Utilization of the Phenylthio Substituent as a Multipurpose Synthetic Tool. Direct Application to the Enantioselective Construction of (−)-Salsolene Oxide

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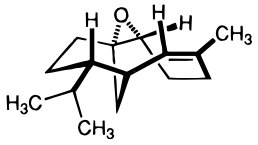
The architecturally unprecedented sesquiterpene (−)-salsolene oxide (**1**) has been synthesized in enantioselective fashion from (*R*)-(−)-carvone. Generation of the phenylthio-substituted vinyl ketene **4** is followed by intramolecular cyclization to the functionalized cyclobutanone **9**. Vinyllithium addition to this intermediate proceeds in that stereocontrolled fashion which enables oxy-Cope rearrangement to operate readily under conditions of kinetic control. After hydride reduction, the desulfurization of **16** proceeds with inversion of bridgehead olefin geometry to deliver **17**. This access route to the thermodynamically more stable geometric arrangement permits direct entry to **1**. Attention is called specifically to the critical 3-fold function played by a phenylthio group introduced at the outset.

The isolation of diverse natural products featuring bridgehead unsaturation in their framework has constituted an exciting branch of structural chemistry and provided challenging targets for total synthesis.[1] This family of compounds includes, but is hardly limited to, paclitaxel,[2,3] taxusin,[4,5] vulgarolide,[6,7] eremantholide A,[8−10] cerorubenic acid-III,[11,12] *O*-methylshikoccin,[13,14] and cleomeolide.[15,16] Equally remarkable has been the discovery by Weyerstahl et al. in 1991 of the architecturally unusual bridgehead oxiranyl sesquiterpenoid **1** from the essential oil of the Himalayan plant *Artemisia salsoloides*.[17] The disclosure of **1**, known as salsolene oxide, constitutes one of the few reports dealing with a more highly oxidized array about the bridgehead site.[14,18]



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The structure and relative stereochemistry of **1** were deduced on the basis of extensive NMR spectroscopic analysis. The very limited quantities of salsolene oxide precluded proper establishment of its absolute configuration and determination of whether **1** is dextro- or levorotatory. We now report the complete details of an enantioselective total synthesis of (−)-**1** having well-defined stereochemistry.[19] The decision to prepare this particular antipode of salsolene oxide was founded on its likely biosynthesis from germacrene D.[17,20]

On this basis, the retrosynthesis of **1** leads back to **2**, which was expected to result from anionic oxy-Cope rearrangement [21] of **3** via a chairlike transition state [22] followed by direct in situ methylation (Scheme 1). Introduction of the *E*-configured bridgehead double bond under kinetic control in this fashion would subsequently

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(20) (a) Fattorusso, E.; Magno, S.; Mayol, L.; Amico, V.; Oriente, G.; Piattelli, M.; Tringali, C. *Tetrahedron Lett.* **1978**, 4149. (b) Bohlmann, F.; Singh, P.; Jakupovic, J. *Phytochemistry* **1982**, *21*, 157.

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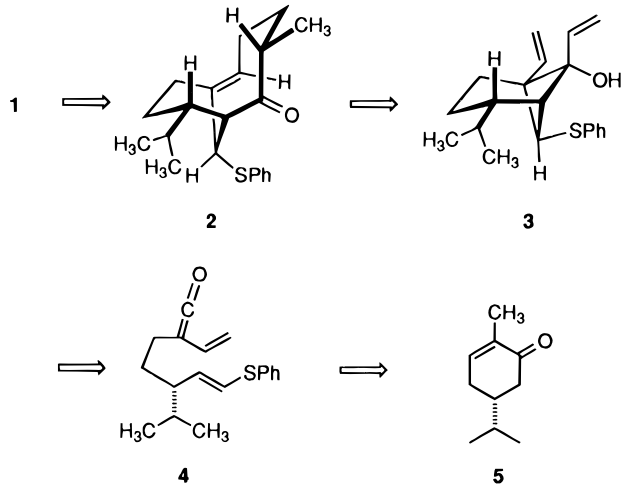
Scheme 1



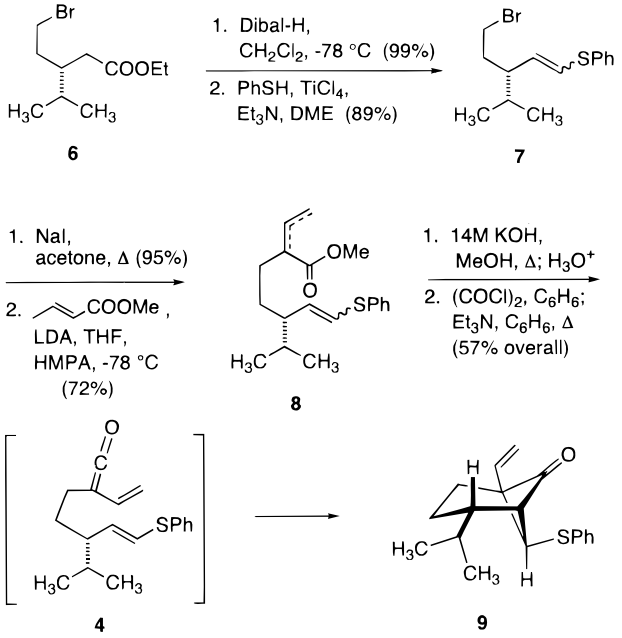
require isomerization to the *Z* isomer prior to arrival at **1**. The ketonic precursor to **3** requires assembly via "type I" intramolecular [2 + 2] cycloaddition[23] within α,β-unsaturated ketene **4**, a highly functionalized reactive intermediate presumed to be accessible by suitable chemical modification of (*R*)-(−)-carvone (**5**).

Specific attention is called to the particularly significant role which the phenylthio substituent will play at three stages of this reaction sequence. The efficiency of "type I" ketene−olefin cycloadditions in a criss-cross mode is appreciably heightened when the alkene component is nucleophilic.[23,24] Accordingly, the PhS group resident in **4** was expected to significantly enhance its suitability as a precursor to the cyclobutanone. In addition, the steric contributions of the PhS substituent in this pivotal ketone precursor should clearly direct the 1,2-addition of vinyllithium to its exo surface as in **3**. Finally, the reductive removal of this substituent has proven to be a protocol crucial to expedient arrival at salsolene oxide.

Results and Discussion

At the outset, advantage was taken of the efficient manner in which bromo ester **6** can be produced from (*R*)-(−)-carvone (**5**).[25] Dibal-H reduction of **6** at −78 °C provided the aldehyde, condensation of which with thiophenol in the presence of $TiCl_4$ and Et_3N afforded a mixture of vinyl sulfides **7** rich in the *E* isomer (*E*:*Z* = 7:3) (Scheme 2). The predominance of the *E* form holds considerable importance since trans-substituted olefins undergo predominantly the requisite trans addition while cis olefins react nonstereospecifically if at all.[23] Submission of **7** to the Finkelstein reaction by heating with sodium iodide in acetone and subsequent exposure of the iodide to the enolate anion of methyl crotonate at −78 °C gave **8** (72%) as a mixture of α,β- and β,γ-unsaturated isomers. The generation of a mixture at this point is of little consequence since subsequent saponification, conversion to the acid chloride, and dehydrochlorination with triethylamine converge to ketene **4** in all cases. The involvement of **4** is, of course, inferred since this intermediate was not isolated but transformed directly into **9** as formed. The overall yield for the conversion of **8** into **9** was 57%. This level of efficiency is notable for such reactions.

Scheme 2



With arrival at **9**, the time had come to incorporate a vinyl group stereoselectively as a prelude to the sigmatropic event. As expected, the strain inherent in 1,2-divinylcyclobutanoxide **10** promoted rapid conversion to enolate anion **11** under the reaction conditions (Scheme 3). This electronic reorganization can be relied upon to proceed stereoselectively[22] and to set the geometry of the bridgehead double bond as shown. Direct methylation of **11** with excess methyl iodide afforded ketone **2**.

The ^{1}H NMR features of **2** are well resolved and readily amenable to assignment on the basis of a DQF−COSY analysis, which allowed to trace the entire atomic connectivity. In particular, allylic coupling (J = 3 Hz) between H-5 and H-11α established the connection between these two fragments. Similarly, homoallylic coupling between H-4α and the downfield methine at δ 4.33 showed that C-7 was likewise attached to the double bond. The relative stereochemistry and preferred conformation shown were deduced from the magnitudes of the vicinal and long-range coupling constants and corroborated by difference NOE experiments (see Supporting Information).

The response of **2** to Raney nickel desulfurization was next examined. The intended reduction proceeded smoothly in refluxing acetone. To reduce volatility and facilitate characterization, the resulting ketone was reduced with lithium aluminum hydride, and a single alcohol was obtained in 55% overall yield. Quite unexpectedly, this compound was not the anticipated product but an isomer in which the bridgehead double bond had migrated to the alternative bridgehead site as in **12**. Due to slow conformational exchange, most of the resonances in the 400 MHz ^{1}H NMR spectrum of **12** appeared broad and extensively overlapped under ordinary conditions in

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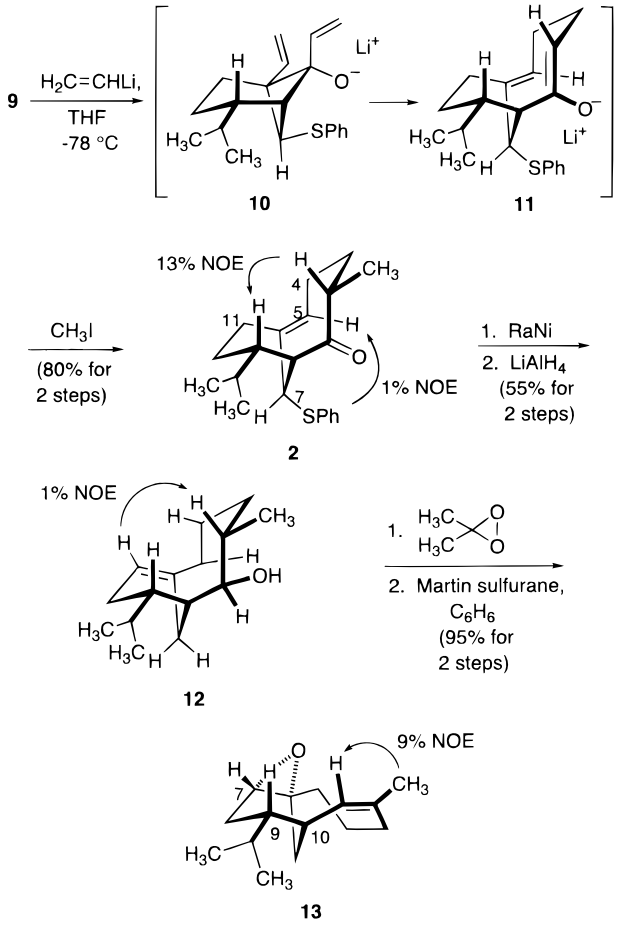
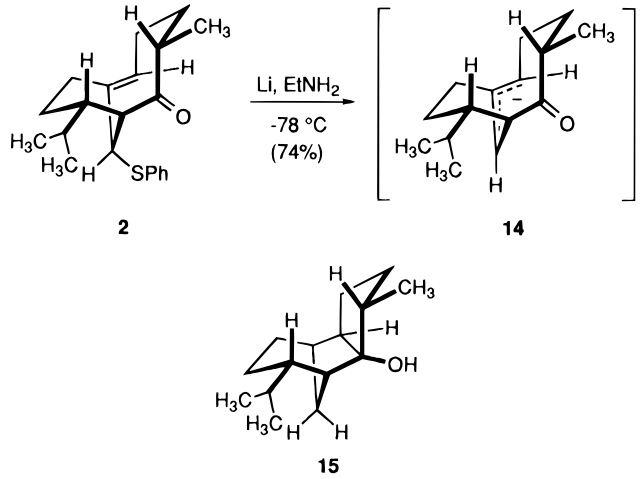
Scheme 3



C_6D_6 solution. The situation improved to some degree upon warming to 65 °C, but interpretation of the DQF−COSY spectrum remained ambiguous. Severe exchange broadening of many resonances surfaced as well in the ^{13}C arena, thereby precluding the recording of a carbon-detected $^1H,^{13}C$ one-bond correlation spectrum. However, these problems could be overcome by recording a $^1H,^{13}C$−HMQC spectrum in DMSO-d_6 at ambient temperature. Complete assignments of shifts and multiplicities now became possible, because in this proton-detected technique the intensities of the cross peaks correlating ^{13}C with directly connected ^1H nuclei depend chiefly on the line width of the proton rather than the corresponding carbon. Consequently, strong cross-peaks are observed for $^{13}C/^1H$ pairs when the ^1H resonance is sharp, even when the corresponding ^{13}C resonance is approaching coalescence and can barely be localized in the ^{13}C spectrum. As a corollary, a weak cross-peak results for a broad ^1H resonance despite the existence of a sharp correlated ^{13}C resonance but can nevertheless be detected due to the significantly higher sensitivity of the proton-detected techinque. Through combination of the assignments of methylene vs methine protons from the HMQC spectrum with the $^1H,^1H$ coupling information from the DQF−COSY spectra, it was possible to trace the entire connectivity of **12**.

As a follow-up, **12** was epoxidized with dimethyldioxirane and dehydrated with the Martin sulfurane reagent.[26] Comparison of the ^1H NMR spectra of **13** and salsolene oxide clearly showed that the two compounds

Scheme 4



are not identical. The close similarity of their ^{13}C NMR features indicated, however, that they were closely related structurally. The connectivity in **13**, identified by careful examination of its COSY spectrum, is confirmatory of its direct formation from **12** with steric approach control. The *Z* geometry of its double bond was assigned on the basis of the strong NOE interaction indicated in Scheme 3. Telltale vicinal coupling constants such as those for H-7/H-8α, H-9/H-8α, H-9/H-10 (all close to zero), H-7/H-8β (3.5 Hz), and H-9/H-8β (7.5 Hz) indicate further that the six-membered ring adopts a boatlike conformation. This conclusion is supported by the observation of W-coupling involving H-9 and one of the methylene bridge protons (see Supporting Information).

As undesirable as the **2** → **12** structural change was, it may well represent a unique example of an isomerization involving the conversion of one bridgehead olefin into another.

In 1980, Naruta demonstrated the feasibility of preparing polyprenyl alcohols by reductive elimination of allylic phenylthio groups with lithium metal in ethylamine.[27] Direct application of these conditions to **2** resulted in the formation of alcohol **15** in 74% yield (Scheme 4). Although the exact stereochemistry of this tricyclic alcohol was not determined, its formation was clearly a result of the close proximity of the carbonyl group and allylic anion in **14**, which lends itself very favorably to transannular bonding across the eight-membered ring.

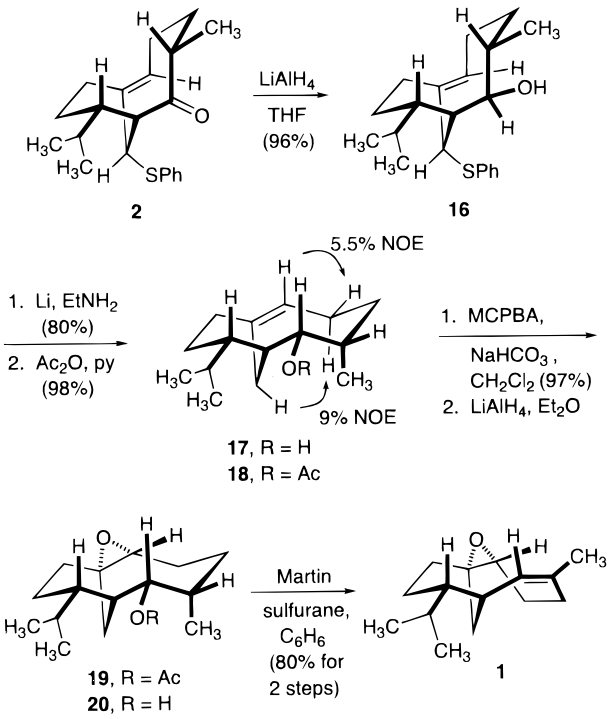
This problem was easily skirted by delaying desulfurization until after reduction of the carbonyl group (Scheme 5). That hydride delivery to **2** occurs from the equatorial direction as anticipated on steric grounds was easily deduced in several ways. The most convincing evidence is the absence of a resolved vicinal coupling between the protons on the carbinol carbon and the adjacent methyl-substituted center. A 90° angular relationship is responsible for the lack of spin−spin interaction.

The reduction of **16** with lithium in ethylamine at −78 °C proceeded cleanly to deliver a single alcohol in 80% yield. To simplify structural analysis, conversion to the acetate preceded detailed NMR analysis. *Remarkably, this dissolving-metal protocol proceeds with inversion of bridgehead olefin geometry precisely as mandated by the target terpenoid!* The ^1H NMR spectra of **18** in $CDCl_3$ or

(26) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327.

(27) Naruta, Y. *J. Org. Chem.* **1980**, *45*, 4097.

Scheme 5

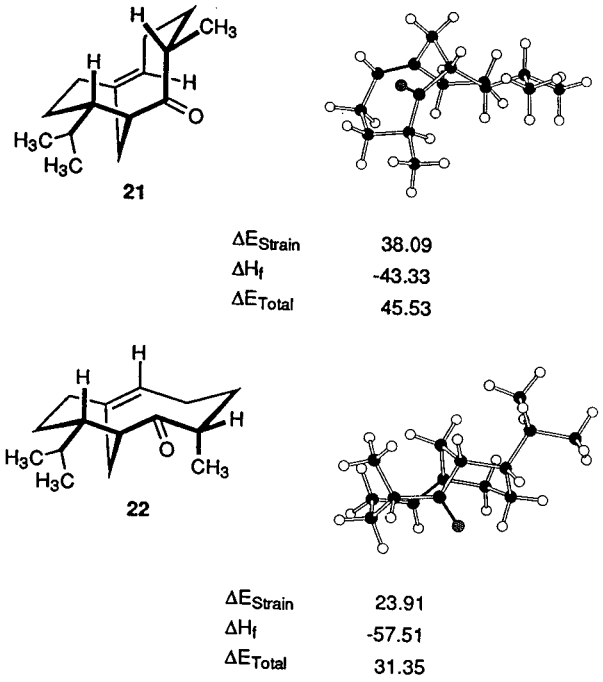


DMSO-d_6 at 25 °C exhibited considerable overlap, and the broad appearance of several resonances suggested that slow conformational exchange was operating. Variable temperature ^{1}H NMR studies conducted in DMSO-d_6 at 75, 100, and 125 °C were confirmatory of this conclusion. For these reasons, the proton connectivities observed in a DQF−COSY spectrum recorded at 25 °C were ambiguous in part. Furthermore, ^{13}C NMR spectra obtained at 25 °C showed several exchange-broadened resonances, and the complete set of 17 resonances surfaced only upon heating to 125 °C in DMSO-d_6. However, all ^{13}C resonances could be localized in proton-detected HMQC (one-bond) and HMBC (multiple-bond) ^{1}H,^{13}C shift-correlation spectra obtained at 25 °C. The information contained in these spectra, in conjunction with the DQF−COSY spectrum, permitted derivation of all ^{1}H and ^{13}C assignments and confirmation of the constitution of the acetoxyalkene to be as shown in **18** (see Supporting Information). Assignment of olefin geometry and relative stereochemistry is based on a variety of NOE enhancements including those shown in Scheme 5.

Molecular mechanics calculations[28] were undertaken to shed light on the thermodynamic relationship between bridgehead olefin isomers of this type. The data computed for enones **21** and **22**, compiled in Chart 1, indicated the *Z* isomer to be more stable by ca. 14 kcal/mol. This stability ordering, which carries over to derivatives such as **17** and **18**, indicates that the original anionic oxy-Cope rearrangement had necessarily to have proceeded via a chairlike transition state under kinetic control.

The ability to accomplish isomerization of the double bond in **16** from *E* to *Z* during transient generation of the allylic anion suggested itself on several fronts. In particular, loss of stereocontrol has been reported for the reduction of allyl phenyl sulfides with lithium *p*,*p*′-di-*tert*-butylbiphenylide,[29] lithium triethylborohydride,[30] and sodium borohydride in the presence of nickel chloride.[31]

Chart 1. Global Minimum Energy Conformations of 21 and 22 As Determined by Molecular Mechanics Calculations (Chem 3-D Output). All Energies Are in Units of kcal/mol



For completion of the salsolene oxide synthesis, epoxidation must be directed to take place on the exo surface of the π-bond. This was not viewed as problematic. Indeed, the reaction of **18** with *m*-chloroperbenzoic acid gave rise to **19** in near-quantitative yield. Perhaps because of an innate sensitivity to acidic conditions, comparable treatment of alcohol **17** eventuated predominantly in decomposition.

Following arrival at **19**, it proved an easy matter to cleave the acetate group by chemoselective reduction, without opening of the oxirane ring. This is because nucleophilic attack from the backside of either C−O bond is very effectively deterred by the steric bulk of the molecular framework. Dehydration of **20** with the Martin sulfurane reagent[26] in benzene at 50 °C once again resulted in the introduction of a *Z* double bond to deliver salsolene oxide (**1**). This volatile substance proved to be identical with the natural specimen by high-field ^{1}H and ^{13}C NMR spectroscopy. The synthetic sample exhibited an $[\alpha]^{22}_D$ of −24° (*c* 0.2, $CHCl_3$). Since optical rotation data on the material produced by nature is not available, an open question remains as to whether the absolute configuration defined by **1** is correct. Suffice it to say that **1** is definitely levorotatory.

A concise synthesis of (−)-salsolene oxide has been described. A phenylthio-substituted double bond in unsaturated ketene **4** provides the proper electronic balance to permit intramolecular cyclization and formation of **9**. The phenylthio group in **9** directs entry of the vinyl anion, setting the stage for an anionic oxy-Cope

(28) MODEL version 2.99 obtained from Prof. K. Steliou was used. We thank Dr. Scott Edmondson for these data.

(29) McCullough, D. W.; Bhupathy, M.; Piccolino, E.; Cohen, T. *Tetrahedron* **1991**, *47*, 9727 and relevant references therein.

(30) Mohri, M.; Kinoshita, H.; Inomata, K.; Kotake, H.; Takagaki, H.; Yamazaki, K. *Chem. Lett.* **1986**, 1177.

(31) Palmisano, G.; Danieli, B.; Lesma, G.; Mauro, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1564.

rearrangement that assembles the desired terpenoid framework readily. The triple-threat role of the phenylthio functionality surfaces finally during the dissolving-metal reduction of **16**, which is accompanied by necessary inversion of the bridgehead double-bond geometry. These tactical elements hold promise for application in other synthetic undertakings.

Experimental Section

All reactions were performed in a flame-dried glass apparatus equipped with rubber septa under a static nitrogen or argon atmosphere. Thin-layer chromatography was performed on EM Reagents precoated silica gel 60 F_{254} analytical plates. Column chromatography was performed on Merck silica gel HG_{254}. The organic extracts were dried over anhydrous magnesium sulfate or sodium sulfate. Solvents were reagent grade and in many cases dried before use. High-resolution mass spectra were recorded at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark, and at Atlantic Microlab, Inc., Norcross, GA.

(1*E*,3*S*)- and (1*Z*,3*S*)-5-Bromo-3-isopropyl-1-pentenyl Phenyl Sulfide (7). A solution of bromo ester **6**[25] (31.86 g, 126.0 mmol, 98% ee) in CH_2Cl_2 (750 mL) was cooled to −78 °C, treated with Dibal-H in toluene (139 mL of 1.0 M in toluene, 139 mmol) during 30 min, stirred at this temperature for 2 h, and quenched with methanol (15 mL). The reaction mixture was allowed to warm to 20 °C and treated with 10% HCl solution. The separated organic layer was washed with a saturated $NaHCO_3$ solution (500 mL) and brine (500 mL), dried, and evaporated to give the bromo aldehyde as a yellow oil (26.0 g, 99%); IR (neat, cm^{-1}) 1725; ^1H NMR (200 MHz, $CDCl_3$) δ 9.78 (t, J = 2.1 Hz, 1 H), 3.49−3.30 (m, 2 H), 2.45 (ddd, J = 16.4, 5.6, 2.0 Hz, 1 H), 2.26 (ddd, J = 16.4, 5.0, 2.1 Hz, 1 H), 2.18−1.67 (series of m, 4 H), 0.99 (d, J = 5.8 Hz, 3 H), 0.86 (d, J = 5.8 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) ppm 202.2, 44.8, 37.0, 34.7, 31.5, 29.7, 19.4, 18.3; MS m/z (M^+) calcd 206.0306, obsd 206.0263; $[\alpha]^{25}_D$ −19.1 (c 1.6, hexanes).

A solution of titanium tetrachloride (13.1 mL, 0.12 mol) in dry 1,2-dimethoxyethane (250 mL) was added to a solution of the above aldehyde (12.32 g, 59.5 mmol) in the same medium (50 mL) over 10 min at 0 °C under N_2. After 10 min, a solution of thiophenol (6.76 g, 65.5 mmol) and triethylamine (9.12 mL, 65.5 mmol) in DME (50 mL) was added over 20 min. The resulting mixture was stirred at room temperature for 3 days, quenched with methanol (100 mL), concentrated in vacuo, and taken up in ether (600 mL). The ethereal solution was washed with brine, dried, and subjected to flash chromatography on silica gel. Elution with 10% ethyl acetate in hexanes gave 12.0 g of sulfide **7** (E:Z = 7:3) and returned 3.0 g of unreacted aldehyde. The adjusted yield of **7** is 89%.

For 7: IR (neat, cm^{-1}) 1590; ^1H NMR (300 MHz, C_6D_6) δ 7.34−7.22 (m, 2 H), 7.05−6.89 (m, 3 H), 6.13 (d, J = 9.3 Hz, 0.3 H), 6.06 (d, J = 15.0 Hz, 0.7 H), 5.40 (dd, J = 15.0, 9.9 Hz, 0.7 H), 5.05 (t, J = 9.9 Hz, 0.3 H), 3.20−2.87 (series of m, 2 H), 2.55−2.49 (m, 0.3 H), 1.94−1.74 (m, 1 H), 1.64−1.18 (m, 2.7 H), 0.80 (d, J = 6.8 Hz, 0.9 H), 0.73 (d, J = 6.8 Hz, 0.9 H), 0.69 (d, J = 6.8 Hz, 2.1 H), 0.62 (d, J = 6.8 Hz, 2.1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 136.2, 136.0, 135.9, 133.4, 128.9, 128.6, 126.3, 126.2, 125.8, 123.7, 48.4, 44.7, 36.1, 34.8, 32.4, 32.1, 31.8, 31.7, 20.6, 20.5, 19.1, 19.0; MS m/z (M^+) calcd 298.0391, obsd 298.0388.

(1*E*,3*S*)- and (1*Z*,3*S*)-5-Iodo-3-isopropyl-1-pentenyl Phenyl Sulfide. A mixture of **7** (10.25 g, 34.3 mmol), sodium iodide (7.80 g, 52.0 mmol), and acetone (220 mL) was refluxed for 15 h, freed of solvent under reduced pressure, taken up in ether (300 mL), and washed with water (2 × 300 mL). The ethereal solution was dried and evaporated to furnish 11.28 g (95%) of iodides (E:Z = 7:3) as a yellow oil: IR (neat, cm^{-1}) 1475; ^1H NMR (300 MHz, C_6D_6) δ 7.41−7.18 (m, 2 H), 7.11−6.88 (m, 3 H), 6.13 (d, J = 9.2 Hz, 0.3 H), 6.09 (d, J = 15.0 Hz, 0.7 H), 5.37 (dd, J = 15.0, 9.9 Hz, 0.7 H), 5.03 (t, J = 9.9 Hz, 0.3 H), 2.95 (dt, J = 4.9, 9.5 Hz, 0.3 H), 2.86−2.75 (m, 1 H), 2.60 (dt, J = 7.2, 9.1 Hz, 0.7 H), 2.46−2.40 (m, 0.3 H), 1.84−1.74 (m, 1 H), 1.63−1.16 (series of m, 2.7 H), 0.80 (d, J = 6.8 Hz, 0.9 H), 0.73 (d, J = 6.8 Hz, 0.9 H), 0.68 (d, J = 6.8 Hz, 2.1 H), 0.61 (d, J = 6.8 Hz, 2.1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 136.0, 135.8, 135.6, 133.1, 128.8, 128.7, 128.3, 126.0, 125.9, 125.7, 123.4, 50.4, 46.6, 37.0, 35.2, 31.8, 31.4, 20.5, 20.4, 19.0, 18.8, 5.8, 4.2; MS m/z (M^+) calcd 346.0252, obsd 346.0268.

Anal. Calcd for $C_{14}H_{19}IS$: C, 48.56; H, 5.53. Found: C, 48.88; H, 5.72.

Iodide Alkylation with Methyl Crotonate. A cold (0 °C), magnetically stirred solution of LDA (37.2 mmol) in THF (125 mL) was treated with dry HMPA (6.48 mL, 37.2 mmol) and stirred for 1.5 h prior to cooling to −78 °C. Methyl crotonate (3.99 mL, 37.7 mmol) was introduced dropwise during 20 min followed by a solution of the iodides (13.3 g, 38.4 mmol) in THF (100 mL). Stirring was maintained at −78 °C for 2 h and at 0 °C for 30 min prior to quenching with water (200 mL) and extraction with ether (300 mL). The organic phase was dried and evaporated, and the residue was purified chromatographically on silica gel (elution with 5% ethyl acetate in hexanes). There was isolated 8.95 g (72%) of **8** as a very pale yellow oil.

For the α,β isomers: IR (neat, cm^{-1}) 1714; ^1H NMR (300 MHz, C_6D_6) δ 7.45−7.41 (m, 1.4 H), 7.36−7.33 (m, 0.6 H), 7.11−6.86 (m, 4 H), 6.29 (d, J = 9.4 Hz, 0.3 H), 6.16 (d, J = 15.0 Hz, 0.7 H), 5.86 (dd, J = 15.0, 9.4 Hz, 0.7 H), 5.58 (dd, J = 10.0, 9.6 Hz, 0.3 H), 3.50 (s, 0.9 H), 3.48 (s, 2.1 H), 2.73−2.25 (series of m, 2 H), 1.87−1.29 (m, 4 H), 1.53 (d, J = 7.1 Hz, 0.9 H), 1.49 (d, J = 7.1 Hz, 2.1 H), 1.00 (d, J = 6.8 Hz, 0.9 H), 0.94 (d, J = 6.8 Hz, 0.9 H), 0.86 (d, J = 6.8 Hz, 2.1 H), 0.81 (d, J = 6.8 Hz, 2.1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.2, 138.7, 137.3, 137.2, 135.8, 133.4, 133.3, 128.9, 128.7, 128.6, 126.0, 124.1, 122.0, 51.6, 51.5, 50.2, 45.9, 32.1, 31.8, 31.3, 24.8, 24.7, 20.8, 20.6, 19.0, 18.8, 14.2, 14.1; MS m/z (M^+) calcd 318.479, obsd 318.165.

Anal. Calcd for $C_{19}H_{26}O_2S$: C, 71.66; H, 8.23. Found: C, 71.87; H, 8.39.

(1*R*,4*S*,5*R*,7*S*)-4-Isopropyl-7-(phenylthio)-1-vinylbicyclo-[3.1.1]heptan-6-one (9). A mixture of **8** (701 mg, 2.2 mmol) and potassium hydroxide (850 mg, 13.2 mmol) in methanol (10 mL) and water (10 mL) was refluxed for 2 days. The methanol was removed under reduced pressure, and the residue was carefully neutralized at 0 °C with 3 N HCl. The acid was extracted into ether, washed with brine, dried, and concentrated to leave 660 mg of material that was directly dissolved in benzene (30 mL) and treated dropwise with oxalyl chloride (1.06 mL, 13.2 mmol). This mixture was stirred for 1 h at 55 °C and for 15 h at 20 °C. The solvent was evaporated, and the acid chloride was taken up in benzene (30 mL), treated with triethylamine (4 mL, 31 mmol), and refluxed for 10 h under N_2. The solvents were removed, and the residue was purified by MPLC on silica gel (elution with 2% ethyl acetate in hexanes) to give 250 mg (57% based on original Z content) of **9** as a pale yellow oil; IR (neat, cm^{-1}) 1783; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.20 (m, 5 H), 5.81 (dd, J = 17.6, 11.9 Hz, 1 H), 5.43 (dd, J = 17.6, 1.4 Hz, 1 H), 5.25 (dd, J = 11.9, 1.4 Hz, 1 H), 3.92 (s, 1 H), 2.95 (s, 1 H), 2.43−2.36 (m, 1 H), 2.29−2.19 (m, 1 H), 2.07−2.02 (m, 1 H), 1.77−1.50 (m, 3 H), 0.81 (d, J = 6.7 Hz, 3 H), 0.62 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.4, 134.4, 132.6, 131.2, 128.9, 127.0, 118.4, 69.3, 64.9, 50.9, 42.0, 36.9, 32.6, 20.9, 20.0, 19.7; MS m/z (M^+) calcd 286.1391, obsd 286.1388; $[\alpha]^{23}_D$ +29.7 (c 2.25, $CHCl_3$).

Anal. Calcd for $C_{18}H_{22}OS$: C, 75.48; H, 7.74. Found: C, 75.38; H, 7.87.

(1*R*,3*S*,6*E*,10*S*,11*S*)-10-Isopropyl-3-methyl-11-(phenylthio)bicyclo[5.3.1]undec-6-en-2-one (2). To tributylvinyltin (190 mg, 0.60 mmol) dissolved in dry THF (3 mL) at −78 °C was added a solution of 2.5 M n-butyllithium in hexanes (0.22 mL, 0.55 mmol). The mixture was stirred for 15 min, and a solution of **9** (143 mg, 0.50 mmol) in THF (0.3 mL) was added. The reaction mixture was stirred at −78 °C for 2 h, warmed to room temperature, and quenched with methyl iodide (1 mL). The mixture was extracted with ethyl acetate (15 mL) and washed with water (2 × 15 mL). The ethereal layer was dried, filtered, and concentrated to leave a residue which was chromatographed on silica gel (elution with 5% ethyl acetate/

hexanes) to furnish 131 mg (80%) of **2** as a colorless oil: IR (neat, cm^{-1}) 1689; ^1H NMR (400 MHz, C_6D_6) δ 7.46 (m, 2 H), 7.02 (m, 2 H), 6.91 (m, 1 H), 6.21 (br ddd, J = 12, 4, 3 Hz, 1 H), 4.33 (br s, 1 H), 2.86 (br s, 1 H), 2.73 (dddd, J = 17, 12, 7.5, 1 Hz, 1 H), 2.59 (br ddq, J = 11.5, 1.5, 7 Hz, 1 H), 2.20 (dddd, J = 12.5, 12.5, 12, 4.5 Hz, 1 H), 2.04 (br m, 1 H), 2.02 (dddd, J = 13, 12, 11.5, 4.5 Hz, 1 H), 1.82 (br ddd, J = 12.5, 4.5, 4 Hz, 1 H), 1.76 (br ddd, J = 11.5, 7.5, 6.5 Hz, 1 H), 1.51−1.32 (m, 3 H), 1.18 (dqq, J = 6.5, 6.5, 6.5 Hz, 1 H), 0.81 (d, J = 7 Hz, 3 H), 0.60 (d, J = 6.5 Hz, 3 H), 0.59 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 216.3, 137.9, 136.4, 129.8, 128.8, 126.0, 123.9, 62.2, 54.4, 41.7, 40.9, 40.2, 33.3, 27.5, 27.2, 23.1, 19.6, 19.1, 18.6; MS m/z (M^+) calcd 328.8661, obsd 328.1866; $[\alpha]^{23}_D$ −16.5 (c 0.75, $CHCl_3$).

Anal. Calcd for $C_{21}H_{28}OS$: C, 76.78; H, 8.59. Found: C, 76.40; H, 8.56.

(1*R*,2*S*,3*S*,7*Z*,10*S*)-10-Isopropyl-3-methylbicyclo[5.3.1]-undec-7-en-2-ol (12). Raney nickel (200 mg, previously stored in ethanol) was refluxed in acetone (15 mL) for 15 min, treated with **2** (50 mg, 0.15 mmol), and heated until TLC analysis indicated that no starting material remained. The reaction mixture was cooled, filtered through Celite (ethyl acetate rinse), washed with water (2 × 40 mL), dried, and concentrated to leave a ketone that was directly reduced.

A cold (−78 °C), magnetically stirred slurry of lithium aluminum hydride (50 mg, 1.35 mmol) in dry THF (30 mL) was treated with a solution of the above ketone in THF (5 mL), allowed to warm to room temperature, quenched with water, and filtered. The aluminum salts were triturated with ethyl acetate (3 × 50 mL), and the filtrate was washed with water (100 mL). The organic layer was dried and evaporated. The residue was purified by MPLC on silica gel (elution with 7% ethyl acetate in hexanes) to give **12** (18 mg, 55%) as a clear oil that decomposed on prolonged standing at room temperature: IR (neat, cm^{-1}) 3382; ^1H NMR (400 MHz, C_6D_6, 65 °C) δ 5.57 (m, 1 H), 3.22 (br s, 1 H), 2.44 (br d, J = 12.5 Hz, 1 H), 2.24 (ddd, J = 12.5, 5.0, 4.5 Hz, 1 H), 1.99 (ddd, J = 14, 7.5, 6 Hz, 1 H), 1.98−1.58 (series of m, 7 H), 1.49 (dqq, J = 6.5, 6.5, 6.5 Hz, 1H), 1.39 (m, 1 H), 1.11 (br m, 1 H), 0.92 (m, 1 H), 0.90 (d, J = 7 Hz, 3 H), 0.87 (d, J = 6.5 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 3 H), 0.81 (br s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) ppm 142.4, 121.4, 78.0,* 44.1,* 43.1, 35.6, 33.4,* 32.5, 30.8,* 28.4, 27.9, 26.0, 25.6,* 20.4, 19.7 (asterisked carbons are near coalescence, chemical shifts extracted from HMQC spectrum); MS m/z (M^+) calcd 222.1984, obsd 222.1985.

(1*R*,2*Z*,7*R*,8*S*,10*S*)-7,8-Epoxy-10-isopropyl-3-methylbicyclo[5.3.1]undec-2-ene (13). Alcohol **12** (8.0 mg, 0.036 mmol) was dissolved in acetone (1 mL), cooled to −78 °C, treated with 10 equiv of a dimethyldioxirane solution in acetone,[32] and allowed to warm to room temperature. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in benzene (1 mL), and this solution was added to Martin's sulfurane (50 mg) dissolved in benzene. This reaction mixture was stirred at 20 °C for 6 h, quenched with saturated $NaHCO_3$ solution, extracted with ether (3 × 20 mL), and concentrated. The residue was subjected to MPLC on silica gel (elution with 2% ethyl acetate in hexanes) and gave 8.0 mg (95%) of **13** as a stable colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.96 (br s, 1 H), 2.72 (br d, J = 3.5 Hz, 1 H), 2.66 (br dd, J = 12.5, 12 Hz, 1 H), 2.41 (br s, 1 H), 2.36 (br dd, J = 15.5, 3 Hz, 1 H), 2.05 (m, 1 H), 2.00 (br d, J = 16 Hz, 1 H), 1.89 (m, 1 H), 1.86 (br dd, J = 15.5, 3 Hz, 1 H), 1.82 (ddd, J = 16, 7.5, 3.5 Hz, 1 H), 1.75 (dd, J = 2, 1 Hz, 3 H), 1.68 (dqq, J = 10.5, 6.5, 6.5 Hz, 1 H), 1.42−1.25 (m, 2 H), 1.20 (br dd, J = 12.5, 5 Hz, 1 H), 0.99 (m, 1 H), 0.91 (d, J = 6.5 Hz, 3 H), 0.80 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.8, 129.2, 59.2, 56.9, 44.3, 37.0, 34.0, 29.8, 29.4, 28.4 (2 C), 24.5, 22.7, 21.9, 21.0; MS m/z (M^+) calcd 220.1827, obsd 220.1816.

(3*S*,4*R*,5*S*,8*R*)-Octahydro-5-isopropyl-3-methyl-4,8-methanoazulen-3a(1H)-ol (15). Lithium metal (10 mg, 1.44 mmol) was added to ethylamine (1.5 mL) at −78 °C, the mixture was warmed to 0 °C until a blue color persisted, and following recooling to −78 °C, a solution of **2** (7 mg, 0.021 mmol) in THF (1 mL) was introduced. After 10 min, the reaction mixture was quenched by the addition of solid NH_4Cl and the ethylamine was allowed to evaporate overnight. The residue was taken up in ether (20 mL) and washed with water (20 mL), the separated aqueous layer was extracted with ether (2 × 20 mL), and the ethereal layers were combined, dried, filtered, and evaporated. Chromatography of the product on Florisil delivered 3.5 mg (74%) of **15** as a white crystalline solid: IR (neat, cm^{-1}) 3600; ^1H NMR (300 MHz, C_6D_6) δ 2.30−2.22 (m, 1 H), 2.12−1.96 (m, 3 H), 1.93−1.84 (m, 1 H), 1.74−1.20 (series of m, 12 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.89 (d, J = 6.5 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 92.5, 59.2, 46.9, 42.2, 37.9, 36.2, 35.7, 34.9, 29.6, 25.0, 24.2, 22.6, 21.3, 21.0, 13.8; MS m/z (M^+) calcd 222.1977, obsd 222.1982; $[\alpha]^{25}_D$ −20.7 (c 0.01, $CHCl_3$).

(1*R*,2*S*,3*S*,6*E*,10*S*,11*S*)-10-Isopropyl-3-methyl-11-(phenylthio)bicyclo[5.3.1]undec-6-en-2-ol (16). To a solution of **2** (32 mg, 0.098 mmol) in dry THF (20 mL) at −78 °C was added lithium aluminum hydride (35 mg, 0.92 mmol). The reaction mixture was stirred for 10 min, quenched with water (15 mL), and filtered. The aluminum salts were washed with ethyl acetate (3 × 20 mL), and the filtrate was washed with water (50 mL). The separated organic layer was dried and evaporated to yield 31 mg (96%) of **16** as a colorless oil: IR (neat, cm^{-1}) 3462; ^1H NMR (300 MHz, C_6D_6) δ 7.46 (dd, J = 8.2, 1.0 Hz, 2 H), 7.06−7.03 (m, 2 H), 6.95−6.89 (m, 1 H), 6.28 (d, J = 12 Hz, 1 H), 4.08 (s, 1 H), 3.40 (dd, J = 9.4, 5.5 Hz, 1 H), 2.79−2.61 (m, 2 H), 2.49 (d, J = 9.5 Hz, 1 H), 2.39 (dq, J = 4.0, 12.3 Hz, 1 H), 2.12−1.76 (m, 4 H), 1.45−1.27 (m, 3 H), 1.16−1.02 (m, 2 H), 0.97 (d, J = 7.2 Hz, 3 H), 0.62 (d, J = 6.4 Hz, 3 H), 0.61 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 137.8, 137.1, 130.7, 129.1, 126.5, 123.9, 82.2, 53.8, 52.3, 42.4, 38.0, 33.6, 33.2, 29.0, 27.7, 27.3, 23.1, 19.5, 19.0; MS m/z (M^+) calcd 330.2010, obsd 330.2014.

(1*R*,2*S*,3*S*,6*Z*,10*S*)-10-Isopropyl-3-methylbicyclo[5.3.1]-undec-6-en-2-ol (17) and Acetate (18). To ethylamine (1.5 mL) at −78 °C was added lithium metal (10 mg, 1.44 mmol). The mixture was warmed to 0 °C until a blue color persisted and then recooled to −78 °C. A solution of **16** (7 mg, 0.021 mmol) in THF (1 mL) was added. After 10 min, the reaction mixture was quenched with solid NH_4Cl and the ethylamine was allowed to evaporate overnight. The resulting mixture was taken up in ether (20 mL) and washed with water (20 mL). The separated aqueous layer was extracted with ether (2 × 20 mL), and the combined ethereal layers were dried and evaporated. Chromatography of the residue on Florisil (elution with 2% ethyl acetate in hexanes) afforded 4 mg (80%) of **17** as a crystalline solid: IR (neat, cm^{-1}) 3513; ^1H NMR (300 MHz, C_6D_6) δ 5.33 (t, J = 7.5 Hz, 1 H), 3.65 (d, J = 7.2 Hz, 1 H), 2.64 (d, J = 12.4 Hz, 1 H), 2.42−2.27 (m, 1 H), 2.20−2.05 (m, 1 H), 2.00−1.83 (m, 3 H), 1.80−1.15 (m, 9 H), 1.07 (d, J = 7.5 Hz, 3 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); the ^{13}C NMR spectrum (75 MHz, C_6D_6) exhibited broadened peaks; those peaks that were discernible under ordinary conditions appear at 141.2, 121.0, 75.7, 46.0, 42.9, 35.9, 32.6, 30.2, 28.1, 26.4, 23.4, 21.5 ppm; MS m/z (M^+) calcd 222.1977, obsd 222.1985; $[\alpha]^{25}_D$ +12.5 (c 0.8, $CHCl_3$).

A solution of **17** (44 mg, 0.20 mmol) in pyridine (0.3 mL) and acetic anhydride (0.2 mL) was stirred overnight and evaporated. The residue was dissolved in ethyl acetate, washed with brine, dried, concentrated, and purified by flash chromatography on silica gel. Elution with 10% ethyl acetate in hexanes gave 52 mg (98%) of **18**: IR (neat, cm^{-1}) 1731, 1368, 1245; ^1H NMR (400 MHz, $CDCl_3$) δ 5.40 (br dd, J = 8, 7 Hz, 1 H), 5.14 (br d, J = 9 Hz, 1 H), 2.64 (br d, J = 12.5 Hz, 1 H), 2.32 (dddd, J = 14, 13, 8, 2.5 Hz, 1 H), 2.14 (m, 1 H), 2.10 (m, 1 H), 2.07 (m, 1 H), 2.00 (s, 3 H), 1.99 (dddd, J = 12, 4.5, 4, 2 Hz, 1 H), 1.86 (dqq, J = 9.5, 6.5, 6.5 Hz, 1 H), 1.82 (dd, J = 12.5, 4 Hz, 1 H), 1.82 (m, 1 H), 1.78 (ABm, 2 H), 1.74 (br m, 1 H), 1.67 (br m, 1 H), 1.13 (br d, J = 7.5 Hz, 3 H), 0.94 (m, 1 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6, 125 °C) ppm 169.3, 139.6, 120.3, 77.5, 41.7, 41.6, 36.1 (br), 34.3, 31.2, 27.1, 25.7, 25.0, 22.0, 20.5, 20.4, 20.2, 13.7 (br); (MS m/z (M^+) calcd 264.2089, obsd 264.2101; $[\alpha]^{22}_D$ 112.7 (c 0.66, ethyl acetate).

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(1*R*,2*S*,3*S*,6*R*,7*S*,10*S*)-6,7-Epoxy-10-isopropyl-3-methylbicyclo[5.3.1]undecan-2-ol Acetate (19). A suspension of **18** (61 mg, 0.23 mmol) and sodium carbonate (97 mg, 1.15 mmol) in CH_2Cl_2 (5 mL) was treated with *m*-chloroperbenzoic acid (176 mg, 0.92 mmol), stirred for 5 h, and quenched with water. The separated aqueous phase was extracted with ether, and the combined organic layers were washed with brine, dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 10% ethyl acetate in hexanes) furnished 63 mg (97%) of **19** as a colorless oil: IR (neat, cm^{-1}) 1732, 1475, 1240; ^1H NMR (300 MHz, C_6D_6) δ 5.23 (br d, J = 9.2 Hz, 1 H), 2.45 (dd, J = 9.2, 4.8 Hz, 1 H), 2.14−2.06 (m, 1 H), 2.04−1.98 (m, 1 H), 1.92−1.26 (series of m, 10 H), 1.66 (s, 3 H), 1.02−0.98 (m, 2 H), 0.85 (d, J = 7.4 Hz, 3 H), 0.80 (d, J = 6.6 Hz, 3 H), 0.79 (d, J = 6.6 Hz, 3 H); MS m/z (M^+) calcd 280.2038, obsd 280.2039; $[\alpha]^{22}_D$ +11.1 (*c* 0.85, ethyl acetate).

(−)-Salsolene Oxide (1). To a solution of **19** (28 mg, 0.10 mmol) in ether (5 mL) was added lithium aluminum hydride (8 mg, 0.2 mmol). The reaction mixture was stirred for 5 h, quenched with ethyl acetate (1 mL) and water (2 drops), and filtered through a plug of basic alumina (ethyl acetate rinse). The filtrate was concentrated, and the resultant alcohol (**20**) was stirred with the Martin sulfurane (135 mg, 0.2 mmol) in benzene (5 mL) at 50 °C under N_2 for 2 h. After being cooled, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ether. The combined ethereal solutions were washed with brine, dried, and concentrated to leave a residue, which was purified by MPLC on silica gel (elution with 2% ether in pentane) to give 18 mg (80%) of salsolene oxide, spectroscopically identical with the natural product:[17] $[\alpha]^{25}_D$ −24 (*c* 0.2, $CHCl_3$).

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Supporting Information Available: ^1H and ^{13}C NMR spectra for intermediates **15**−**19** together with detailed analyses of the structure and stereochemistry of **2**, **12**, **13**, and **18** (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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