Bridgehead Oxiranyl Sesquiterpenoids. Asymmetric Total Synthesis of (−)-Salsolene Oxide

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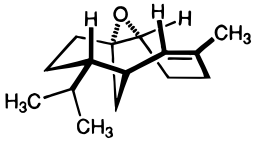
In 1991 during the course of phytochemical studies involving odoriferous plants from the Himayalan region of India, Weyerstahl *et al.* isolated from the essential oil of *Artemisia salsoloides* the architecturally unusual sesquiterpene **1** termed salsolene oxide.[1] Whereas remarkable progress has been made in the assembly of naturally occurring bridgehead olefinic systems,[2] little attention has previously been paid to oxidized forms thereof since this class of compounds was of limited interest[3] prior to the disclosure of **1**.



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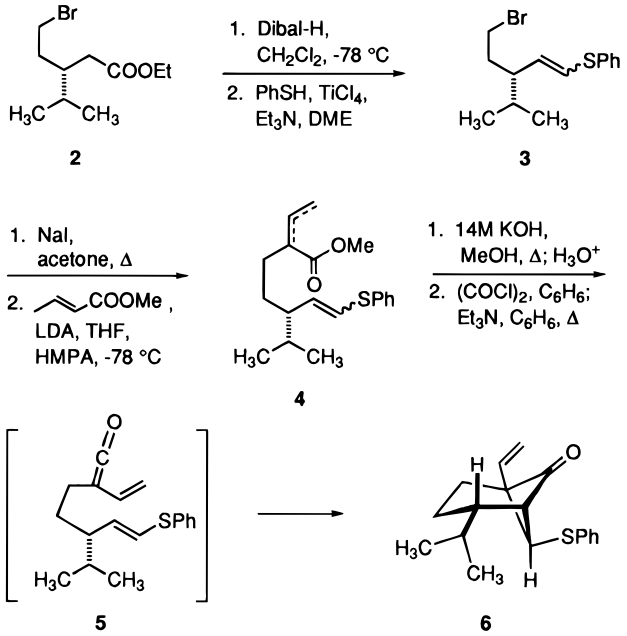
The structure and relative stereochemistry of **1** were deduced on the basis of extensive NMR studies. Central to the molecular array are its unsaturated bicyclo[5.3.1]undecane core and trisubstituted oxirane, both in strictly defined geometric settings. Although the limited quantities of natural **1** previously precluded the definition of absolute stereochemistry, its likely biogenesis from germacrene D suggested the direction to be taken in an asymmetric synthesis of this target.

The brief, stereocontrolled elaboration of (−)-**1** described herein demonstrates the powerful and multifaceted manner in which a phenylthio substituent can direct the regio- and stereoselectivity of *three* key transformations. In the first, the PhS group effectively guides intramolecular ketene−olefin cyclization into the "type I" manifold.[4] For steric reasons, the sulfur substituent in bridged bicyclic ketone **6** eventuates only in an exo orientation (other side chains show little stereocontrol)[4,6b] and subsequently directs attack of vinyllithium to the carbonyl group from that direction ideally suited to spontaneous anionic oxy-Cope rearrangement[5] and kinetically-controlled formation of a bridgehead olefin.[6] Finally, its ultimate reductive removal under dissolving metal conditions is shown to proceed with inversion of bridgehead olefin geometry[7] as mandated by the target terpenoid. The multiple use of a single functional group in this manner constitutes a particularly effective synthetic tactic.

Arrival at ketone **6** began with the diisobutylaluminum hydride (DIBAL-H) reduction of bromo ester **2**, which is

Scheme 1



efficiently derived from (*R*)-(−)-carvone[8] (Scheme 1). Treatment of the resultant aldehyde (99%) with thiophenol in the presence of $TiCl_4$ and Et_3N afforded a mixture of vinyl sulfides **3** rich in the requisite *E*-isomer (*E*/*Z* = 7:3, 89%). Without purification, **3** was subjected to the Finkelstein reaction with sodium iodide (93%) and directly condensed with the enolate anion of methyl crotonate at −78 °C to give **4** (70%).

Snider has earlier elucidated three key factors relevant to intramolecular [2 + 2] ketene−olefin cycloadditions: (a) trans-substituted olefins undergo addition predominantly with retention of stereochemistry, while cis olefins react nonstereospecifically, if at all;[6,9] (b) nucleophilic alkenes are particularly efficient reaction partners; (c) α,β-unsaturated ketenes exhibit a predilection for criss-cross behavior when matched with b. From this perspective, intermediate **5** appeared to be an ideal precursor to **6**. Indeed, dehydrochlorination of the acid chloride derived from **4** with triethylamine in refluxing benzene gave rise to **6** (57% based on the *E*-isomer content) alongside a minor isomer that was not characterized.

In addition to facilitating the intramolecular cycloaddition in the necessary criss-cross mode, the PhS substituent also directs the 1,2-addition of vinyllithium cleanly to the exo surface of **6** as in **7**[10] (Scheme 2). The ring strain inherent in 1,2-divinylcyclobutanoxide **7** is sufficient to promote [3,3] sigmatropy under the reaction conditions.[5,6,11] This electronic reorganization proceeds stereoselectively to deliver enolate anion **8**, direct methylation of which with excess methyl iodide furnished **9** (87%).[12] The structural assignment to **9** is based on the magnitude of vicinal coupling constants and confirmed by the results of several NOE difference experiments.

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(1) Weyerstahl, P.; Marschall, H.; Wahlburg, H.-C.; Kaul, V. K. *Liebigs Ann. Chem.* **1991**, 1353.
(2) Paquette, L. A. *Chem. Soc. Rev.* **1995**, *24*, 9.
(3) For an example, consult: Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277.
(4) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793.
(5) (a) Paquette, L. A. *Synlett* **1990**, 67. (b) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609.
(6) (a) Snider, B. B.; Allentoff, A. J.; Walner, M. B. *Tetrahedron* **1990**, *46*, 8031. (b) Snider, B. B.; Allentoff, A. J. *J. Org. Chem.* **1991**, *56*, 321. (c) Zucker, P. A.; Lupia, J. A. *Synlett* **1990**, 729.
(7) McCullough, D. W.; Bhupathy, M.; Piccolino, E.; Cohen, T. *Tetrahedron* **1991**, *47*, 9727 and relevant references cited therein.
(8) Paquette, L. A.; Dahnke, K.; Doyon, J.; He, W.; Wyant, K.; Friedrich, D. *J. Org. Chem.* **1991**, *56*, 6199.
(9) Snider, B. B.; Walner, M. *Tetrahedron* **1989**, *45*, 3171.
(10) Although examples of bicyclo[3.1.1]heptanones related to **6** but without substituents on the methano bridge are uncommon [see Lee, S. Y.; Kulkarni, Y. S.; Burbum, B. W.; Johnson, M. I.; Snider, B. B. *J. Org. Chem.* **1988**, *53*, 1848], comparably stereoexclusive 1,2-additions to the carbonyl group are not expected.
(11) Wilson, S. R. *Org. React.* **1993**, *43*, 93.
(12) A referee has pointed out that if the vinyllithium addition had occurred with the opposite stereochemistry, the oxyanionic Cope reaction would have produced directly the desired stereochemistry of the bridgehead alkene. While this is true with regard to the configuration of the existing isopropyl-substituted stereogenic center, issues such as the stereochemistry of the methylation and eventual dehydration persist as elements of serious concern.

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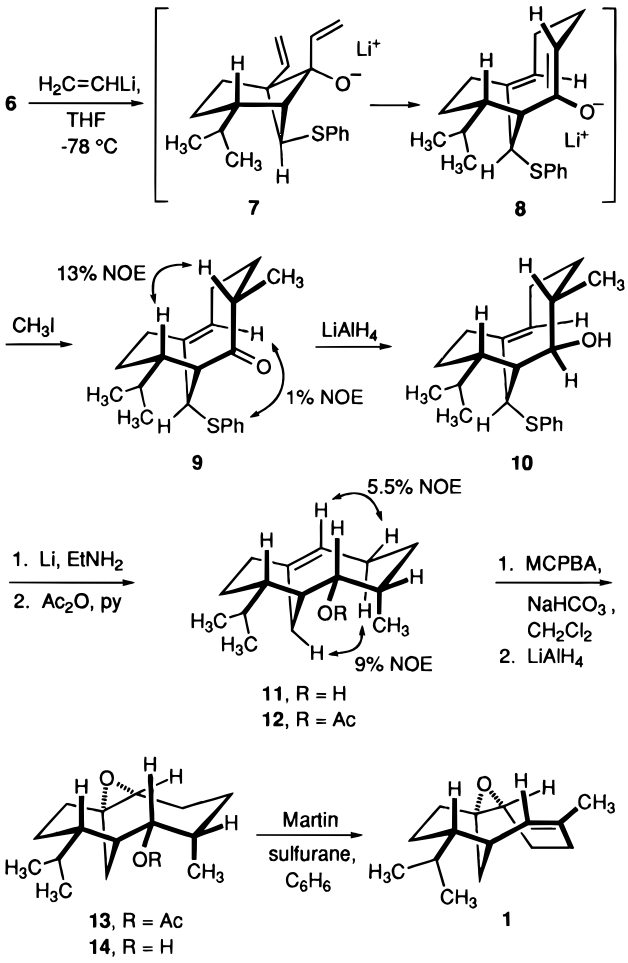
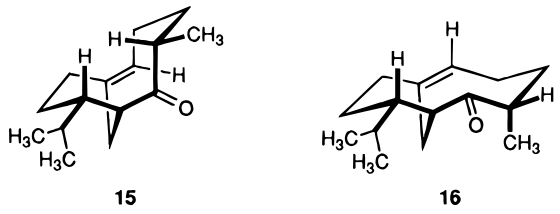
Scheme 2



Undesirable structural changes were best skirted by delaying desulfurization until after reduction of the carbonyl group.[13] All of the salient structural features of the resulting alcohol **10** were revealed by 2-D NMR methods. Subjection of **10** to the action of lithium in ethylamine at −78 °C[14] generated **11** (80%) and set the stage for arrival at **1**.

Molecular mechanics calculations[15] performed on enones **15** and **16** have indicated the *Z*-isomer **16** to be more stable by *ca.* 14 kcal/mol. This ordering of thermodynamic stability, which carries over to alcohols such as **11**, indicates that the conversion of **6** to **9** had necessarily proceeded via a chairlike transition state under kinetic control. Beyond this, the ability to accom-



15 **16**

plish isomerization of the double bond in **10** from *E* to *Z* during transient generation of the allylic anion suggested itself on several fronts. Thus, loss of stereocontrol has been reported for the reduction of allyl phenyl sulfides with lithium *p,p′*-di-*tert*-butylbiphenylide,[7] lithium triethylborohydride,[16] and $NaBH_4$ in the presence of nickel chloride.[17]

For characterization, the rather labile **11** was converted into its acetate **12** (98%). The olefin geometry is defined as *Z* primarily on the strength of an intense NOE interaction between an allylic proton and a second proton resident on the methylene bridge. In addition, the olefinic proton shows NOE to the complementary allylic proton as shown.

The final phase of the synthesis involved the sequential epoxidation of **12** (97%), reduction with $LiAlH_4$, and dehydration with the Martin sulfurane reagent[18] in benzene at 50 °C (80% for 2 steps). The volatile product, identical with naturally derived salsolene oxide by high-field ^1H and ^{13}C NMR spectroscopies, exhibited $[\alpha]^{22}_D$ −24° (*c* 0.2, $CHCl_3$). Although the elimination of water occurs in trans fashion, this process need not operate within the precise conformation shown. In actuality, the NMR spectral features of all the intermediates depicted in Scheme 2 reveal their capacity for dynamic conformational change at ambient temperatures.

The reaction sequence developed here, by virtue of one's ability to assemble the salsolene oxide framework very efficiently and to control the stereochemistry by utilizing the PhS group in a triple-threat role, holds promise for other applications in synthetic organic chemistry.

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Supporting Information Available: Spectroscopic data for **6**, **9**, **12**, and **13** (1 page). See any current masthead page for ordering and Internet access instructions.

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(15) MODEL version 2.99 obtained from Prof. K. Steliou was used. We thank Dr. Scott Edmondson for these data.
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(17) Palmisano, G.; Danieli, B.; Lesma, G.; Mauro, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1564.
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