ORGANIC LETTERS

2004
Vol. 6, No. 9
1493−1495

Multicomponent Linchpin Coupling of Silyl Dithianes Employing an *N*-Ts Aziridine as the Second Electrophile: Synthesis of (–)-Indolizidine 223AB

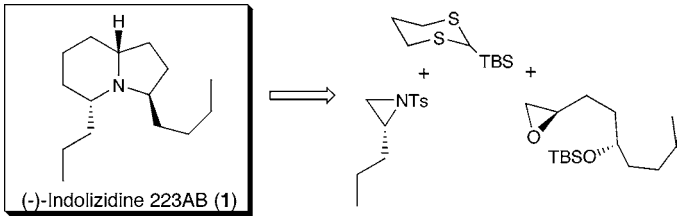
Amos B. Smith, III* and Dae-Shik Kim

Department of Chemistry, Monell Chemical Senses Center and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania 19104

smithab@sas.upenn.edu

Received March 3, 2004

ABSTRACT



An efficient, stereocontrolled assembly of the indolizidine alkaloid, (–)-indolizidine 223AB, exploiting a three-component linchpin coupling employing an *N*-Ts aziridine as the second electrophile, followed by a one-pot sequential construction of the indolizidine ring system, has been achieved. The longest linear sequence was 10 steps, proceeding in 10% overall yield.

Dithianes, important umpolung linchpins in organic chemistry,[1] are frequently employed both for the stereocontrolled generation of protected aldol products[2] and for the union of advanced fragments in complex molecule synthesis.[3] In 1997, we introduced a variant of dithiane chemistry, specifically the use of silyl dithianes for multicomponent linchpin couplings of diverse epoxide electrophiles, exploiting a solvent-controlled Brook rearrangement.[4] This tactic now comprises the central strategic element in several completed and ongoing synthetic ventures in our laboratory.[5] To advance this synthetic tactic further we have recently explored the use of nitrogen-containing electrophiles such as *N*-Ts aziridines[6] as the second electrophilic agent in the

(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**, *1*, 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.

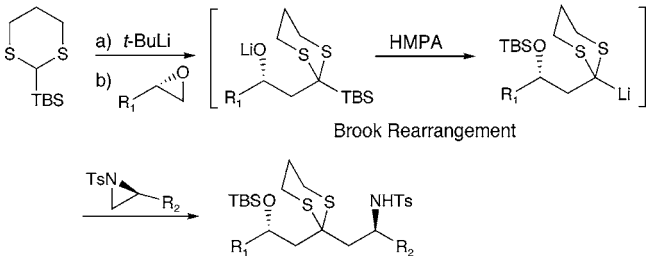
(4) (a) Smith, A. B., III; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925. Also see: (b) Smith, A. B., III; Pitram, S. M.; Boldi, A. M.; Gaunt, M. J.; Sfouggatakis, C.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 14435.

(5) (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. (g) 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.

10.1021/ol049601b CCC: $27.50
Published on Web 03/31/2004

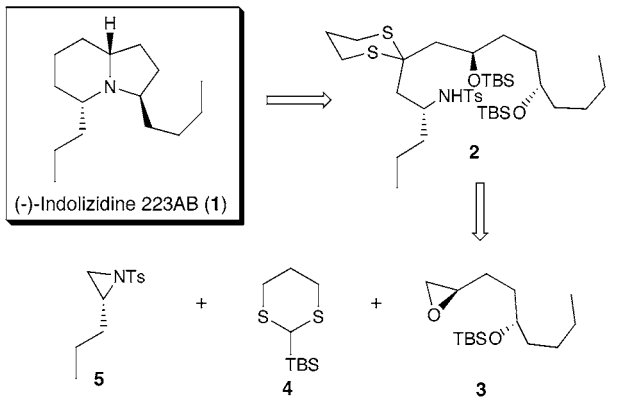
multicomponent linchpin protocol for accessing protected 1,5-amino alcohols in a stereocontrolled fashion (Scheme 1).[7]

Scheme 1



In this Letter, we report application of this tactic for the efficient construction of (−)-indolizidine 223AB (**1**), a representative alkaloid isolated from the skin of the neotropical dart-poison frogs belonging to the genus *Dendrobates* (Scheme 2).[8] Our synthetic approach calls for the construc-

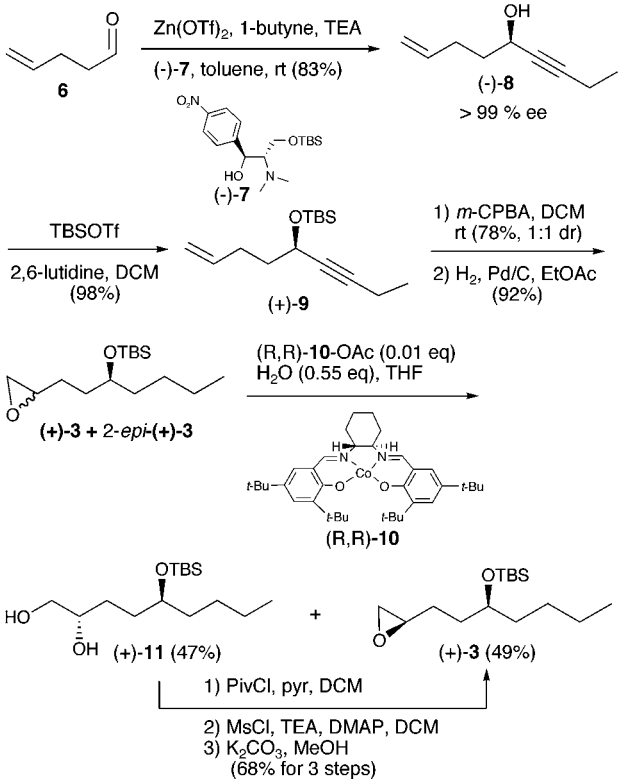
Scheme 2



tion of **2**, via a three-component linchpin coupling of silyl dithiane **4** with epoxide **3** and known aziridine **5**,[9] followed by sequential conversion to the indolizidine alkaloid.

We began this venture with the ready construction of scalemic epoxide **3**, exploiting Carreira alkyne methodology,[10] in conjunction with a Jacobsen hydrolytic kinetic resolution (HKR)[11] (Scheme 3). Toward this end, propargylic alcohol (−)-**8**[12] (Scheme 3) was prepared from commercially available 4-pentenal **6** both in high yield and with excellent enantioselectivity (>99% ee determined by chiral HPLC)

Scheme 3



via the Carreira protocol, using the Jiang chiral ligand (−)-**7**.[13] Protection of the hydroxyl functionality as the TBS ether, followed in turn by nonstereoselective epoxidation with *m*-CPBA and complete hydrogenation of the triple bond, furnished (+)-**3** and 2-*epi*-(+)-**3**, as a diastereomeric mixture

(6) For *N*-Ts aziridine ring-opening reactions of 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.

(7) There is one report of an intramolecular linchpin reaction between a dithiane and the 1,4-biselectrophile, 1,2-epimino-3,4-epoxy-(*N*-Ts)butane, in which the aziridine moiety played a role as the second electrophile; Harms, G.; Schaumann, E.; Adiwidjaja, G. *Synthesis* **2001**, *4*, 577.

(8) (a) Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M. M.; Meyers, C. W. *Toxicon* **1978**, *16*, 163. (b) Tokuyama, T.; Nishimori, N.; Karle, I. K.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986**, *42*, 3453. For 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.

(9) (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.

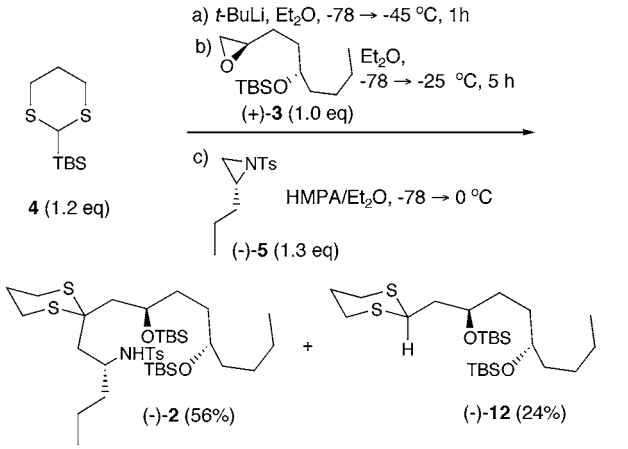
(10) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.

(11) (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.

(12) 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.

(13) (a) Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* **2002**, 1524. Using (+)-*N*-methyl ephedrine as a chiral ligand, we obtained (−)-**8** in 44 % isolated yield and 96 % ee. For preparation of (−)-**7**, see: (b) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451.

Scheme 4

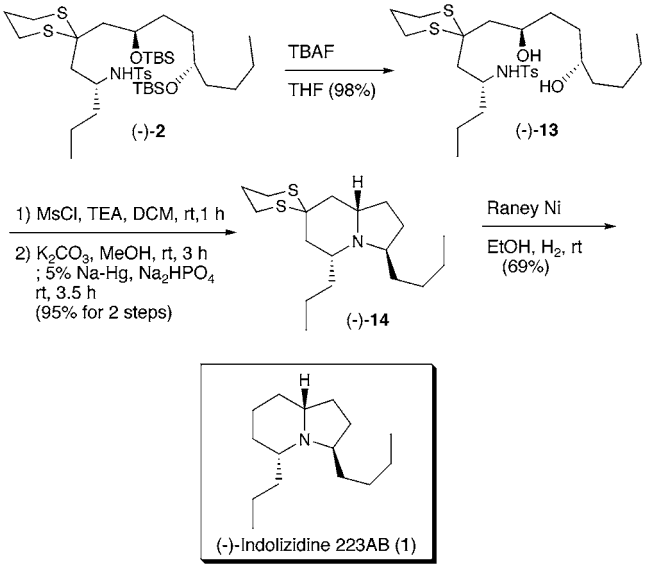


(ca. 1:1). Jacobsen−HKR employing **10**[11] as the catalyst led to the desired epoxide (+)-**3** along with diol (+)-**11**, both diastereomerically pure (e.g., ^{1}H and ^{13}C NMR).[14] After separation by flash chromatography, diol (+)-**11** was transformed to (+)-**3** by chemoselective pivaloylation, followed by mesylation of the secondary alcohol and ring closure employing potassium carbonate.[15] In this way, the mixture of (+)-**3** and 2-*epi*-(+)-**3** was transformed into pure (+)-**3**, with an overall efficiency of 81%.

With epoxide (+)-**3** and known aziridine (−)-**5** available,[9] the latter readily prepared from D-norvaline in two steps,[9a] we executed the multicomponent linchpin coupling. Pleasingly, lithiation of dithiane **4** in Et_2O (−78 °C), followed in turn by addition of epoxide (+)-**3**, warming to −25 °C over a period of 1 h, stirring the reaction mixture for an additional 4 h at −25 °C, and then adding aziridine (−)-**5** in Et_2O containing HMPA (0.6 equiv) and warming to 0 °C, furnished (−)-**2** in 56% isolated yield, accompanied by dithiane (−)-**12** (24%) not having undergone reaction with aziridine (−)-**5** (Scheme 4).[16] The structure of (−)-**2** was secured by careful ^{1}H and ^{13}C NMR experiments.

Having arrived at the carbon backbone of (−)-indolizidine 223AB (**1**), we now faced the task of constructing the indolizidine ring system (Scheme 5). Toward this end, removal of the TBS groups in (−)-**2** (TBAF/THF) furnished diol (−)-**13** in high yield. Mesylation (MsCl, TEA, DCM, 1 h), followed without purification of the bismesylate by treatment with potassium carbonate in MeOH for 3 h and then addition of excess sodium amalgam (5%) directly to the reaction mixture to liberate the secondary amine, led to (−)-**14**, the product of double cyclization. The yield for this sequential construction of the indolizidine ring system was excellent (95%). Importantly, the dithiane moiety proved to be critical (i.e., reactive rotamer effect) in this transformation.[17] Reductive removal of the dithiane with Raney Ni then completed the synthesis of (−)-indolizidine 223AB (**1**),[18] which possessed spectral data (e.g., 500 MHz ^{1}H and 125 Hz ^{13}C) identical in all respects to the spectral data of authentic synthetic (−)-indolizidine 223AB (**1**)[8l] provided by Professor Eun Lee (Seoul National University).

Scheme 5



In summary, an efficient, highly stereocontrolled synthesis of (−)-indolizidine 223 AB (**1**) has been achieved. Highlights of the synthesis include the three-component linchpin coupling of (+)-**3**, **4**, and (−)-**5**, followed by a one-pot sequential cyclization to construct the indolizidine ring. The longest linear sequence from 4-pentenal (**6**) to (−)-**1**, proceeding in an overall yield of 10%, was 10 steps. Importantly, the synthetic strategy holds promise for the construction of a wide variety of indolizidine, quinolizidine, and quinolizine alkaloids, simply by altering the epoxide and aziridine of the three-component linchpin coupling protocol. Studies both to employ this tactic for alkaloid synthesis and to exploit other nitrogen-containing electrophiles are underway in our laboratory and will be reported in due course.

Acknowledgment. Financial support was provided by the National Institutes of Health (Institute of General Medical Sciences) through Grant GM-29028. We also thank Professor Eun Lee, Seoul National University, for kindly providing the 300 MHz ^{1}H and 75 MHz ^{13}C NMR of (−)-indolizidine 223AB.

Supporting Information Available: Spectroscopic and analytical data and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049601B

(14) Relative and absolute configurations were confirmed by Kakisawa analysis[12] of the Mosher esters of diol **11**.

(15) Chang, J.; Paquette, L. A. *Org. Lett.* **2002**, *4*, 253.

(16) In step C, rapid warming to 0 °C after addition of aziridine (−)-**5** proved to be more consistent and furnished better yields. Slow warming over 1−2 h resulted in capricious behavior (ca. 30∼50%), in conjunction with large amounts of (−)-**12**.

(17) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224. Without the dithiane moiety, the first cyclization was very slow (40 h), resulting in low yield (55% for mesylation and the first cyclization).

(18) Optical rotations in two solvents were $[\alpha]_D$ −43° (*c* 0.47, *n*-hexane) (lit.[8b] −44° (*c* 1.0, *n*-hexane)) and $[\alpha]_D$ −85° (*c* 0.42, MeOH) (lit.[8h] −88° (*c* 0.50, MeOH)).