 500 MHz ^{1}H, 125 Hz ^{13}C NMR, IR, HRMS, and optical rotation) with the spectra derived from synthetic (−)-indolizidine (**1**).[24]

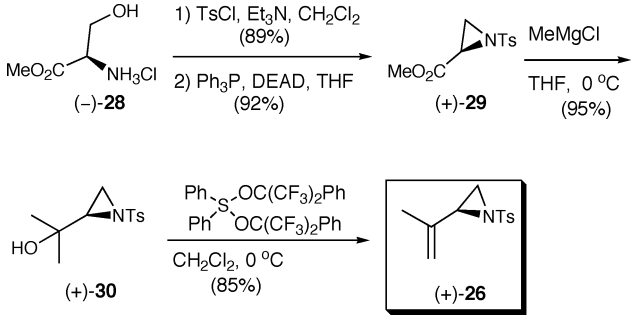
Total Synthesis of Alkaloid (−)-205B: An Initial Synthetic Plan. Given the successful completion of (−)-indolizidine 223AB, we envisioned a similar approach to the structurally more complex tricyclic alkaloid (−)-205B (**2**); a three component linchpin coupling of TBS dithiane **5** with epoxide **27** and aziridine **26**, followed by our recently devised one-flask sequential cyclization of **25**, would deliver the requisite 3,5-disubstituted indolizidine ring embedded in alkaloid (−)-205B (Scheme 10). A successful ring closing metathesis (RCM) would

SCHEME 10



then secure the 8b-azaacenaphthylene skeleton. To complete the synthesis, we would next face the task of introducing the C(6) axial methyl, removing the dithiane, and incorporating of the 3,4-trisubstituted olefin. The latter transformation was employed by Toyooka et al. in their synthesis of the un-natural enantiomer of alkaloid 205B (**2**).[13] That introduction of the C(6) axial methyl substituent might prove problematic was clearly recognized (vide infra).

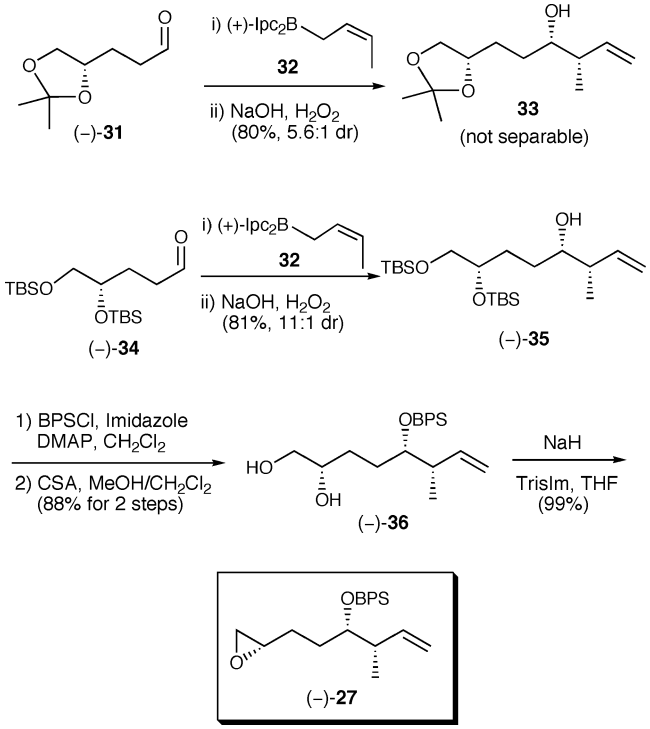
SCHEME 11



Construction of Linchpin Components: Aziridine 26 and Epoxide 27. We initiated the synthesis of alkaloid (−)-205B (**2**) with construction of aziridine **26** (Scheme 11). Tosylation of the nitrogen of commercially available serine methyl ester hydrochloride (−)-**28**, followed by Mitsunobu ring closure, furnished aziridine (+)-**29**,[25] which upon treatment with MeMgCl led to tertiary alcohol (+)-**30**. Dehydration with Martin sulfurane[26] afforded aziridine (+)-**26**; the overall yield for the four-step sequence was 66%.

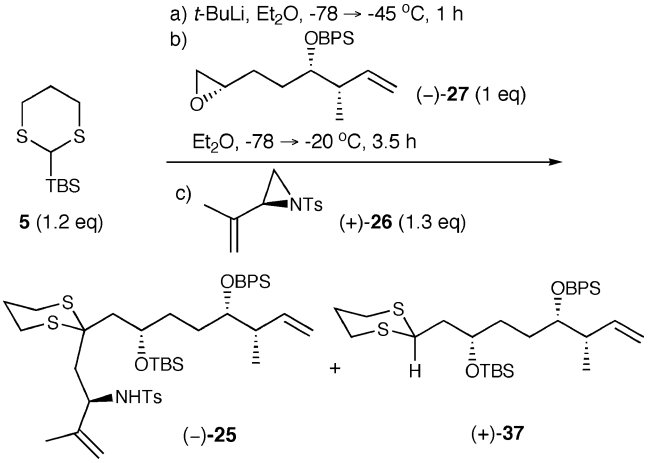
To construct epoxide **27**, we turned to Brown asymmetric crotylation[27] of known aldehyde (−)-**31**[28] employing (*Z*)-crotylborane **32** to provide homoallylic alcohol **33** in good yield (80%), albeit as an inseparable diastereomeric mixture (5.6:1) of secondary alcohols (Scheme 12). With the enantiomeric

SCHEME 12



aldehyde (+)-**31**, a similar diastereoselectivity (ca. 6:1) was observed under the same reaction conditions, suggesting that we were not dealing with a mismatched case. To eliminate the

TABLE 1. Solvent Controlled Three-Component Linchpin Union with Aziridine (+)-26



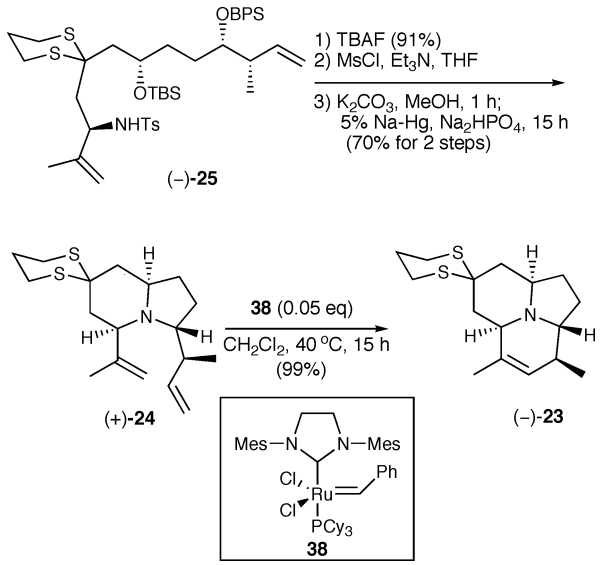
entry	conditions in step C	yield (%) (−)-**25**	yield (%) (+)-**37**
1	Et_2O, HMPA (3 equiv) 10 min at −60 °C then 0 °C to rt over 12 h	15	40
2	THF, HMPA (0.8 equiv) 10 min at −78 °C then, 14 h at −25 °C	12	63
3	THF, 10 min at −78 °C then, 5 h at 0 °C	33	46

possibility of chelation with the existing chiral center,[29] we replaced the acetonide with TBS groups. Pleasingly, Brown crotylation of known aldehyde (−)-**34**[30] with (*Z*)-crotylborane **32** furnished a significantly improved diastereomeric mixture (ca. 11:1). Protection of the resulting secondary alcohol (−)-**35** as BPS ether, followed by removal of the TBS groups, next led to diol (−)-**36**. Completion of epoxide (−)-**27** was then achieved via an efficient one-flask Fraser−Reid diol to epoxide transformation.[31]

The Solvent Controlled Three-Component Linchpin Union. With aziridine (+)-**26** and epoxide (−)-**27** in hand, we executed the multicomponent union (Table 1). In this case, use of HMPA resulted at best in low yields (entries 1 and 2). Somewhat better results were obtained with THF as the cosolvent to trigger the Brook rearrangement. However, the yield of coupling product (−)-**25** remained moderate (33%), accompanied by a significant amount of dithiane (+)-**37** (entry 3). Notwithstanding the moderate yield of (−)-**25**, we continued with the synthesis. We will return to this linchpin union in our second-generation approach (vide infra).

Elaboration of the 8b-Azaacenaphthylene Ring System. Sequential closure of the two rings that comprise the 3,5-disubstituted indolizidine ring, embedded in the 8b-azaacenaphthylene tricyclic ring of alkaloid (−)-**2**, was next achieved in good yield (70%) via the previously devised sequential cyclization protocol (Scheme 13). Equally pleasing, RCM with the second generation Grubbs catalyst **38**[32] proved highly efficient, furnishing tricyclic amine (−)-**23** in near quantitative yield.

SCHEME 13



Installation of the Axial Methyl Group at C(6): A Difficult Transformation. From the outset, we recognized that reduction of the trisubstituted olefin in (+)-**39** derived from (−)-**23** (Scheme 14) would at best be difficult, given that molecular modeling of the ketone suggested a concave/convex conformation (**39A**) in favor of the more plane conformation (**39B**) by ca. 5 kcal/mol (Figure 2).

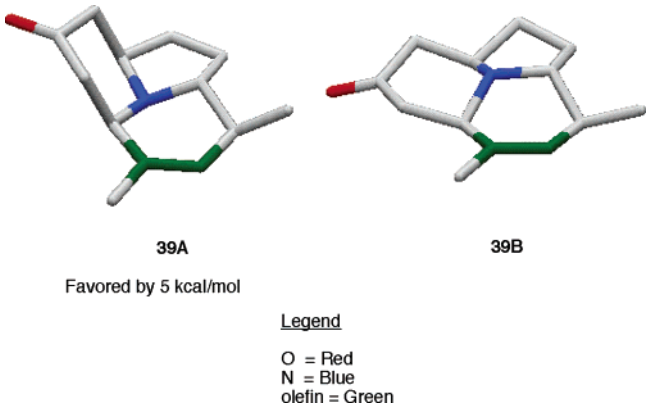


FIGURE 2. Comparison of two conformations of the hydrogenation substrate (+)-**39** (Monte Carlo conformational search, 1000 steps, chloroform GB/SA solvation model).

(24) We thank Professor Eun Lee, Seoul National University, for kindly providing the 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra of synthetic (−)-indolizidine 223AB.

(25) (a) Baldwin, J.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309. (b) Bergmeier, S. C.; Seth, P. P. *J. Org. Chem.* **1997**, *62*, 2671. (c) Fujii, N.; Nakai, K.; Tamamura, H.; Otaka, A.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1359.

(26) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

(27) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.

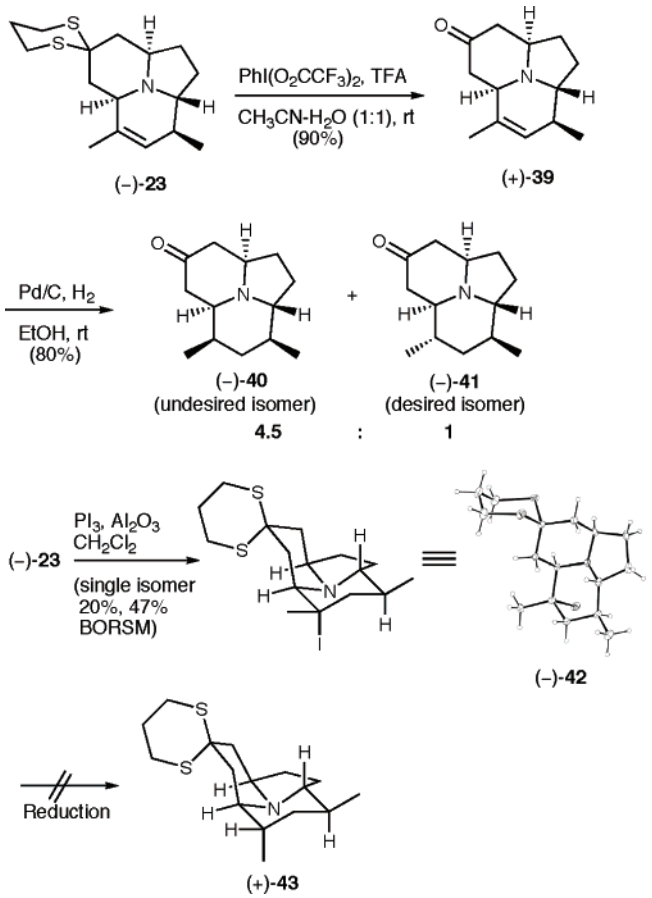
(28) Schmidt, U.; Lieberknecht, A.; Kazmaier, U.; Griesser, H.; Jung, G.; Metzger, J. *Synthesis* **1991**, 49.

(29) Berninger, J.; Koert, U.; Eisenberg- Höhl, C.; Knochel, P. *Chem. Ber.* **1995**, *128*, 1021.

(30) (a) Shimizu, A.; Nishiyama, S. *Tetrahedron Lett.* **1997**, *38*, 6011. (b) Chattopadhyay, S.; Mamdapur, V. R.; Chadha, M. S. *Tetrahedron* **1990**, *46*, 3667. Aldehyde (−)-**34** was prepared in 4 steps and 95% overall yield from commercially available ethyl (*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenoate (**i**): See Supporting Information for details.

We nonetheless felt compelled to explore the hydrogenation scenario. Removal of the dithiane moiety in (−)-**23** employing the Stork protocol[33] [e.g., bis(trifluoroacetoxy)-iodobenzene] furnished ketone (+)-**39**, which was subjected to hydrogenation (Scheme 14). Not surprisingly, the undesired epimer (−)-**40** was obtained as the major product (ca. 4.5:1).

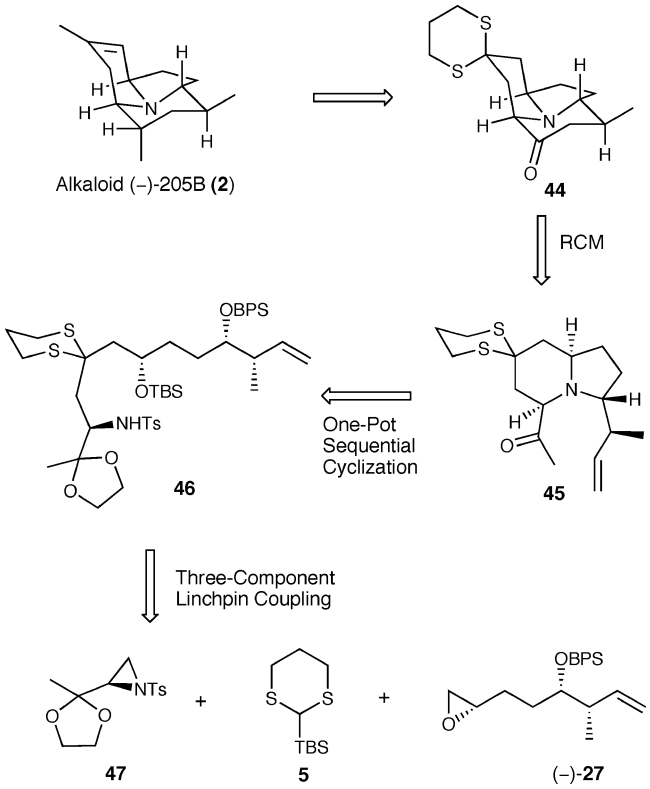
SCHEME 14



We also explored hydroiodination[34] of (−)-**23** with PI_3 followed by stereoselective reduction of the corresponding iodide (−)-**42** as a possible scenario to access (−)-**41**; unfortunately, none of the desired axial product was obtained. The structure and absolute configuration of iodide (−)-**42** were confirmed by X-ray crystallographic analysis.

A Second Generation Approach. Given that vinyl aziridine (+)-**26** proved less than an optimal second electrophile in the three-component linchpin union (Table 1), in conjunction with the inherent difficulty in installing the axial methyl group, we revised our synthetic plan. In particular, we envisioned that the C(6) axial methyl group might be installed employing ketone **44** given the anticipated attack from the less encumbered convex surface (Scheme 15). Ketone **44** in turn would be obtained via RCM of the corresponding kinetic enol ether derived from

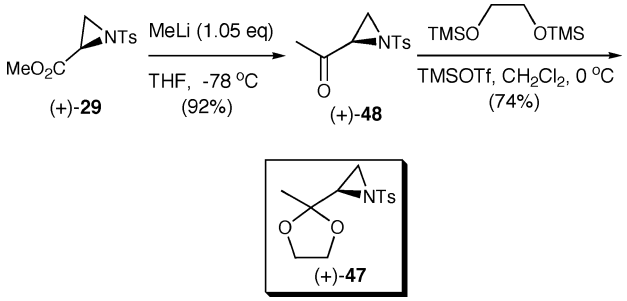
SCHEME 15



ketone **45**, the latter available again exploiting our three-component linchpin union, now employing aziridine **47**, followed by an effective one-flask sequential cyclization.

Aziridine **47** proved readily available from the previously prepared (+)-**29**, via treatment with MeLi (1.05 equiv) at −78 °C to furnish ketone (+)-**48** in excellent yield (92%); protection of the carbonyl as the ethylene ketal employing the Noyori protocol[35] then led to (+)-**47** (Scheme 16).

SCHEME 16



The Three-Component Linchpin Union with Aziridine (+)-47. As in the case of aziridine (+)-**26**, use of HMPA or DMPU to trigger the Brook rearrangement resulted only in poor yields (Table 2; entries 1−3). A solvent system comprising tetrahydrofuran, containing 3.2 equiv of 1,2-dimethoxyethane (DME), however led to a significant improvement, furnishing the three-component adduct (+)-**46** in 53% yield, albeit still mixed with 31% of (+)-**37**, the latter not having undergone the second alkylation (entry 5).

(31) (a) Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203. (b) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 8122.

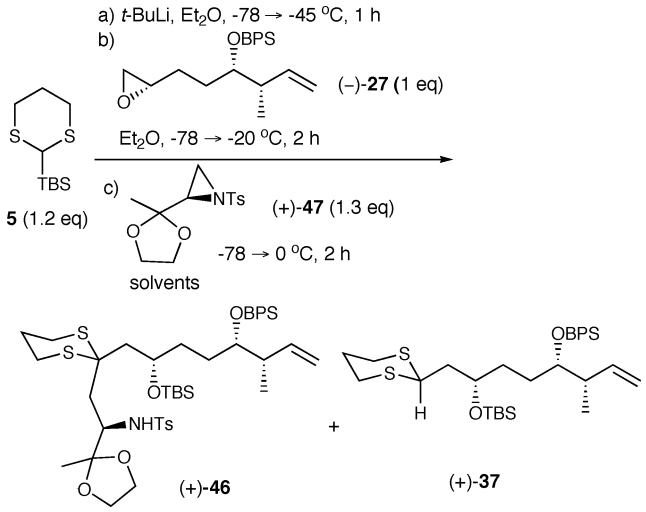
(32) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(33) (a) Fleming, F. F.; Funk, L.; Altundas, R.; Tu, Y. *J. Org. Chem.* **2001**, *66*, 6502. (b) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

(34) Kropp, P. J.; Daus, K. A.; Tubergen, M. W.; Kepler, K. D.; Wilson, V. P.; Craig, S. L.; Baillargeon, M. M.; Breton, G. B. *J. Am. Chem. Soc.* **1993**, *115*, 3071.

(35) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

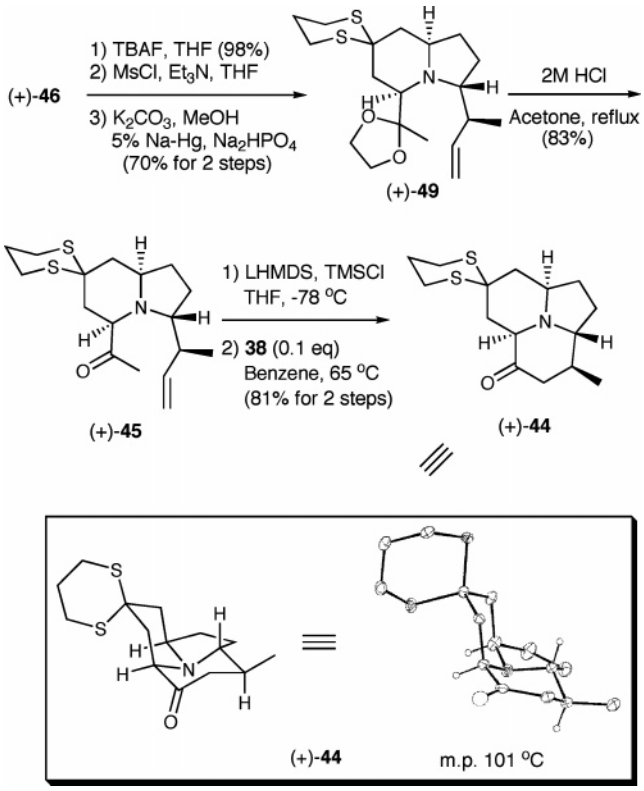
TABLE 2. Three-Component Linchpin Union with Aziridine (+)-47



entry	solvents	yield (%) (+)-46	yield (%) (+)-37
1	Et_2O, HMPA (0.7 equiv)	6	56
2	THF, HMPA (0.4 equiv)	12	70
3	THF, DMPU (1 equiv)	no desired product	
4	THF	39	24
5	THF, DME (3.2 equiv)	53	31

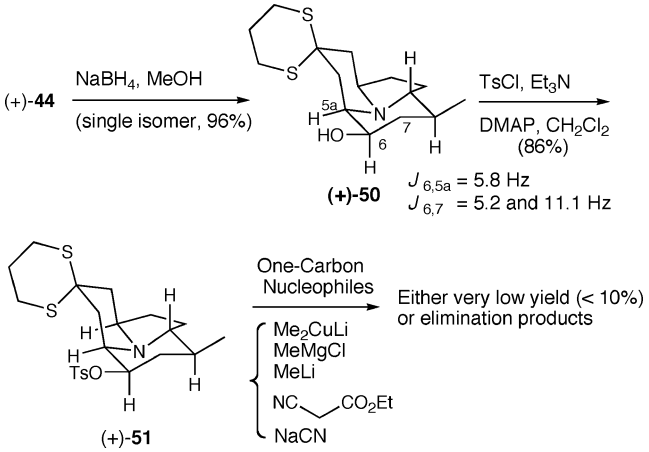
Ring Closing Metathesis Construction of 8b-Azacenaphthylene Ring System. Removal of the two silyl groups in (+)-**46** with TBAF next furnished the corresponding diol, which was subjected to the one-flask sequential cyclization protocol (Scheme 17); pleasingly, indolizidine (+)-**49** was obtained in 70% yield. Acid promoted removal of the acetonide then provided ketone (+)-**45**, which upon treatment with lithium hexamethyldisilazide (LHMDS) in the presence of TMSCl furnished the kinetic silyl enol ether. RCM employing the second generation Grubbs catalyst (**38**) efficiently led to the requisite advanced tricyclic dithiane (+)-**44** as a beautiful crystalline solid (mp 101 °C) in 81% yield for the two steps.[36] Single-crystal X-ray analysis established both the structure and relative stereochemistry of (+)-**44**.

SCHEME 17



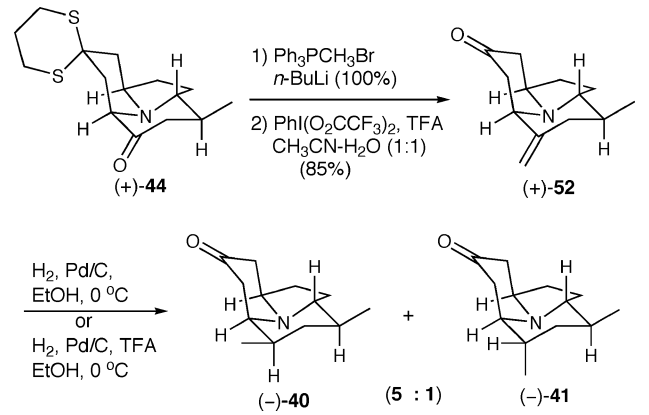
Stereoselective Installation of the C(6) Axial Methyl Group. To install the requisite axial methyl group at C(6) in (+)-**44** via an S_N2 tactic, equatorial alcohol (+)-**50** was prepared by reduction of (+)-**44** with $NaBH_4$; a single isomer resulted (Scheme 18). The stereogenicity of the newly generated secondary hydroxyl was secured by NMR analysis. Unfortunately, all attempts to displace the derived tosylate in (+)-**51** with a variety of nucleophiles either proceeded in low yield or furnished elimination products.

SCHEME 18



We next turned to the C(6) exomethylene derivative (+)-**52**, prepared from (+)-**44** via Wittig olefination, followed by removal of the dithiane (Scheme 19). Not surprisingly, hydrogenation again proceeded from the less hindered α face to furnish predominately the C(6) equatorial methyl congener (−)-**40** (ca. 5:1) under both neutral or acidic conditions.

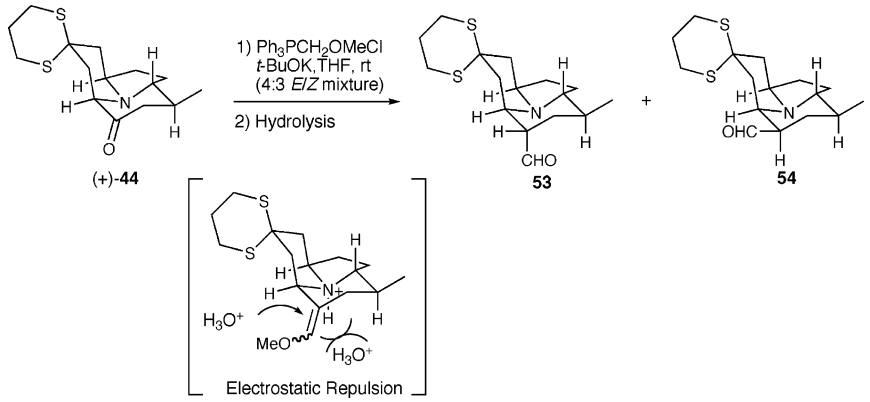
SCHEME 19



Undaunted, we explored the methyl enol ether derived from ketone (+)-**44**, reasoning that it might be possible to modulate

(36) (a) Okada, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 8023. (b) Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8029.

TABLE 3. Hydrolysis of Methyl Enol Ethers with HCl



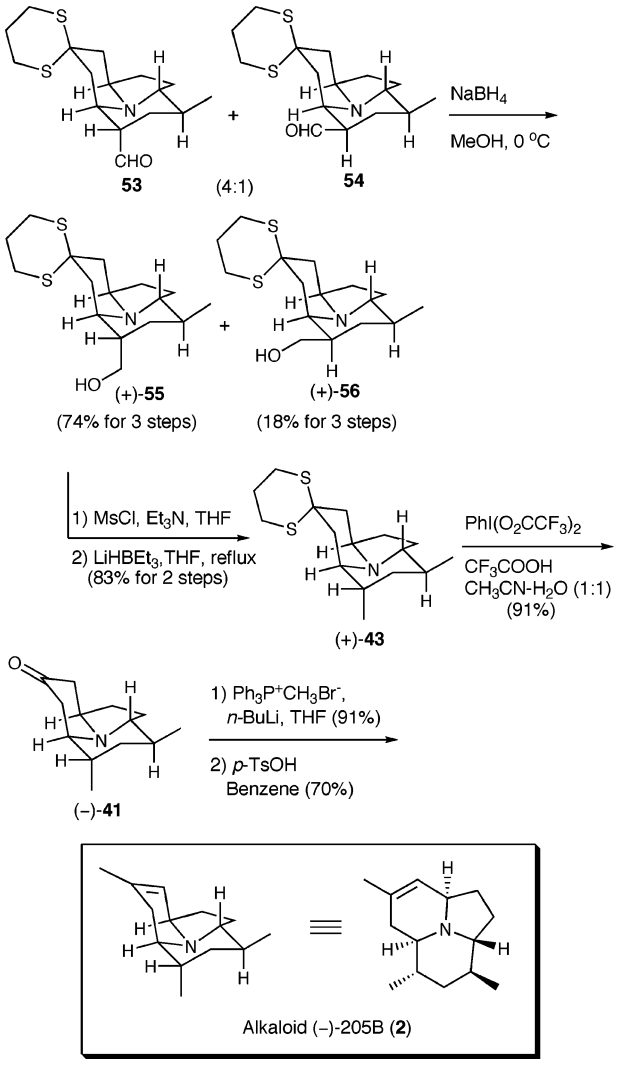
entry	conditions	temp (°C)	time (h)	**53**/**54**[a]	conversion[a] (%)
1	4 M HCl/THF (1/1)	23	12	1.2/1	100
2	6 M HCl/THF (1/1)	0	14	6/1	70
3	6 M HCl/THF (1/1)	0	24	4/1	93
4	6 M HCl/THF (1/1)	−20	45		0

[a] Determined by ^{1}H NMR on the crude reaction mixtures.

the direction of protonation during the subsequent hydrolysis of the enol ether. Toward this end, Wittig olefination of (+)-**44** (Table 3) with methoxymethyl triphenylphosphonium chloride employing *t*-BuOK to generate the ylide furnished an *E*/*Z* mixture (ca. 4:3) of methyl enol ethers, which were not separated. Initial hydrolysis at room temperature with 4 M HCl for 12 h led to a mixture (ca. 1:1) of aldehydes (entry 1). However, when the hydrolysis was conducted with 6 M HCl at 0 °C for 14 h, the desired axial aldehyde **53** was obtained as the major diastereomer (6:1; ^{1}H NMR), at a conversion of 70% (entry 2). After 24 h, further conversion resulted (93%) with a moderate reduction in selectivity (4:1), due to equilibration between the two epimeric aldehydes (entry 3). At low temperatures, the hydrolysis process not surprisingly proved to be very slow (entry 4). These results, while clearly very pleasing, were striking given that the β face of the enol ether olefin is sterically more hindered than the α face. To account for these observations, we invoke an explanation based upon electrostatic repulsion; that is, axial delivery of a proton, the first step in the enol ether hydrolysis, would be encumbered electronically by repulsion between an incoming hydronium ion and the positive charge of the protonated nitrogen, thus favoring equatorial delivery.

Final Elaboration of Alkaloid (−)-205B: Application of the Toyooka End-Game. Without separation of the epimeric aldehydes (**53** and **54**), reduction with $NaBH_4$ furnished alcohol (+)-**55** in 74% isolated yield, after careful removal of the equatorial congener (+)-**56** by flash chromatography (18%; Scheme 20).[37] Mesylation of (+)-**55**, followed by reduction with Super-Hydride ($LiHBEt_3$) and removal of the dithiane next furnished ketone (−)-**41**, which was subjected to the Toyooka endgame sequence,[13] comprising Wittig methylenation and acid-catalyzed isomerization of the resultant exomethylene alkene to the internal olefin. The natural enantiomer of alkaloid (−)-205B was obtained as the major product (6.2:1; NMR). Separation by flash chromatography furnished (−)-**2**; the yield for the two-step end game was 64%. Synthetic (−)-**2** possessed spectral data {e.g., 400 and 500 MHz ^{1}H and 125 MHz ^{13}C NMR; $[\alpha]_D = -8.3$ (*c* 0.12, $CHCl_3$); lit.[12] −8.5 (*c* 0.59, $CHCl_3$)} identical in all

SCHEME 20



(37) The stereochemistry of (+)-**55** was later confirmed by comparison of the NMR data of (−)-**41** with those of known (+)-**41**; see ref 13.

respects to those reported for both the natural[12] and synthetic antipodes {$[\alpha]_D = +8.1$ (*c* 1.05, $CHCl_3$)},[13] except, of course, in the latter case for the chiroptical properties.[38]

Conclusion

An efficient, highly stereocontrolled general strategy for the construction of 3,5-disubstituted indolizidine alkaloids has been developed, exploiting a three-component linchpin union of TBS dithiane employing *N*-Ts aziridines as the second electrophile, followed in turn by a one-flask sequential cyclization. To showcase the utility of this synthetic strategy, (−)-indolizidine 223AB was constructed in 10 steps, in 10% overall yield from aldehyde **7**. The synthetic strategy was then extended to the total synthesis of the natural enantiomer of alkaloid (−)-205B, a sequence which proceeded with a longest linear sequence of 19 steps and an overall yield of 5.6% from aldehyde (−)-**34**.

Experimental Section

Procedure for Three-Component Linchpin Union: (−)-*N*-((1*R*)-1-{2-[(2*R*,5*S*)-2,5-bis-(*tert*-Butyl-dimethyl-silyloxy)-nonyl]-[1,3]dithian-2-ylmethyl}-butyl)-4-methyl-benzenesulfonamide (3). A solution of dithiane **5** (0.351 g, 1.50 mmol, 1.20 equiv) in Et_2O (3 mL) was cooled to −78 °C and treated with a 1.5 M solution of *t*-BuLi (1.04 mL, 1.56 mmol, 1.25 equiv) dropwise via syringe. The resulting solution was warmed to −45 °C over 1 h and then cooled to −78 °C. A solution of epoxide (+)-**4** (0.340 g, 1.25 mmol) in Et_2O (2 mL) was added dropwise to the reaction mixture at −78 °C via cannula. The resultant solution was warmed to −25 °C over 1 h, stirred for an additional 4 h at −25 °C, and cooled to −78 °C. A solution of aziridine (−)-**6** (0.390 g, 1.63 mmol, 1.30 equiv) in Et_2O (2 mL) and HMPA (0.15 mL, 0.82 mmol, 0.65 equiv) was added dropwise to the reaction mixture at −78 °C via cannula. After 10 min, the reaction vessel was transferred to a 0 °C bath and stirred for 7 h at 0 °C. The resultant mixture was poured into saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel, using diethyl ether/hexanes (1:20) and then ethyl acetate/hexanes (1:12) as eluant, provided (−)-**3** (0.521 g, 0.700 mmol, 56% yield) as a colorless oil and dithiane (−)-**15** (0.150 g, 0.300 mmol, 24% yield). For (−)-**3**: R_f 0.50 (hexanes/ethyl acetate 5/1); $[\alpha]^{20}_D$ −6.4 (*c* 0.75, $CHCl_3$); IR (film) 3228 (m, br), 2955 (s), 2930 (s), 2857 (m), 1463 (m), 1330 (m), 1254 (m), 1160 (s), 1051 (m, br), 836 (s), 774 (m), 663 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 6.36 (d, J = 3.7 Hz, 1H), 4.11−4.08 (m, 1H), 3.75−3.72 (m, 1H), 3.57−3.55 (m, 1H), 2.79−2.63 (m, 4H), 2.40 (s, 3H), 2.26 (dd, J = 15.3 and 9.8 Hz, 1H), 2.06 (br d, J = 15.1 Hz, 1H), 1.95−1.90 (m, 3H), 1.81 (d, J = 14.8 Hz, 1H), 1.63−1.60 (m, 1H), 1.53−1.48 (m, 2H), 1.45−1.37 (m, 4H), 1.36−1.20 (m, 7H), 0.95 (s, 9H), 0.91(app t, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.82 (app t, J = 7.3 Hz, 3H), 0.16 (s, 3H), 0.15 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 139.0, 129.3, 127.3, 72.4, 71.4, 51.5, 50.6, 41.6, 40.9, 39.2, 37.3, 35.2, 32.5, 27.3, 26.3, 26.0, 25.9, 25.6, 25.2, 22.9, 21.5, 18.2, 18.1, 18.0, 14.1, 14.0, −3.0, −4.3, −4.4; high-resolution mass spectrum (ESI) *m*/*z* 768.3975 $[(M + Na)^+$; calcd for $C_{37}H_{71}NO_4NaSi_2S_3$: 768.3982].

Procedure for One-Flask Sequential Cyclization: (−)-(3′*R*,5′*R*,8′a*S*)-3′-Butylhexahydro-5′-propyl-spiro[1,3-dithiane-2,7′(1′*H*)-indolizine] (17). Diol (−)-**18** (0.055 g, 0.106 mmol) was dissolved in THF (5 mL), and triethylamine (0.090 mL, 0.64 mmol, 6.0 equiv) was added. The mixture was cooled to 0 °C, and MsCl (25 μL, 0.323 mmol, 3.0 equiv) was added dropwise. The solution was warmed to ambient temperature and stirred for 1 h. The resultant mixture was poured into water (5 mL) and extracted with Et_2O (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mesylates were dissolved in MeOH (5 mL), and K_2CO_3 (0.060 g, 0.43 mmol, 4.1 equiv) was added. After the mixture was stirred for 3 h at ambient temperature, Na_2HPO_4 (0.80 g, 5.63 mmol, 53 equiv) was added. Then, 5% Na−Hg (0.6 g × 4) was added every 40 min for 2 h, and the mixture was stirred for an additional 1.5 h. The mixture was filtered through Celite and washed with EtOAc. Brine (10 mL) was added to the mixture, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel, using ethyl acetate/hexanes (1:1) as eluant, afforded (−)-**17** (0.033 g, 0.101 mmol, 95% over 2 steps) as a colorless oil: R_f 0.35 (hexanes/ethyl acetate 1/1); $[\alpha]^{20}_D$ −71.7 (*c* 0.30, $CHCl_3$); IR (film) 2954 (s), 2929 (s), 2869 (m), 1465 (m), 1422 (m), 1379 (m), 1276 (w), 1166 (m, br), 1089 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.26 (app t, J = 8.3 Hz, 1H), 2.96−2.87 (m, 4H), 2.76 (ABXY, J_{AB} = 14.4, J_{AY} = 7.3, J_{AX} = 4.4, J_{BY} = 6.5, J_{BX} = 4.4, $\Delta\nu_{AB}$ = 21.1 Hz, 2H), 2.47 (app dt, J = 13.1 and 2.4 Hz, 1H), 2.40 (app dt, J = 13.4 and 2.4 Hz, 1H), 2.02−1.97 (m, 2H), 1.91−1.85 (m, 2H), 1.67−1.62 (m, 1H), 1.55−1.37 (m, 6H), 1.37−1.22 (m, 5H), 1.12−1.08 (m, 2H), 0.94 (app t, J = 7.0 Hz, 3H), 0.90 (app t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 58.1, 53.8, 51.4, 49.3, 43.4, 42.7, 35.2, 29.4, 29.1, 26.7, 26.3, 26.1, 25.7, 25.5, 22.9, 18.7, 14.4, 14.2; high-resolution mass spectrum (ESI) *m*/*z* 328.2145 $[(M + H)^+$; calcd for $C_{18}H_{34}NS_2$: 328.2133].

(−)-Indolizidine 223AB (1). A suspension of Raney Ni in water (Raney Ni 2800 from Aldrich, 1 mL) was added to a solution of dithiane (−)-**17** (0.021 g, 0.064 mmol) in EtOH (4 mL). The mixture was stirred under H_2 (1 atm) vigorously for 12 h at ambient temperature. The mixture was filtered through Celite and washed with EtOH (20 mL). The filtrate was evaporated and diluted with Et_2O (20 mL), and 5 M KOH (5 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. After basifying silica gel with NH_4OH/ether/pentane (1/12/87), flash chromatography on the basified silica gel, using ethyl acetate as eluant, provided (−)-**1** (0.0098 g, 0.044 mmol, 69% yield) as a pale yellow oil: R_f 0.55 (CH_2Cl_2/methanol 5/1); $[\alpha]^{20}_D$ −43 (*c* 0.47, *n*-hexane), $[\alpha]^{20}_D$ −85 (*c* 0.42, MeOH); IR (film) 2956 (s), 2926 (s), 2856 (m), 2789 (m), 1462 (m), 1454 (m), 1379 (m), 1180 (w), 1130 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.30 (app br t, J = 9.1 Hz, 1H), 2.40−2.36 (m, 2H), 1.90−1.84 (m, 2H), 1.78−1.71 (m, 3H), 1.67−1.65 (m, 1H), 1.49−1.40 (m, 4H), 1.38−1.17(m, 6H), 1.16−1.01 (m, 4H), 0.92 (app t, J = 7.2 Hz, 3H), 0.90 (app t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 59.0, 58.5, 56.5, 35.9, 32.4, 31.0, 30.1, 29.1, 26.4, 25.0, 24.7, 23.0, 19.0, 14.5, 14.2; high-resolution mass spectrum (CI) *m*/*z* 223.2300 $[(M)^+$; calcd for $C_{15}H_{29}N$: 223.2300].

(+)-*N*-[(1*R*)-2-{2-[(2*S*,5*S*,6*S*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-5-(*tert*-butyl-diphenyl-silanyloxy)-6-methyl-oct-7-enyl]-[1,3]dithian-2-yl}-1-(2-methyl-[1,3]dioxolan-2-yl)-ethyl]-4-methyl-benzenesulfonamide (46): R_f 0.40 (hexanes/ethyl acetate 3/1); $[\alpha]^{20}_D$ +7.50 (*c* 1.00, $CHCl_3$); IR (film) 3207 (m, br), 3070 (w), 2956 (s), 2932 (s), 2892 (s), 2857 (s), 1640 (w), 1599 (w), 1471 (m), 1427 (m), 1323 (m), 1255 (m), 1153 (s), 1107 (s), 1090 (s), 1043 (s), 919 (m), 837 (m), 756 (m), 704 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72−7.69 (m, 6H), 7.42−7.35 (m, 6H), 7.20 (d, J = 8.1 Hz, 2H), 6.34 (d, J = 3.5 Hz, 1H), 5.95 (ddd, J = 17.3, 10.7 and 7.0 Hz, 1H), 5.00−4.97 (m, 2H), 4.07 (dd, J = 9.3 and 3.3 Hz, 1H), 3.97−3.89 (m, 2H), 3.75−3.68 (m, 2H), 3.66−3.61 (m, 2H), 2.86 (ddd, J = 14.4, 8.4 and 2.7 Hz, 1H), 2.73 (ddd, J = 14.1, 8.5 and 2.6 Hz, 1H), 2.62 (ddd, J = 14.3, 7.7 and 2.9 Hz, 1H), 2.51−2.47 (m, 1H), 2.46 (dd, J = 15.6 and 10.8 Hz, 1H), 2.38 (s, 3H), 2.27−2.30 (m, 2H), 2.25 (dd, J = 15.0 and 9.8 Hz, 1H), 2.0−1.87 (m,

(38) We thank Dr. John W. Daly, National Institutes of Health, for kindly providing the 400 MHz 1H NMR and the proton/carbon HMBC spectra for the natural antipode of alkaloid 205B.

2H), 1.86 (d, J = 15.3 Hz, 1H), 1.62−1.50 (m, 2H), 1.44−1.38 (m, 1H), 1.27−1.21 (m, 1H), 1.11 (s, 3H), 1.05 (s, 9H), 0.98 (d, J = 6.8 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 141.6, 140.7, 136.1, 136.0, 134.8, 134.2, 129.52, 129.49, 128.6, 127.49, 127.46, 126.9, 114.1, 110.3, 77.6, 72.3, 64.5, 64.2, 54.5, 52.0, 41.9, 40.1, 37.1, 34.6, 29.5, 27.1, 26.3, 25.8, 25.4, 21.5, 19.7, 19.5, 18.2, 14.2, −2.9, −4.8; high-resolution mass spectrum (ESI) *m*/*z* 934.4049 [(M +Na)$^+$; calcd for $C_{48}H_{73}NO_6NaSi_2S_3$: 934.4036].

(+)-(3′*R*,5′*R*,8′a*R*)-Hexahydro-5′-(2-methyl-1,3-dioxolan-2-yl)-3′-[(1*S*)-1-methyl-2-propenyl]-spiro[1,3-dithiane-2,7′(1′*H*)-indolizine] (49): R_f 0.60 (hexanes/ethyl acetate 4/1); mp 122 °C; $[\alpha]^{20}_D$ +53.0 (*c* 1.00, $CHCl_3$); IR (film) 3074 (w), 2949 (s), 1636 (m), 1422 (m), 1379 (m), 1137 (m), 1049 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83−5.76 (m, 1H), 4.95 (ddd, J = 6.8, 1.9 and 1.6 Hz, 1H), 4.92 (d, J = 1.6 Hz, 1H), 4.10−3.96 (m, 1H), 3.95−3.87 (m, 3H), 3.47−3.41 (m, 2H), 3.35 (dd, J = 11.2 and 3.1 Hz, 1H), 3.09−3.05 (m, 1H), 3.01 (ddd, J = 14.3, 9.2 and 3.2 Hz, 1H), 2.86−2.79 (m, 2H), 2.71 (ddd, J = 14.4, 7.1 and 3.3 Hz, 1H), 2.58 (app dt, J = 13.6 and 2.9 Hz, 1H), 2.20 (app dt, J = 12.9 and 2.9 Hz, 1H), 2.03−1.96 (m, 2H), 1.76−1.70 (m, 2H), 1.61−1.55 (m, 2H), 1.37−1.26 (m, 2H), 1.32 (s, 3H), 0.99 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 112.2, 111.9, 64.5, 64.2, 60.8, 57.2, 54.6, 49.6, 43.0, 37.5, 36.7, 29.9, 26.2, 26.0, 25.4, 22.8, 19.9, 14.2; high-resolution mass spectrum (ESI) *m*/*z* 370.1861 [(M + H)$^+$; calcd for $C_{19}H_{32}NO_2S_2$: 370.1874].

Procedure for Ring Closing Metathesis Construction of 8b-Azacenaphthylene Ring System: (+)-(2′a*R*,5′a*R*,8′*S*,8′a*R*)-Octahydro-8′-methyl-spiro[1,3-dithiane-2,4′-[4*H*]pyrrolo[2,1,5-de]-quinolizin]-6′(2′*H*)-one (44). To a solution of LiHMDS (1.0 M in THF, 0.29 mL, 1.5 equiv) in THF (3 mL) at −78 °C was added trimethysilyl chloride (0.074 mL, 0.583 mmol, 3.0 equiv) and a solution of ketone (+)-45 (63 mg, 0.194 mmol) in THF (2 mL). After 2 h at −78 °C, the reaction was quenched by addition of saturated $NaHCO_3$ aqueous solution (2 mL), and the mixture was allowed to warm to ambient temperature. The mixture was poured into water (5 mL) in a separatory funnel and extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo to afford the crude enol ether. To a solution of the crude enol ether in benzene (150 mL) was added Grubbs second generation catalyst (**38**) (16 mg, 0.019 mmol, 0.10 equiv). The reaction mixture was stirred at 65 °C overnight, then cooled to ambient temperature and concentrated in vacuo. Flash chromatography on silica gel using hexanes/ethyl acetate (10/1 → 5/1 → 2/1) as eluant afforded (+)-**44** (0.047 g, 0.158 mmol, 81% yield for 2 steps) as a white solid: R_f 0.25 (hexanes/ ethyl acetate 1/1); mp 101 °C; $[\alpha]^{20}_D$ +93.5 (*c* 1.00, $CHCl_3$); IR (film) 2951 (s), 1714 (s), 1424 (m), 1241 (m), 1144 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.98 (dd, J = 12.2 and 3.0 Hz, 1H), 3.57−3.52 (m, 1H), 3.04 (ddd, J = 13.9, 10.6 and 2.7 Hz, 1H), 2.91−2.83 (m, 2H), 2.74 (ddd, J = 14.2, 6.1 and 3.0 Hz, 1H), 2.66 (ddd, J = 14.4, 5.8 and 3.1 Hz, 1H), 2.47 (dd, J = 17.0 and 4.5 Hz, 1H), 2.25 (app dt, J = 13.5 and 2.6 Hz, 1H), 2.10−2.00 (m, 4H), 1.98−1.84 (m, 3H), 1.83−1.73 (m, 1H), 1.64 (app t, J = 12.7 Hz, 1H), 1.47−1.40 (m, 2H), 0.95 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 63.1, 59.1, 54.6, 49.9, 45.8, 39.5, 35.9, 33.4, 29.2, 28.5, 26.2, 26.1, 25.9, 18.8; high-resolution mass spectrum (CI) *m*/*z* 297.1221 [(M)$^+$; calcd for $C_{15}H_{23}NOS_2$: 297.1221].

Procedure for Stereoselective Installation of the C(6) Axial Methyl Group: (+)-(2′a*R*,5′a*R*,6′*R*,8′*S*,8′a*R*)-Decahydro-8′-methyl-spiro[1,3-dithiane-2,4′-[4*H*]pyrrolo[2,1,5-de]quinolizine]-6′-methanol (55). To a mixture of methoxymethyl triphenylphosphonium chloride (0.356 g, 1.04 mmol, 10 equiv) and potassium *tert*-butoxide (0.111 g, 0.989 mmol, 9.5 equiv) was added THF (7 mL) at ambient temperature. After 2 min, a solution of (+)-**44** (31 mg, 0.104 mmol) in THF (3 mL) was added dropwise via cannula. After 20 min, water (1 mL) was added, and the mixture was diluted with EtOAc (70 mL), washed with brine (2 × 5 mL), and dried over K_2CO_3. The solvent was removed in vacuo. Quick flash chromatography on silica gel, using acetone/hexanes (1:1) as eluant, afforded a mixture (ca. 4:3) of methyl enol ethers containing some phosphine impurity. The mixture was then dissolved (without further purification) in THF (4 mL) and cooled to 0 °C, and precooled (0 °C) 6 M HCl (4 mL) was added. After the reaction mixture was stirred for 24 h at 0 °C, saturated $NaHCO_3$ aqueous solution (40 mL) was added slowly at 0 °C. The resulting solution was extracted with ether (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford the crude aldehyde. To a solution of the crude aldehyde in MeOH (5 mL) at 0 °C was added $NaBH_4$ (0.019 g, 0.50 mmol, 4.8 equiv). After 40 min, saturated NH_4Cl aqueous solution (1 mL) was added, and solvents were removed in vacuo. The residue was partitioned between ethyl acetate (50 mL) and water (5 mL), and the organic layer was separated. The aqueous layer was then extracted with ethyl acetate (2 × 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by preparative-TLC (hexanes/acetone, 1/1, 500 μm plate) afforded (+)-**55** (24.0 mg, 0.0765 mmol, 74% yield for 3 steps) as a colorless oil and (+)-**56** (5.7 mg, 0.018 mmol, 18% yield for 3 steps) as a colorless oil. For (+)-**55**: R_f 0.20 (hexanes/acetone 1/1); $[\alpha]^{20}_D$ +4.8 (*c* 0.50, $CHCl_3$); IR (film) 3378 (m, br), 2925 (s), 1456 (m), 1375 (w), 1275 (w), 1144 (w), 1040 (w), 754 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (ABX, J_{AB} = 10.1, J_{AX} = 4.8, J_{BX} = 3.5, $\Delta\nu_{AB}$ = 76.3 Hz, 2H), 3.73 (d, J = 12.7 Hz, 1H), 3.65−3.58 (m, 1H), 2.95−2.86 (m, 2H), 2.82−2.73 (m, 2H), 2.54−2.49 (m, 1H), 2.10 (app t, J = 13.1 Hz, 1H), 2.04−1.92 (m, 4H), 1.86 (d, J = 13.6 Hz, 1H), 1.76 (d, J = 14.3 Hz, 1H), 1.75−1.70 (m, 1H), 1.70 (dd, J = 13.9 and 11.9 Hz, 1H), 1.64 (ddd, J = 13.8, 3.5 and 2.0 Hz, 1H), 1.59 (br s, 1H), 1.36−1.23 (m, 3H), 0.86 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 67.7, 58.0, 54.9, 51.7, 50.5, 39.9, 37.3, 34.0, 33.9, 33.3, 28.1, 27.1, 25.9, 25.4, 25.4, 18.9; high-resolution mass spectrum (ESI) *m*/*z* 314.1614 [(M + H)$^+$; calcd for $C_{16}H_{28}NOS_2$: 314.1612].

Alkaloid 205B (−)-2: R_f 0.20 (ethyl acetate); $[\alpha]^{20}_D$ −8.3 (*c* 0.12, $CHCl_3$); IR (film) 2959 (m), 2924 (m), 2841 (m), 1655 (w), 1458 (m), 1376 (m), 1170 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (br s, 1H), 3.79 (br s, 1H), 2.98 (dd, J = 11.4 and 4.6 Hz, 1H), 2.17−2.10 (m, 3H), 1.93−1.88 (m, 1H), 1.71−1.79 (m, 1H), 1.62 (s, 3H), 1.49−1.26 (m, 6H), 1.18 (d, J = 7.2 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H); ^{1}H NMR (500 MHz, C_6D_6) δ 5.19 (br s, 1H), 3.87 (br s, 1H), 2.95 (dd, J = 11.5 and 4.6 Hz, 1H), 2.15 (dd, J = 9.8 and 5.2 Hz, 1H), 2.06 (app t, J = 14.3 Hz, 1H), 2.02−1.95 (m, 1H), 1.84−1.79 (m, 1H), 1.59 (s, 3H), 1.60−1.53 (m, 1H), 1.39−1.21(m, 6H), 1.29 (d, J = 7.1 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.5, 125.6, 60.5, 58.1, 56.5, 35.5, 32.6, 32.4, 29.2, 28.4, 28.4, 23.5, 20.2, 18.8;^{13}C NMR (125 MHz, C_6D_6) δ 129.9, 126.9, 61.0, 59.0, 57.0, 36.4, 33.4, 33.2, 30.2, 29.2, 28.7, 24.2, 20.8, 19.4; high-resolution mass spectrum *m*/*z* 205.1830 [(M)$^+$; calcd for $C_{14}H_{23}N$: 205.1831].

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all other new compounds. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. Crystallographic information files (CIF) of (−)-**42** and (+)-**44**. This material is available free of charge via the Internet at http://pubs.acs.org.

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