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[4 + 1] Cycloaddition of Bis(alkylthio)carbenes with Vinyl Isocyanates. Total Synthesis of (±)-Mesembrine

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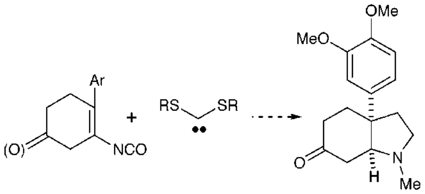
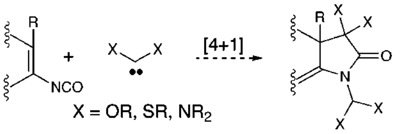
ABSTRACT



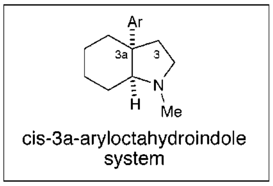
The *Sceletium* alkaloid mesembrine has been synthesized in 13% overall yield by a sequence featuring a [4 + 1] cycloaddition of a bis(alkylthio)carbene with a functionalized vinyl isocyanate.

The rapid and efficient construction of partially reduced nitrogen heterocycles continues to present an important challenge to the synthesis of structurally complex alkaloid targets. So-called nucleophilic carbenes[1,2] have recently emerged as powerful 1,1-dipole equivalents for the assembly of functionalized pyrrolidone derivatives via a novel [4 + 1] cycloaddition with vinyl isocyanates (Scheme 1).[3]

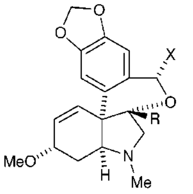
Scheme 1



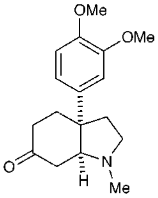
The *cis*-3a-aryloctahydroindole nucleus is a prominent substructural motif in the *Amaryllidaceae* and *Sceletium* alkaloids and represents a considerable synthetic challenge as a result of the presence of the highly congested quaternary center at C_{3a}. Several amaryllis alkaloids of this structural type, such as tazettine (**1a**) and pretazettine (**1b**), exhibit an oxidized C_3 position that renders them ideal targets for nucleophilic carbene-based synthesis, since these reactive intermediates deliver a carbon atom at the carbonyl oxidation level.[4]



cis-3a-aryloctahydroindole
system



1a, R = OH, X = H
1b, R = H, X = OH



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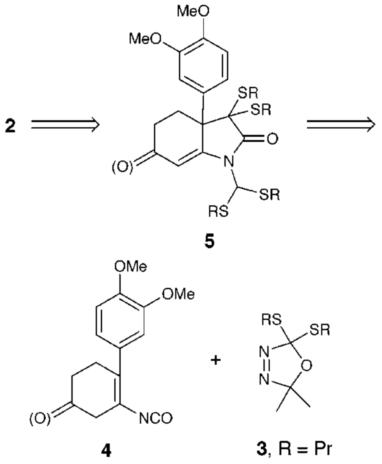
(1) (a) Rigby, J. H.; Cavezza, A.; Ahmed, G. *J. Am. Chem. Soc.* **1996**, *118*, 12848. (b) Rigby, J. H.; Laurent, S.; Cavezza, A.; Heeg, M. J. *J. Org. Chem.* **1998**, *63*, 5587. (c) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *Tetrahedron Lett.* **1999**, *40*, 2973.

(2) For an excellent overview of nucleophilic carbene chemistry, see: Warkentin, J. In *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; JAI: Greenwich, 1998; Vol. 2, pp 245−95.

10.1021/ol005706c CCC: $19.00

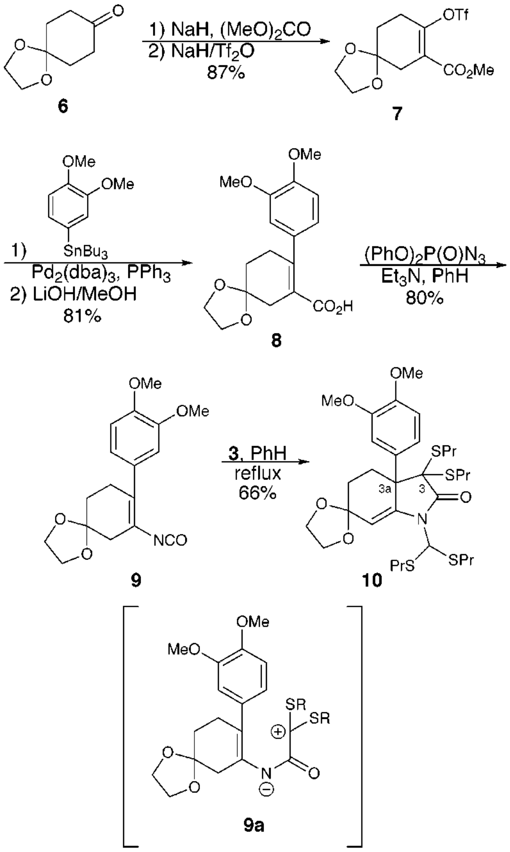
Aryloctahydroindole alkaloids possessing a fully reduced carbon at C_3 are quite common, and their synthesis by a similar strategy would require the use of a nucleophilic carbene partner at the corresponding reduced oxidation level such as methylene itself or, more reasonably, one that is readily reduced to the desired oxidation state after cycloaddition. A potential solution to this problem has been introduced recently in the form of bis(alkylthio)carbenes.[5] These species have been shown to exhibit a reaction profile similar in many respects to that of dialkoxycarbenes; however, they also offer the opportunity to serve as methylene equivalents via post-cycloaddition reductive desulfurization. We wish to disclose that this notion has been brought to practice in an efficient synthesis of the *Sceletium* alkaloid, (±)-mesembrine (**2**).[6] The basic strategy for this synthesis is outlined in Scheme 2. The key strategy-level transformation is a thermal decomposition of dithiooxadiazoline **3**, giving the corresponding carbene, which would undergo cycloaddition with *β*-aryl-substituted vinyl isocyanate **4** to afford hydroindolone **5**. Desulfurization and enamide reduction would complete the synthesis of mesembrine.

Scheme 2



The synthesis commences with commercially available monoprotected dione **6**, which is transformed in four steps via vinyl triflate **7**[7] to the key *β*-aryl-α,*β*-unsaturated acid **8**[7] in 71% overall yield (Scheme 3). Exposure of **8** to DPPA[8]/TEA followed by attempted purification on silica gel of the resultant acyl azide gave, surprisingly, the rearranged vinyl isocyanate **9**, which was immediately heated in refluxing benzene in the presence of excess oxadiazoline **3**[5a] to afford the crucial 2:1 adduct **10**.[7] This material possesses a fully intact 3a-aryloctahydroindole structure. The success of this transformation highlights in dramatic fashion the power of nucleophilic carbenes for ring construction even at very sterically hindered locations. In the case at hand, there is considerable congestion in the vicinity of the newly created bond between C_3 and C_{3a}, and it is presumed that the reaction proceeds through intermediate **9a** in which the crucial bond formation benefits from intramolecularity.

Scheme 3



With hydroindolone **10** in hand, the projected reductive desulfurization step becomes important. It should be noted

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(3) For a review of vinyl isocyanate chemistry, see: Rigby, J. H. *Synlett.* **2000**, 1.

(4) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 3664.

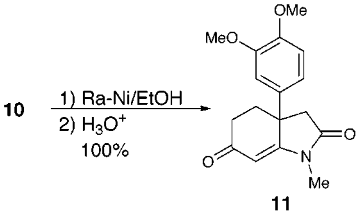
(5) (a) Rigby, J. H.; Laurent, S. *J. Org. Chem.* **1999**, *64*, 1766. (b) Rigby, J. H.; Danca, M. D. *Tetrahedron Lett.* **1999**, *40*, 6891.

(6) For previous synthesis of mesembrine, see: (a) Kamikubo, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1998**, 783. (b) Yamada, O.; Ogasawara, K. *Tetrahedron Lett.* **1998**, *39*, 7747. (c) Dalko, P. I.; Brun, V.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 8979. (d) Mori, M.; Kuroda, S.; Zhang, C.-S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263. (e) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675. (f) Rajagopalan, P. *Tetrahedron Lett.* **1997**, *38*, 1893. (g) Takano, S.; Samizu, K.; Ogasawara, K. *Chem. Lett.* **1990**, 1239. (h) Winkler, J. D.; Muller, C. L.; Scott, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 4831. (i) Hoshino, O.; Sanaki, S.; Shimamura, N.; Onodera, A.; Umezawa, B. *Chem. Pharm. Bull.* **1987**, *35*, 2734. (j) Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776. (k) Kochhar, K. S.; Pinnick, H. W. *Tetrahedron Lett.* **1983**, *24*, 4785. (l) Sanchez, I. H.; Soria, J. J.; Larraza, M. I.; Flores, H. J. *Tetrahedron Lett.* **1983**, *24*, 551. (m) Keck, G. E.; Webb, R. R., II. *J. Org. Chem.* **1982**, *47*, 1302. (n) Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479. (o) Takano, S.; Imamura, Y.; Ogasawara, K. *Chem. Lett.* **1981**, 1385. (p) Strauss, H. F.; Wiechers, A. *Tetrahedron Lett.* **1979**, 4495. (q) Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391. (r) Stevens, R. V.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5580. (s) Keely, S. L., Jr.; Tahk, F. C. *J. Am. Chem. Soc.* **1968**, *90*, 5584. (t) Shamma, M.; Rodriguez, H. R. *Tetrahedron* **1968**, *24*, 6583. (u) Curphey, T. J.; Kim, H. L. *Tetrahedron Lett.* **1968**, 1441.

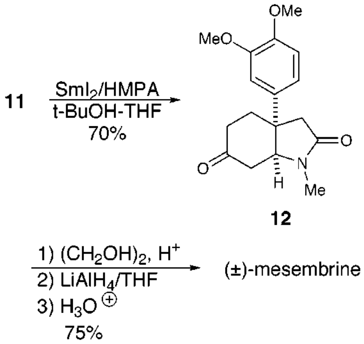
(7) This compound exhibited spectral (^{1}H NMR, ^{13}C NMR, IR) and analytical (combustion analysis and/or HRMS) data fully consistent with the assigned structure.

(8) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

at this juncture that the [4 + 1] cycloaddition not only inserted a new carbon atom at C_3 amenable to subsequent reduction but simultaneously installed the carbon atom required for conversion into the *N*-methyl group of the target structure as well. In light of this result, it was anticipated that both centers could be reduced to their requisite oxidation levels in one operation. Thus, Ra−Ni-mediated reductive cleavage of all four carbon−sulfur bonds delivered the requisite enamide **11**[7] after acetal hydrolysis. The efficiency of these two steps is noteworthy.



Reduction of the remaining enamide alkene to the cis-fused aryloctahydroindole system **12**[7] was achieved after considerable effort by employing an interesting SmI_2-based reduction protocol reported initially by Molander and McKie several years ago.[9] A routine series of operations followed to afford mesembrine in 75% yield for the three steps and in 13% overall yield from **6**. The preparation of mesembrine was confirmed by comparison of the ^1H and ^{13}C NMR spectra of the synthetic material with those reported for the natural product.[6e]



In summary, a novel [4 + 1] cycloaddition between a bis(alkylthio)carbene and a functionalized vinyl isocyanate afforded the *Sceletium* alkaloid, (±)-mesembrine, after appropriate oxidation level adjustments.

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[9] Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186.