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THE SYNTHESIS OF CYCLODECANE DERIVATIVES BY INTRAMOLECULAR ALKYLATION OF AN α-PHENYLSULFENYL KETONE

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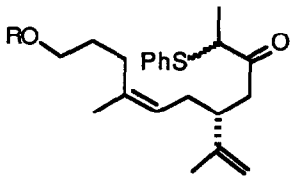
Abstract. The acyclic ω-tosyloxy-α-phenylsulfenyl ketone **1a**, derived from R-(-)-carvone, underwent intramolecular alkylation to give the cyclodecenone derivative **2a** in good yield. Oxidation of the sulfide to the sulfoxide and thermal elimination of phenylsulfinic acid gave the ketone **8**, presumably resulting from Diels-Alder dimerization of the exomethylene ketone **9**, as the major product and the endocyclic α,β-unsaturated ketone **7** as the minor product. Reduction of **7** with LAH and treatment of the allylic alcohol product **10** with the sulfur trioxide-pyridine complex followed by LAH gave the (Z),(Z)-1,6-cyclodecadiene **11** and three other minor products, possibly including the sesquiterpene, helminthogermacrene (**3**). In contrast to the keto sulfoxide **2b**, which mainly underwent exo elimination of phenylsulfinic acid, the hydroxy sulfoxide **12b**, prepared from ketone **2a**, underwent largely endo elimination to give the allylic alcohol **13** containing a (Z),(Z)-1,5-cyclodecadiene system.

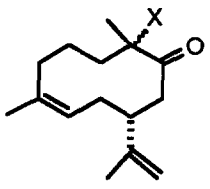
Intramolecular alkylations of acyclic resonance- and heteroatom-stabilized anions have been widely used for the generation of cyclodecane ring systems found in various germacrene sesquiterpenes.[1] We have recently shown that acyclic ω-substituted α-phenylsulfenyl ketones can be prepared by tandem retroaldol-Wittig reactions between cyclic β-hydroxy-α-phenylsulfenyl ketones and oxido ylids.[2] It appeared that intramolecular alkylation of the enolate of an appropriate acyclic ketone containing a leaving group at the omega position might provide a useful route to functionalized cyclodecane derivatives. Herein we report the results of experiments involving the cycloalkylation of the ω-tosyloxy-α-phenylsulfenyl ketone **1a** and various transformations of the C-cycloalkylation product **2a**, including an attempted synthesis of an optically active form of the sesquiterpene, helminthogermacrene (**3**).[1h,3]

The synthesis of the ω-hydroxy-α-phenylsulfenyl ketone **1b** was accomplished by a tandem retroaldol-Wittig reaction of the β-hydroxy-α-phenylsulfenyl derivative **4** of R-(-)-carvone with the δ-oxido phosphorane **5a**. Ketone **4** was prepared by the method described previously for its enantiomer.[2] The δ-oxido ylid **5a** was prepared *in situ* by the method described for the synthesis of the γ-oxido species **5b**,[2,4] i.e., a THF solution of the δ-oxido phosphorane **5c**[5] was

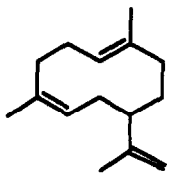
reacted with 1.0 equiv of methyl iodide and the phosphonium salt which precipitated was treated with 1.0 equiv of n-butyllithium. (Reagent **5a** produced in this manner was usually contaminated with up to 10% of the unmethylated species **5c**.) After addition of 5.0 equiv of HMPA, treatment of the phosphorane solution with 0.5 equiv of β-ketol **4** gave the acyclic ω-hydroxy-α-phenylsulfenyl ketones **1b** in approximately 80% yield. By analogy with the results obtained for the reaction of the enantiomer of **4** with the γ-oxido phosphorane **5b**,[2] it was anticipated that the mixture of diastereomeric α-phenylsulfenyl ketones **1b** would contain a Z-trisubstituted double bond. The Z configuration of **1b** was confirmed by an NOE experiment in which it was found that irradiation of the ^{1}H NMR signal for the vinyl methyl group at C-8 led to an 18% enhancement of the signal for the adjacent C-7 vinyl proton. Treatment of the diastereomeric mixture of alcohols **1b** with tosyl chloride in anhydrous pyridine gave the corresponding diastereomeric tosylates derivatives **1a** as a viscous oil in 76% yield.



1a. R = Ts
b. R = H



2a. X = SPh
b. X = S(O)Ph



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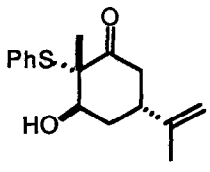

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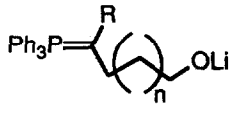
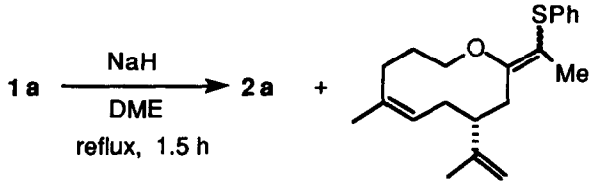


5a. n = 1, R = Me
b. n = 0, R = Me
c. n = 1, R = H

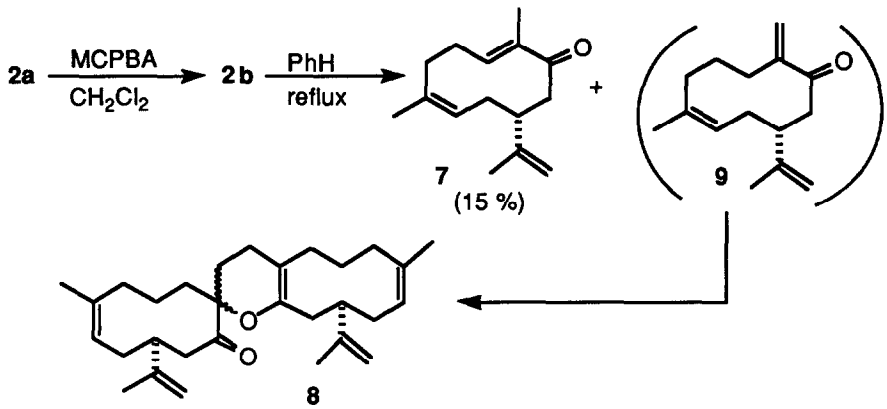
Cycloalkylation of **1a** was first attempted using LDA/THF as the base-solvent combination, but no reaction occurred after an extended period at 25°C. Also, cyclization occurred very slowly when the enolate generated with sodium hydride in THF was warmed at 40°C over an extended time period. Addition of HMPA to a THF solution of the sodium enolate of **1a** dramatically increased the rate of cycloalkylation; but, unfortunately, a significant amount of O-cycloalkylation occurred under these conditions. For example, a 1:4 mixture of the α-phenylsulfenyl ketone **2a** and the isomeric O-cycloalkylation product **6** was produced when the reaction was conducted in the presence of 6.0 equiv of HMPA. Fortunately, a change of the solvent from THF to DME proved beneficial. Thus, when the enolate was prepared using NaH in DME and the solution refluxed for 1.5 h, a 9:1 mixture of the C- and O-alkylation products **2a** and **6** was produced in over 70% yield

(Eq. 1). The C- and O-cycloalkylation products were readily separable by flash chromatography on silica gel. Compounds **2a** and **6** appeared to be homogeneous by TLC and spectroscopic analysis. However, mixtures of diastereomers may be present. In any case, the stereochemistry at C-2 in **2a** or of the enol ether double bond in **6** was not determined.



(63%) **6** (7%) (Eq. 1)

Oxidation of **2a** with MCPBA in methylene chloride gave the corresponding α-phenylsulfinyl ketone **2b** which, without purification, was refluxed in benzene to cause thermal elimination of phenylsulfinic acid (Scheme 1).[6] These steps produced a mixture of three compounds having R_f values of 0.68, 0.59 and 0.45 in a *ca.* 3:2:1 ratio by TLC analysis using 4% ethyl acetate-hexane as the solvent. When the mixture was allowed to stand at room temperature overnight, the middle TLC spot disappeared and the major spot increased in intensity. At this point, the ratio of the major to the minor component was *ca.* 5:1. Column chromatography of the mixture led to the isolation of the pure minor and major components in 15% and 37% yields, respectively. The spectral properties of the minor component showed that it was the 2(E), 6(Z)-cyclodecadienone derivative **7**. The configuration of the 2,3- double bond was established by an NOE experiment which showed that when the ^{1}H NMR absorption for the C-2 methyl group was irradiated the intensity of the C-3 proton was unaffected. On the other hand, irradiation of the vinyl methyl group at C-6 caused a ~10% increase in the signal for the C-7 proton. The major product had spectral properties consistent with the structure **8**. A doublet of doublets at 3.16 δ (J =12 and 17 Hz) in the ^{1}H NMR spectrum was attributed to the deshielding of one of the protons at C-10 (α to the carbonyl group) by the oxygen atom at C-2. Apparently, the molecule adopts an important conformation in which these two nuclei are held in a 1,3-diaxial relationship. However, the configuration at C-2 of **8** was not determined. It seems likely that the middle TLC spot observed immediately after the elimination reaction was the exomethylene ketone **9** which underwent facile intermolecular Diels-Alder dimerization to give **8**.[7] These results suggest that there was an approximately 5:1 preference for exo over endo elimination during loss of phenylsulfinic acid from the sulfoxide **2b**. Since endo elimination leading to **7** occurred in low yield and since a 2(Z),6(Z)-cyclodecadienone derivative was not produced during the thermolysis, a conformation of the sulfoxide **2b** which allows syn elimination involving a C-3 proton must be rather difficult to attain.

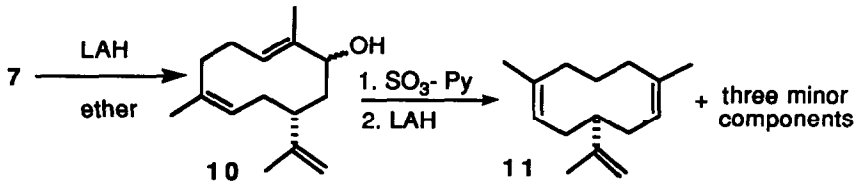


Scheme 1

Although only a limited quantity of trienone **7** was available, an attempt was made to convert it into the sesquiterpene, helminthogermacrene (**3**). Reduction of **7** with LAH in ether gave a mixture of alcohols **10** in good yield. It was hoped that mesylation of **10** followed by metal hydride reduction would yield **3**. However, treatment of **10** with methanesulfonyl chloride in anhydrous pyridine at 0° to -5°C overnight followed by normal workup of the reaction mixture gave a mixture of hydrocarbons rather than the expected mesylate. Apparently, the mesylate was unstable and underwent cleavage of the C-O bond to give an allylic carbocation which was capable of rearrangement and other reactions leading to a hydrocarbon mixture.

Two other methods for removal of the hydroxyl group from the alcohol mixture **10** were investigated. First, treatment of **10** with the sulfur trioxide-pyridine followed by LAH in ether according to the procedure of Corey and Achiwa[8] gave a mixture of hydrocarbons in 70% yield which contained ~90% of one major component and three minor components each in ~3% yield according to GLC analysis (Scheme 2). The major component and a mixture of the three minor components was collected by preparative GLC. The ^{1}H NMR spectrum of the major isomer showed a singlet at δ 1.68 for two vinyl methyl groups, a singlet at δ 1.76 for one vinyl methyl group, singlets at δ 4.69 and δ 4.73 for an exomethylene group and a broad absorption at δ 5.07 for two vinyl protons on trisubstituted double bonds. These spectral properties were similar but not identical to those reported for helminthogermacrene[1h,3,9] or its known isomer with both endocyclic double bonds in a Z configuration.[1b] This component also showed no optical rotation which indicated that it was an achiral molecule. On the basis of these data, we have assigned the (Z),(Z)-1,6-diene structure **11** to the major component. Apparently, the allylic sulfate mixture derived from reaction of **10** with sulfur trioxide or the allylic cation which would result from cleavage of the C-O bond underwent attack of hydride ion largely at C-3. This is likely to be the

result of thermodynamic control since it is known that in cyclodecadiene itself the (Z),(Z)-1,6-isomer is more thermodynamically stable than the (Z),(E)-1,5- or the (Z),(Z)-1,5-isomer.[10]



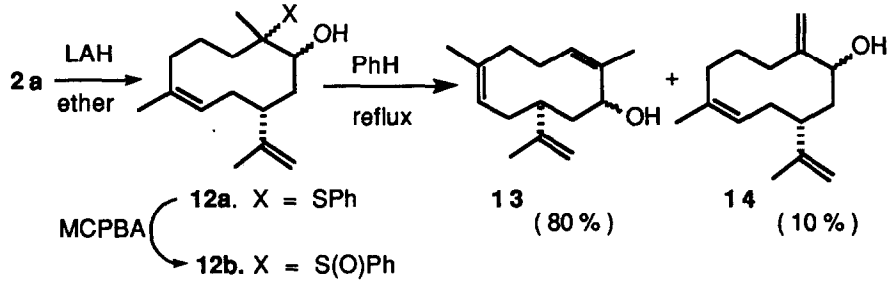
Scheme 2 (63%) (7%)

The mixture of minor components showed ^{1}H NMR absorptions in the same range as those reported for helminthogermacrene (**3**).[1h,3,9] Additionally, GC/MS comparison of the mixture with a hexane extract of *amitermes wheeleri* termite heads[12] which contained **3** showed that one of the minor components had an identical retention time and mass spectrum to that of the natural product. However, an insufficient quantity of this material was available to permit its further purification or positive identification.

The mixture of allylic alcohols **10** was also reacted with lithium-liquid ammonia-ethanol to effect reductive removal of the hydroxyl group.[12] The major product of this reaction, which was produced in low yield, was the trienone **11**. Apparently, protonation of the allylic carbanion intermediate involved in the reaction occurred exclusively at C-3 to give the thermodynamically stable (Z),(Z)-1,6-cyclodecadiene system.

Since the conversion of ketone **2a** into trienone **7** proceeded in low yield, another possible route to the (E),(Z)-1,5-cyclodecadiene system found in **3** was explored (Scheme 3). Thus, α-phenylsulfenyl ketone **2a** was reduced with LAH in ether to give a diastereomeric mixture of alcohols from which the major component was isolated in 75% yield by flash chromatography on silica gel. On the basis of its analysis and spectral properties, this compound was assigned the structure **12a.** Although the sample appeared to be homogeneous by spectral and TLC analysis, the configurations at C-1 and C-2 were not assigned. The hydroxy sulfide **12a** was oxidized to the hydroxy sulfoxide **12b** with MCPBA. Without purification, the product was refluxed in benzene to effect thermal elimination of phenylsulfinic acid.[6] Subjection of the resulting material to chromatography on silica gel allowed the isolation of allylic alcohol **13**, which contained an endocyclic 2,3-double bond, and the allylic alcohol **14**, which contained an exomethylene group at C-2 in 80% and 10% yields, respectively. The spectral properties of the major isomer were similar to those of trienol **10**. However, an NOE experiment in which irradiation of the vinyl methyl region of the ^{1}H NMR spectrum led to a ~10% increase in the intensity of both the C-3 and the C-7 protons established that both of the endocyclic double bonds had a Z configuration. The ^{1}H NMR spectrum of the minor allylic alcohol showed the presence of two vinyl methyl groups and five vinylic protons as well as an absorption for the

carbinol proton at C-1. This confirmed the presence of an exocyclic methylene group at the 2-position on the ten-membered ring.



Scheme 3

We were not able to detect the formation of any allylic alcohol such as **10**, which contained the desired (E),(Z)-1,5-cyclodecadiene system, from the thermolysis of **12b**. Nevertheless, it is of interest to note that reduction of the carbonyl group to an alcohol caused such a dramatic change in the regiochemistry of the elimination of phenylsulfinic acid in going from ketone **2b** to alcohol **12b**. However, a detailed analysis of these thermolysis reactions is unwarranted because the configurations at the relevant chiral centers of the two substrates are unknown.

EXPERIMENTAL SECTION

General. Melting points are uncorrected. Unless otherwise indicated, all reagents and solvents were purchased from Aldrich Chemical Company or Fisher Scientific Company and used without further purification. THF and diethyl ether were freshly distilled from sodium/benzophenone ketyl prior to use. DME was distilled from LAH prior to use. HMPA was distilled from sodium at reduced pressure prior to use. Benzene was dried over sodium prior to use. Flash chromatography was carried out using E. Merck 60 silica gel (250-400 mesh). TLC analyses were carried out on E. Merck silica gel 60F-254 (0.25 mm) precoated glass plates.

^{1}H NMR spectra were recorded at 90 MHz on a Bruker WH-90, at 200 MHz on a Nicolet 293A, or at 360 MHz on a Bruker AM-360 spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard. IR spectra were recorded on either a Perkin-Elmer 283B or a Perkin-Elmer 1420 spectrophotometer as neat liquids using NaCl plates or in $CHCl_3$ solution using 0.1 mm NaCl cells. Low resolution mass spectra were obtained by electron impact ionization at 70 eV or by chemical ionization (CI) using a Hewlett-Packard model 5985 quadrupole mass spectrometer. The high resolution mass spectrum was obtained by Mr. Terry D. Marriot, Department of Chemistry, Rice University, Houston, Texas, using a CEC/DuPont 21-110B mass spectrometer. GLC analyses were performed on a Hewlett-Packard 5790A gas chromatograph using a 12.5 m

X 0.2 mm glass capillary column coated with cross-linked dimethylsilicone. Preparative GLC was carried out on a Varian Aerograph 90-P gas chromatograph using a 10' X 0.25" stainless steel column containing 20% silicone SE-30 on 80/100 mesh Chromosorb W. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

All reactions requiring anhydrous conditions were conducted under an atmosphere of prepurified nitrogen. Anhydrous solvents were transferred via a syringe. During workup of reactions solutions were dried over anhydrous magnesium sulfate and solvents were removed *in vacuo* using a rotary evaporator operated at water aspirator pressure.

(5(R),7(Z))-11-Hydroxy-8-methyl-5-(methylethenyl)-2-phenylsulfenyl-undec-7-en-3-one(1b). - n-Butyllithium (27.6 mL of a 10.0 M solution in hexane) was added to a chilled solution of 57.34 g (0.14 mol) of (4-hydroxybutyl)-triphenylphosphonium bromide in 250 mL of dry THF at such a rate that the temperature did not rise above 10°C. The reaction mixture was stirred for 30 min at 0°C, 19.60 g (0.14 mol) of methyl iodide was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The precipitated phosphonium salt was allowed to settle and the supernatant liquid was removed via a syringe. After the addition of dry THF (250 mL) and dry HMPA (180 mL) the reaction mixture was cooled to 0°C and n-butyllithium (13.8 mL of a 10.0 M solution in hexane) was added dropwise with stirring. The resulting solution was stirred for 1.0 h at 0°C and a solution of 14.23 g (0.05 mol) of β-ketol **4**, prepared by the method previously described for the synthesis of its enantiomer,[2] was added dropwise with stirring and the solution was allowed to warm to room temperature and stirred for 1.0 h. The reaction mixture was poured into a mixture of 250 mL of cold saturated aqueous LiBr and 300 mL ether. The organic layer was washed with three 50-mL portions of saturated aqueous LiBr, dried and the solvent was removed. Column chromatography of the residue (25% ethyl acetate in hexane) gave 14.89 g (85%) of the diastereomeric ketols **1b** as an oil: IR (neat) 3400, 3080, 2940, 2870, 1710, 1645, 1585, 1480, 1440, 1375, 1060, 1025, 890, 790, 750 and 690 cm^{-1}; ^1H NMR (200 MHz) δ 1.37 (m, 3H), 1.57-1.90 (m, 8H, including singlets at 1.66 (3H) and 1.72 (3H) for the vinyl methyl groups), 1.97-2.30 (m, 4H), 2.61-2.84 (m, 3H), 3.56-3.83 (m, 3H), 4.62-4.80 (br s, 3H), 5.07 (m, 1H), 7.22-7.42 (m, 5H); *Anal.* Calcd for $C_{21}H_{30}O_2S$: C, 72.79; H, 8.73; S, 9.25. Found: C, 72.69; H, 8.76; S, 9.33.

In some runs, careful analysis of the ^1H NMR spectrum of the product revealed that it contained up to 10% of the 8-normethyl derivative of **1b**. The C-7, C-8 vinyl protons in this compound showed a broad absorption at δ 5.38.

(5(R),7(Z))-8-Methyl-5-(methylethenyl)-2-phenylsulfenyl-11-tosyloxyundec-7-en-3-one(1a). - TsCl, 2.26 g (0.01 mol), was added to a solution of ketol **1b** in 8.0 mL dry pryidine at 0°C. The mixture was swirled in an ice bath until all the solid dissolved and then placed in a refrigerator at 3°C overnight. The resulting reaction mixture was added to a mixture

of 100 mL ether and 100 mL water and shaken until the precipitated pyridinium hydrochloride dissolved. The layers were separated and the aqueous layer was extraced with 25 mL ether. The combined organic layers were washed with 50 mL saturated aqueous NaCl and dried. Removal of the solvent followed by flash column chromatography of the residue (15% ethyl acetate-hexane) afforded 4.20 g (76%) of the tosylate **1a** as a viscous oil: IR (neat) 3060, 2960, 2920, 1705, 1640, 1595, 1580, 1470, 1430, 1350, 1180, 1160, 1090, 950, 920, 810, 790, 685, and 655 cm^{-1}; ^1H NMR (200 MHz) δ 1.36 (br s, 3H), 1.58-1.81 (m, 7H, including singlets at 1.62 (3H) and 1.66 (3H) for the vinyl methyl groups), 1.84-2.20 (m, 4H), 2.45 (s, 3H), 2.51-2.83 (m, 3H) 3.64-3.82 (m, 1H), 3.49-4.10 (m, 2H), 4.52-4.81 (m, 2H), 5.08 (m, 1H), 7.21-7.50 (m, 7H) and 7.79 (d, J = 8 Hz, 2H); MS, m/e (70 eV): 500 (M^+), 137 (100), 320 (85), 95 (63), and 91 (40); *Anal.* Calcd for $C_{28}H_{36}O_4S$: C, 67.17; H, 7.25. Found: C, 67.10; H, 7.30.

Preparation of the C- and O-Cycloalkylation Products 2a and 6. - A solution of 2.36 g (4.7 mmol) of the tosylate **1a** in 140 mL of dry DME was added slowly to 0.38 g (15 mmol) of oil-free NaH. The mixture was stirred and refluxed for 1.5 h. During this period, evolution of hydrogen was observed. The mixture was cooled to room temperature and 20 mL of water was added dropwise with stirring. The mixture was then poured into a mixture of 100 mL water and 100 mL ether. The aqueous layer was saturated with NaCl, the layers were separated, and the aqueous layer was extracted with 40 mL of ether. The combined etheral extracts were dried and the solvent removed. TLC analysis of the residue using 3% ethyl acetate-hexane as the eluant showed one minor spot (R_f = 0.49) and one major spot (R_f = 0.32). Flash column chromatography of the material (3% ethyl acetate-hexane) gave 0.11 g (7%) of the enol ether **6**: IR (neat) 3080, 2985, 2915, 2885, 1645, 1630, 1585, 1480, 1440, 1375, 1295, 1240, 1120, 1085, 1070, 1020, 890, 740 and 690 cm^{-1}; ^1H NMR (200 MHz) δ 1.60-2.83 (m, 18H, including singlets at 1.72, 1.79 and 1.92 for three vinyl methyl groups), 3.30-3.82 (m, 2H), 4.69 (s, 1H), 4.84 (s, 1H), 5.26 (t, J = 6 Hz, 1H), 7.13-7.31 (m, 5H); MS, m/e (70 eV): 328 (M^+), 219 (100), 220 (18), 145 (14). *Anal.* Calcd for $C_{21}H_{28}OS$: C, 76.78; H, 8.59; Found: C, 76.85; H, 8.62.

Continued elution of the column gave 0.97 g (63%) the cyclodecenone **2a**: IR (neat) 3080, 2990, 2910, 2880, 1700, 1645, 1590, 1460, 1440, 1375, 1315, 1235, 1130, 1115, 1080, 1070, 1025, 890, 745 and 690 cm^{-1}; ^1H NMR (200 MHz) δ 1.31 (s, 3H), 1.51-1.65 (m, 1H), 1.67 (s, 3H), 1.69-2.51 (m, 10H, including a singlet at 1.84 for a vinyl methyl group), 2.53-2.90 (m, 2H), 3.12-3.24 (m, 1H), 4.69 (s, 1H), 4.82 (s, 1H), 5.17 (m, 1H), and 7.31 (br s, 5H); MS, m/e (70 eV), 328 (M^+), 163 (57), 109 (41), 95 (100), 81 (70): *Anal.* Calcd. for $C_{15}H_{28}OS$: C, 76.78; H, 8.59; S, 9.76. Found: C, 76.85; H, 8.64; S, 9.67.

Oxidation and Thermolysis of Cyclodecenone 2a. - A solution of 0.74 g (4.3 mmol) of 85% MCPBA in 25 mL anhydrous CH_2Cl_2 was added dropwise with stirring to a solution of 1.21 g (3.4 mmol) of cyclodecenone **2a** in 35 mL anhydrous CH_2Cl_2 at -5°C. After the

solution was stirred for 10 min at -5°C, TLC analysis indicated that no starting material remained. The solution was poured into a mixture of 100 mL of ether and 50 mL of a saturated aqueous solution NaCl. The layers were separated and the organic layer was washed with three 30-mL portions of 10% aqueous $NaHSO_3$ and dried. Removal of the solvent gave 1.21 g of the crude diastereomeric mixture of keto sulfoxides **2b** whose ^1H NMR spectrum was essentially identical to that of the starting material **2a** except that a broad singlet was observed at 7.56 δ rather than 7.31 δ for the aromatic ring protons of the phenylsulfinyl group.

Without purification, a solution of crude **2b** in 30 mL dry benzene was refluxed for 1 h, cooled to room temperature and poured into 50 mL water. The organic layers were separated and the aqueous layer was extracted with three 50-mL portions of ether. The organic layers were combined and dried and the solvent was removed to give an oily residue which showed three spots with R_f values of 0.68, 0.59 and 0.45 in a *ca.* 3:2:1 ratio on TLC analysis using 4% ethyl acetate-hexane as the eluant.

However, after the mixture was allowed to stand for several hours and then subjected to flash column chromatography (4% ethyl acetate-hexane) only the trienone **7**, 0.12 g (15%), and the ketone **8**, 0.60 g (37%) were isolated. Compound **7** (R_f = 0.45) showed: IR (neat) 3080, 2985, 2970, 2865, 1665, 1450, 1375, 1285, 1160, 1080 and 890 cm^{-1}; ^1H NMR (200 MHz, 60°C) δ 1.76 (br s, 9H), 1.91-2.57 (m, 8H), 2.60-2.94 (m, 1H), 4.65 (s, 1H), 4.78 (s, 1H), 5.22 (t, J = 7 Hz, 1H); 6.62 (br s, 1H); MS, m/e (70eV): 218 (M^+), 93 (17), 86 (15), 84 (24), 82 (100); *Anal.* Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.41; H, 10.21.

Compound **8** (R_f = 0.68) showed: MP 95-97°C; IR ($CHCl_3$) 3080, 2985, 2910, 1710, 1640, 1450, 1375, 1255, 1245, 1135, 1105, 1080, and 890 cm^{-1}; ^1H NMR (360 MHz) δ 1.50-2.75 (m, 38H, including singlets at 1.63, 1.64, 1.79, and 1.85 for four vinyl methyl groups), 3.16 (dd, J = 12 and 17 Hz, 1H), 4.61 (s, 1H), 4.66 (s, 1H), 4.78 (s, 1H), 4.86 (s, 1H), 5.06 (m, 1H); 5.13 (m, 1H); MS, m/e (CI): 436 (M^+), 437 (M^+ + 1), 201 (100), 175 (72), 107 (63), 95 (80); *Anal.* Calcd. for $C_{30}H_{44}O_2$: C, 82.52; H, 10.16. Found: C, 82.37; H, 10.23.

Reduction of Trienone 7 with LAH. - Trienone **7**, 0.20 g (0.92 mmol), was added with stirring to a slurry of 0.04 g (1.0 mmol) of LAH in 15 mL anhydrous ether at 0°C. The mixture was slurred at ambient temperature for 1.5 h and 5.0 mL of a saturated aqueous solution of NH_4Cl was added. The layers were separated and the aqueous layer was extracted with 20 mL ether. The combined ether layers were dried and the solvent was removed to give viscous oily residue. Flash chromatography (silica gel, 15% ethyl acetate-hexane) gave 0.19 g (86%) of a diastereomeric mixture of allylic alcohols **10**: IR (neat) 3400, 2970, 2940, 2870, 1645, 1450, 1375, 1100, 910, 890, 805, and 690 cm^{-1}; ^1H NMR (90 MHz) δ 1.56-2.75 (m, 19H, including singlets at 1.65 (3H) and 1.73 (6H) for three vinyl methyl groups), 4.24 (br s, 1H), 4.76 (br s, 2H,

5.10 (m, 1H), and 5.55 (m, 1H); high resolution mass spectrum, M^+ calcd for $C_{15}H_{24}O$: 220.1827. Found: 220.1825.

Reaction of Alcohol 10 with the Sulfur Trioxide-Pyridine Complex Followed by LAH. - To a solution of 0.10 g (0.45 mmol) of alcohol **10** in 5.0 mL anhydrous ether was added 0.14 g (0.90 mmol) of the sulfur trioxide-pyridine complex with stirring at O°C. After 2 h at O°C, TLC analysis of the mixture showed that no starting material was present. Then, a slurry of 0.03 g (1.35 mmol) of LAH in 5.0 mL anhydrous ether was added via a syringe with vigorous stirring at O°C. After 1 h, ~5 mL of a saturated solution of aqueous NH_4Cl was added. The resulting slurry was filtered under vacuum using a fitted glass funnel and the solid residue was washed with three 10-mL portions of ether. The etheral extracted were combined and dried and the solvent was removed to give 0.064 g (70%) of a yellow oil. GLC analysis of the mixture showed that it contained ~90% of one major component and three minor components in (~3% each). The major component and a mixture of the three minor components was collected by preparative GLC. The major component which was assigned the structure **11** showed: $[\alpha]^{25}$ = O° (0.5%, $CHCl_3$); IR (neat) 3080, 2980, 2860, 1650, 1455, 1380, 890, and 850 cm^{-1}; ^1H NMR (360 MHz) δ 1.57-2.50 (m, 20 H, including singlets at 1.68 (6 H) and 1.76 (3 H) for three vinyl methyl groups), 4.69 (s, 1 H), 4.75 (s, 1 H), 5.07 (m, 2 H), MS, m/e (70 eV): 204 (M^+), 161 (84), 107, (100), 93 (89), 81 (77): *Anal.* Calcd. for $C_{15}H_{24}$: C, 86.52; H, 13.48. Found: C, 86.59; H, 13.75.

An insufficient quantity of material was available to allow purification of any of the three minor components. However, MS/GC analysis of the mixture revealed that one of the components showed the same R_f value and mass spectrum as that of (-)-helminthogermacrene, a component in the hexane extract of *amitermes wheeleri* termite heads.[11]

Reduction of alcohol 10 with Lithium in Liquid Ammonia. - A solution of 0.10 g (0.45 mmol) of trienol **10** in 5 mL ether was added dropwise with stirring to a solution of 0.50 g (72 g-atom) lithium in 30 mL anhydrous liquid ammonia at -33°C. The mixture was stirred for 1.0 h, and 20 mL of a 1:1 ethanol-water solution was added dropwise over 1.5 h. The liquid ammonia was allowed to evaporate overnight, 50 mL ether was added, and 10 mL of water was added dropwise with stirring. The organic layer was separated and the aqueous layer was extracted with two 20-mL portions of ether. The organic layers were combined and dried and the solvent was removed to give 0.045 g (50%) of a yellow oil. Gas chromatographic analysis of this material showed that it contained *ca.* 85% of triene **11** and several minor components, none of which made up as much as 5% of the mixture.

Reduction of Ketone 2a with LAH. - To a slurry of 0.32 g (9.6 mmol) of LAH in 20 mL anhydrous ether at 25°C was added dropwise with vigorous stirring a solution of 1.40 g (4.2 mmol) ketone **2a** in 5 mL anhydrous ether. The mixture was stirred for 0.5 h and a saturated

aqueous solution of NH_4Cl was added dropwise with vigorous stirring. The mixture was then poured into a mixture of 20 mL ether and 10 mL of saturated aqueous NaCl. The organic layer was separated and dried and the solvent was removed to yield an oily residue. Flash chromatography of the material on silica gel using 5% ethyl acetate as the eluant gave 1.06 g (75%) of an alcohol, R_f = 0.28 (5%, ethyl acetate-hexane), which was assigned the structure **12a**. Although the configurations of the stereocenters bearing the phenylsulfenyl and hydroxyl groups were not assigned, the sample appeared to be homogeneous. It showed: IR (neat) 3560, 3090, 2980, 2940, 2880, 1650, 1590, 1480, 1445, 1380, 1220, 1100, 1070, 1055, 1035, 885, 750, 705, and 690 cm^{-1}; ^1H NMR (90 MH_Z) δ 1.04 (s, 3H), 1.21-2.80 (m, 19H, including singlets at 1.67 (3 H) and 1.90 (3 H) for two vinyl methyl groups, 4.01 (dd, J = 8 and 2 Hz, 1H), 4.91 (s, 2H), 7.27-7.36 (m, 3H), 7.49-7.60 (d, J = 7 Hz, 2H). *Anal.* Calcd. for $C_{21}H_{30}OS$: C, 76.31; H, 9.15. Found: C, 76.22; H, 9.22.

Further elution of the column gave 0.28 g (20%) of a second more polar material, R_f = 0.16, (5% ethyl acetate-hexane), which also appeared to be homogenous. This compound was presumably a stereoisomer of structure **12a**, but it was not conclusively identified.

Oxidation and Thermolysis of Hydroxy Sulfide 12a. - A solution of 0.65 g (3.74 mmol) of 85% MCPBA in 20 mL of CH_2Cl_2 was added over 10 min to a stirred solution of 1.00 g (3.03 mmol) of hydroxy sulfide **12a** in 25 mL CH_2Cl_2 at -5°C. The solution was stirred for 10 min and poured into 50 mL ether. The solution was washed with three 20-mL portions of 10% aqueous $NaHSO_3$ and dried and the solvent was removed to give an oily residue containing the hydroxy sulfoxide **12b**. A solution of the crude product in 10 mL dry benzene was refluxed for 1.5 h. After cooling to room temperature, the solution was poured into 30 mL water, the layers were separated, and the aqueous layer was extracted with two 30-mL portions of ether. The combined organic extracts were dried and the solvent was removed to give an oil. Flash chromatography of this material (5% ethyl acetate-hexane) gave 0.55 g (80% from **12a**) of the allylic alcohol **13**, MP 52-54°C; IR (neat) 3500, 2980, 2945, 2880, 1645, 1450, 1370, 1100, 1050, 1020, 915, 890, and 735 cm^{-1}; ^1H NMR (200 MHz) δ 1.59-2.60 (m, 19H, including singlets at 1.65 (3H), 1.73 (3H), and 1.75 (3H) for three vinyl methyl groups), 4.23 (br s, 1H), 4.76 (s, 2 H), 5.19 (br, s, 1H), 5.62 (m, 1H); MS, m/e (70 eV): 220 (M^+), 159 (40), 95 (60), 109 (100), 81 (50): *Anal.* calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.72; H, 11.10.

Further elution of the column gave 0.06 g (10%) of the allylic alcohol **14**: MP 70-72°C, IR (neat) essentially the same as that of **13**; ^1H NMR (200 MHz) δ 1.43-2.65 (m, 18H, including singlets at 1.68 (3H) and 1.84 (3H) for two vinyl methyl groups), 4.14 (m, 1H), 4.68-5.35 (m, 5H): MS, m/e (70 eV): 220 (M^+), 159 (40), 95 (60), 109 (100), 81 (50): *Anal.* Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found C, 81.82; H, 11.15.

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