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6-Exo-spiro (Alkoxycarbonylamino)methyl Radical Cyclization: Highly Regio- and Stereoselective Synthesis of (−)-Sibirine

Masato Koreeda,*,†,‡ Yamin Wang,† and Liming Zhang‡

Departments of Chemistry and Medicinal Chemistry, University of Michigan, Ann Arbor, Michigan 48109-1055

koreeda@umich.edu

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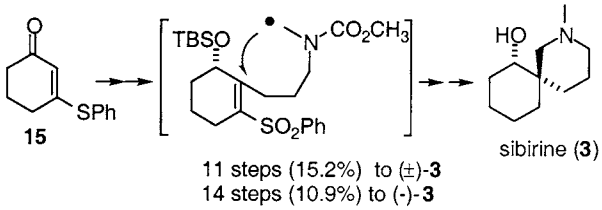
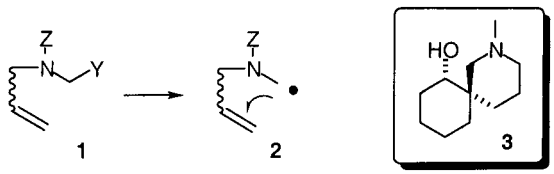
ABSTRACT



The (methoxycarbonylamino)methyl radical can be readily generated from its PhSe precursor and undergoes preferential 6-exo-spiro cyclization when $PhSO_2$ is attached at the distal alkene carbon. This property was applied to the synthesis of the racemic and optically active spirocyclic alkaloid sibirine.

Regio- and stereocontrolled generation of quaternary carbon centers continues to remain a formidable challenge in organic synthesis.[1] Among a number of such methods currently available, those based on radical cyclization are often quite effective due to the exceptional predilection of most of the reactive radical species to form bonds at the proximately disposed unsaturated center.[2] In connection with our continued interest in developing synthetic methods through the use of radicals next to a heteroatom such as **2**, the synthesis of the spirocyclic alkaloid (−)-sibirine (**3**)[3] was investigated.



Notwithstanding a substantial literature on a radical α to a nitrogen atom,[4] its application in synthesis is by no means straightforward. Although the generation of the radical **2** from a precursor such as **1** could readily be achieved due to the

† Department of Chemistry.
‡ Department of Medicinal Chemistry.

(1) For reviews on the synthesis of quaternary carbon centers, see: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419−460. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066. For reviews on the synthesis of spiro systems, see: (c) Corey, E. J. *Angew. Chem., Ed. Engl.* **1998**, *53*, 6031−6035. (d) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007−9071.

(2) For some leading references, see: (a) Set, L.; Cheshire, D. R.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1205−1207. (b) Bennett, S. M.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 878−880. (c) Harling, J. D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1988**, 1380−1382. (d) Hart, D. J.; Wu, S. C. *Tetrahedron Lett.* **1991**, *32*, 4099−4102. (e) Cossy, J.; Bouzide, A.; Leblanc, C. *Synlett* **1993**, 202−204. (f) Srikrishna, A.; Nagaraju, S.; Raghava Sharma, G. V. *J. Chem. Soc., Chem. Commun.* **1993**, 285−288. (g) Back, T. G.; Gladstone, P. L.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 3806−3814. For a review, see: (h) pp 9062−9066 in ref 1d.

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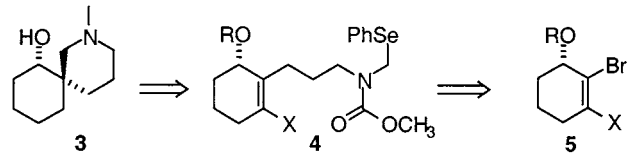
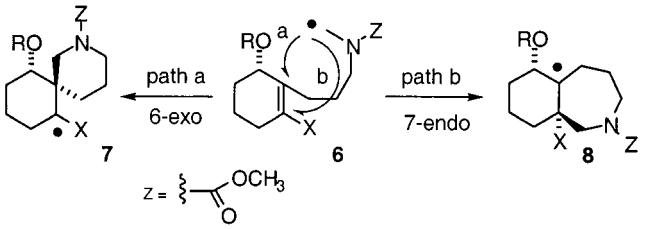
stabilizing interaction between the incipient radical and the N lone pair,[5] this stability seems to adversely influence the reactivity of the ensuing radical reaction.[4,6] It appears that for a successful outcome to a radical cyclization reaction, the rates of these two processes need to be fine-tuned through highly system-dependent choices of groups Y and Z. A literature survey seemed to point to the notion that in general, a radical having an electron-withdrawing group attached to the nitrogen atom is effective in both.[4,6] In this context, a carbamate[7] was chosen as Z (**1**) in our study since it can readily be converted to either CH_3 or H. The results of our preliminary study indicated that while the generation of radical **2** from the sulfide precursor [**1**: Y = SPh; Z = C(=O)OMe] is sluggish, that of the corresponding selenide[8] [**1**: Y = SePh; Z = C(=O)OMe] is in a fine balance with the subsequent radical cyclization reaction in a number of systems we examined.[9]

On the basis of these results, the study toward the synthesis of (−)-sibirine[10] was initiated predicated upon the retrosynthesis shown in Scheme 1. Of particular significance in this study was the regio- and stereochemical outcome of the cyclization of the radical intermediate **6** to be generated from **4**. The transition state for the 6-exo mode of cyclization with the radical center approaching from the opposite face of the axially disposed OR group appeared clearly less strained over that of the 7-endo. However, the effect of a group X on the extent of selectivity between the two modes of cyclization was of particular interest.

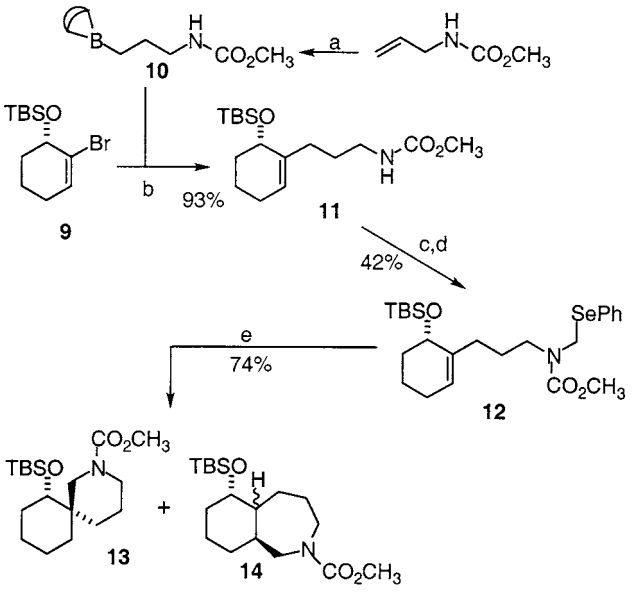
Scheme 1





The synthesis of the radical precursor **4** (R = TBDMS) with X = H is summarized in Scheme 2. Thus, the introduction of the carbamate-protected side chain amine **11**

Scheme 2[a]



[a] Reagents and conditions: (a) 9-BBN (1.5 mol equiv)/THF, rt, 3 h; (b) $Pd(PPh_3)_4$ (3 mol %), NaOH/THF/H_2O, reflux, 1.5 h; (c) NaH (1.2 mol equiv)/THF, rt, 15 min; then $ICH_2Sn(n\text{-}Bu)_3$ (1.06 mol equiv), rt, 12 h (85%); (d) *n*-BuLi (1.2 mol equiv)/THF, −78 °C; $(PhSe)_2$ (1.02 mol equiv)/THF, −78 °C, 0.5 h (49%); (e) $(n\text{-}Bu)_3SnH$ (1.5 mol equiv), AIBN (cat.)/toluene, reflux, 13 h.

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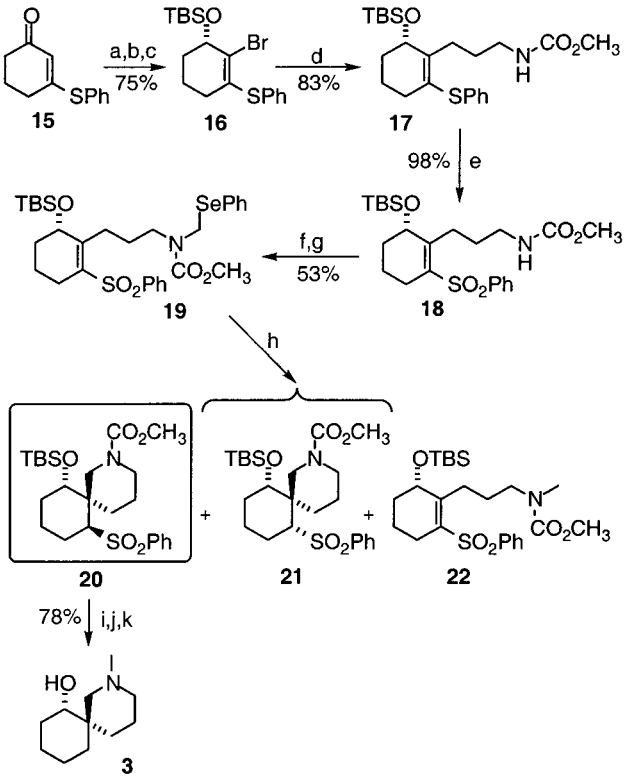
was smoothly achieved by the Suzuki coupling reaction of the *tert*-butyldimethylsilyl (TBS)-protected bromide **9** with the borane **10**[11] generated from allylamine methyl carbamate. Carbamate **11** was first converted to its tri(*n*-butyl)stannylmethyl derivative and transmetalation of the stannane with *n*-BuLi followed by treatment with diphenyl diselenide to produce phenyl selenide **12** in an unoptimized overall yield of 42%. Subjection of phenyl selenide **12** to radical reaction conditions resulted in the effective generation of the expected radical, which underwent cyclization cleanly with only a small amount of the reduction product (i.e., H in place of PhSe in **12**) detected. However, the cyclized products consisted of an inseparable mixture of spirobicycle **13** (one stereoisomer) and bicyclic sytem **14** (as a 2:1 stereoisomeric mixture),[12] indicating only a meager difference in transition state energies between the 6-exo- and 7-endo modes of radical cyclization processes.

In an effort to increase the formation of the spirocyclization product (i.e., pathway a) from radical **6**, it was contemplated that the use of a sterically demanding group for X might impede the competing 7-endo mode of cyclization. In this context, a phenylsufonyl group was selected because, in addition to its steric size, the radical **7** to be generated as a result of the 6-endo cyclization could be stabilized by this group.[13] The synthesis of the sulfone-containing radical precursor **19** that commences with 3-phenylthio-2-cyclohexen-1-one (**15**)[14] is outlined in Scheme 3. While the carbamate-protected side chain could readily be attached by the Suzuki coupling reaction as above, the introduction of the $PhSeCH_2$ unit by the two-step sequence [(i) NaH; ICH_2-Sn(*n*-Bu)$_3$ (43%). (ii) *n*-BuLi/THF, −78 °C; $(PhSe)_2$ (5%)] proved to be ineffective. The problem was circumvented by first oxidizing the PhS to the $PhSO_2$ group (see **17** to **18**). Interestingly, the presence of the sulfone group on the cyclohexenyl ring appears to exert a considerable influence in making the NH readily accessible for deprotonation. Thus, sulfone **18** was converted to the selenide radical precursor **19** via its *N*-hydroxylmethyl derivative in 53% overall yield.[15]

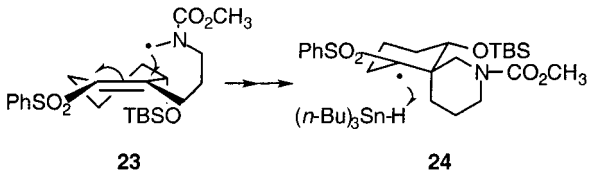
Treatment of phenyl selenide **19** with tri(*n*-butyl)tin hydride in the presence of a catalytic amount of AIBN in refluxing toluene provided spirocycle **20** in 60% yield together with a 1:1 inseparable mixture of **21**, the sufone epimer of **20**, and the reduction product **22** (15%).[16] The

Scheme 3[a]



[a] Reagents and conditions: (a) NBS (1.5 mol equiv)/CCl_4, rt, 24 h (81%); (b) $NaBH_4$ (1.1 mol equiv), $CeCl_3$ (1.1 mol equiv)/methanol, rt, 0.5 h (97%); (c) TBS-Cl, imidazole, DMF, rt (95%); (d) **10**, $Pd(PPh_3)_4$ (3 mol %), NaOH/THF, H_2O, reflux, 3 h; (e) MCPBA (2.4 equiv)/CH_2Cl_2, rt, 2.5 h; (f) *t*-BuOK (2.0 mol equiv), paraformaldehyde (excess)/*t*-BuOH, rt, 1 h (75%); (g) PhSeH (excess), *p*-TsOH (cat.), rt, 2 h (71%); (h) (*n*-Bu)$_3$SnH (2.0 mol equiv), AIBN (cat.), toluene, reflux, 7 h; (i) Na (20 mol equiv)/ethanol (20 mol equiv), from −20 °C to rt, 2 h at rt (92%); (j) $LiAlH_4$ (10 mol equiv)/THF, rt, 30 min; (k) CH_3CN/45% aq HF (20:1), rt, 1.5 h (85% for steps j and k).

inspection of the H^1 NMR spectrum in $CDCl_3$ revealed that the OTBS and $PhSO_2$ groups in the major product **20** adopt, respectively, equatorial and axial orientations. The selective formation of the axial sulfone seems to suggest that the initially cyclized radical undergoes ring inversion to adopt a conformation such as **24** and that the observed outcome may be a reflection of the preferential approach by the (*n*-Bu)$_3$SnH from the equatorial face (see **24**).



The combined yield of the desired spirocycle alkaloids **20** and **21** approached close to 70%. However, due to the difficulty of removing the contaminant **22** from the mixture of **21** and **22**, the single stereoisomer **20** was subjected to

(11) (a) Brosius, A. D.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 440−441. (b) Kamatani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743−8744. Reviews: (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (d) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag: Weinheim, Germany, 1998; pp 44−97.

(12) Due to the presence of the rotational isomers of the carbamate group in each of the three products, analysis of the ^{1}H NMR spectrum of the mixture of **13** and **14** was severely hampered. Therefore, the mixture was reduced with $LiAlH_4$ and the resulting, still inseparable mixture of the *N*-methyl compounds was analyzed.

(13) For the use of the phenylsulfonyl group as a radical acceptor, see, e.g.: (a) Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem.* **1990**, *55*, 1786−1792. (b) Simpkins, N. S. *Chem. Soc. Rev.* **1990**, *19*, 335−354.

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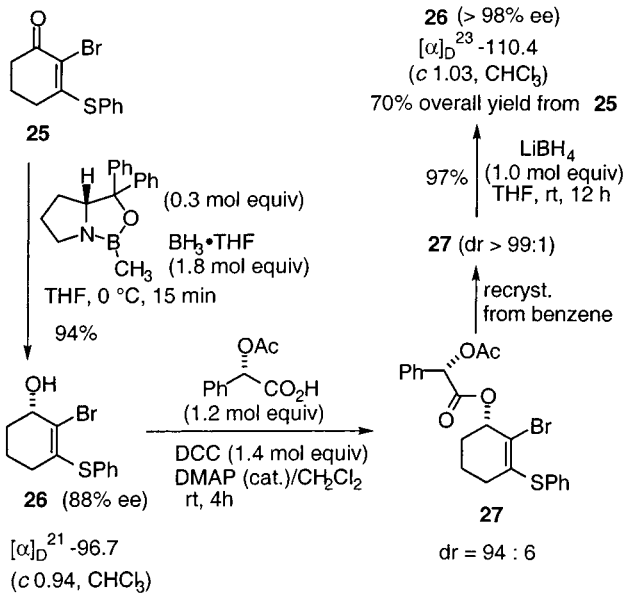
(15) For some unknown reason, the two-step sequence toward **19** via the tri(*n*-butyl)stannylmethyl derivative of **18** proved to be much less efficient.

(16) In addition, the dealkylated product **18** was also isolated (<10%).

the subsequent three-step sequence (78% overall yield) to complete the synthesis of racemic sibirine (**3**).

The asymmetric synthesis of (−)-sibirine (**3**) was achieved through the use of the chiral allylic alcohol **27** (Scheme 4).

Scheme 4



As in the case of 2-bromo-2-cyclohexen-1-one,[17] the CBS-oxazaborolidine-mediated reduction[18] of its 3-PhS analogue, **15**, required an ambient temperature for the reaction to proceed. The enantiomeric excess of the resulting allylic alcohol **26** was found to be only 88%. Enantiomerically pure **26** was accessed by the formation of diastereomeric esters of this alcohol with (*S*)-*O*-acetylmandelic acid. Single recrystallization of the resulting esters **27** from benzene provided ester **27** with a diastereomeric ratio over 99:1. Removal of the mandelate portion from **27** proved to be somewhat problematic. While the use of DIBAL, $LiAlH_4$, or nucleophilic alkaline conditions resulted in the formation of a complex mixture of products, that of $LiBH_4$ in THF led to the clean removal of the mandelate unit, providing allylic alcohol **26** with >98% ee. The stereochemical integrity of the resulting allylic alcohol thus obtained was ascertained by conversion to its (*S*)-*O*-acetylmandelate and the 400 MHz ^1H NMR analysis of the ester. The enantiomerically pure alcohol was then converted to its TBS ether **16**, and the entire sequence developed for the racemic series was repeated, thus achieving the synthesis of (−)-sibirine; $[\alpha]^{23}_D$ −29.7 (*c* 0.63, $CHCl_3$) [lit.[3d] $[\alpha]_D$ −22.5 (*c* 0.81, $CHCl_3$)]. While the synthesis of racemic sibirine (**3**) was achieved in 11 steps from 2-phenylthio-2-cyclohexen-1-one (**15**) in 15.2% overall yield, that of (−)-sibirine (**3**) required 14 steps from **15** with 10.9% overall yield.

In summary, we have shown that a (methoxycarbonylamino)methyl radical can readily be generated from the phenylselanyl precursor and the radical undergoes highly 6-exo stereo- and regioselective spirocyclization to a cyclohexene unit bearing the sterically demanding and radical stabilizing phenylsulfonyl group at the distal alkene carbon. This observation has been applied to the effective synthesis of racemic and (−)-sibirine.

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Supporting Information Available: Experimental details as well as analytical and spectroscopic data for new compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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