Synthesis of Macrocyclic Terpenoids by Intramolecular Cyclization. XIV.[1] Cyclization of 13,14-Epoxygeranylgeranyl Phenyl Sulfide

Mitsuaki KODAMA,* Kazuyoshi FUKUZUMI and Mitsushige KUMANO

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, Japan. *Received October 11, 1988*

Cyclization of 13,14-epoxygeranylgeranyl phenyl sulfide (2) was examined to determine whether 13- or 14-membered ring formation is preferred in the case of a disubstituted epoxide; the *cis*- and *trans*-epoxides were both found to cyclize to the 13-membered ring.

Keywords α-sulfenyl carbanion; intramolecular cyclization; 13,14-epoxygeranylgeranyl phenyl sulfide; 13-membered ring formation; sarcophytol A

In the series of papers reported previously,[2] we have demonstrated that intramolecular reactions between α-sulfenyl carbanion and an epoxide provide an efficient method for the synthesis of medium-sized and macrocyclic terpenoids. In these syntheses, however, trisubstituted epoxides have always been used as a leaving group, leading to the formation of a single size of ring. Thus, there was no possibility of the formation of another size of ring because of the significant difference in steric hindrance between the two reacting points. In connection with synthetic studies on sarcophytol A (**1**), we were interested in the intramolecular reaction of a disubstituted epoxide with α-sulfenyl carbanion. Herein, we describe the cyclization of 13,14-epoxygeranylgeranyl phenyl sulfide (**2**). The major interest in this study was to establish the regioselectivity of this type of cyclization in the case of a disubstituted epoxide. Furthermore, if a 14-membered ring is formed in the reaction of **2**, the product **3** should serve as a potential intermediate for the synthesis of **1**. Sarcophytol A is a cembrane type alcohol isolated from *Sarcophyton* species of soft coral.[3] This compound, though the structure is rather simple, has attracted much attention recently from the viewpoint of protection from chemical carcinogenesis, because it has been reported to exhibit a potent inhibitory activity against tumor promoters.[4]

The precursor **2** for the cyclization was synthesized by employing as a key step Claisen rearrangement using an acetal **6** and an allylic alcohol **8**. The acetal **6**, one partner of the rearrangement, was synthesized from the known hydroxy-ketone **4**[5] as shown in Chart 2. The other partner, the allylic alcohol **8**, was accessible readily by ring opening of the epoxide **7**[1b] with aluminum isopropoxide. When the mixture of **6** and **8** in toluene was heated at 125 °C in the presence of a catalytic amount of 2,4-dinitrophenol, two Claisen rearrangement products **9** (65%) and **10** (13%) were formed through two enol ethers. The α-benzoyl-ketone **9** was then reduced with sodium borohydride to yield the alcohol **11** as á diastereomeric mixture. Although the mixture could be separated by careful chromatography, it

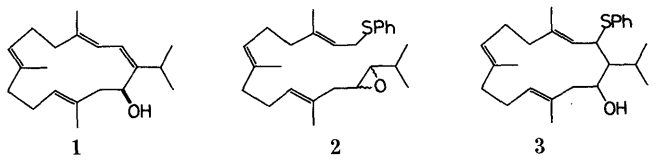

Chart 1

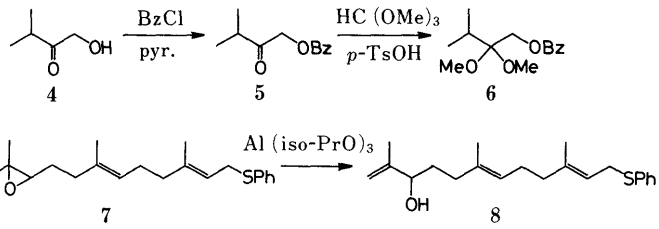

Chart 2

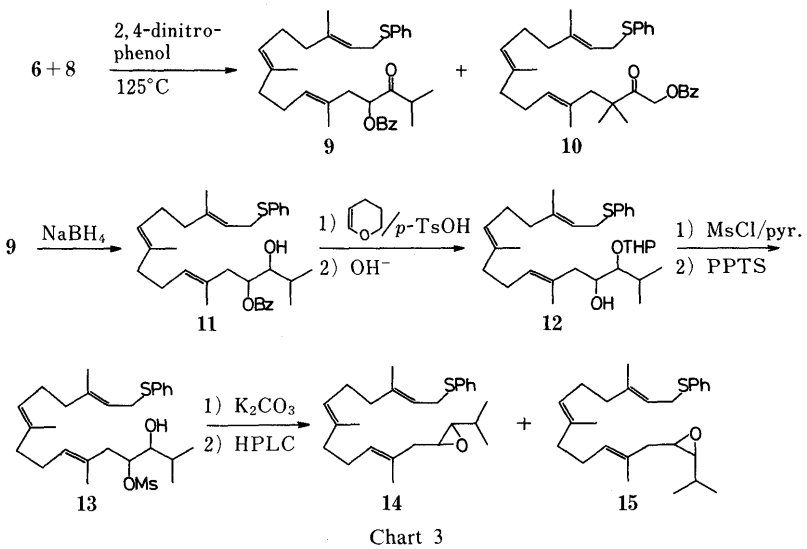

Chart 3

was converted into the epoxides **14** and **15** without separation because the epoxides were found to be separable by high pressure liquid chromatography (HPLC).

The hydroxyl group in **11** was protected as a tetrahydropyranyl ether and the benzoate group was hydrolyzed to yield **12**. Mesylation of **12** followed by deprotection with pyridinium *p*-toluenesulfonate (PPTS) afforded the diol monomesylate **13**. Finally, the mesylate **13** was treated with potassium carbonate to furnish a mixture of *trans*- (**14**) and *cis*-epoxides (**15**) (*ca.* 4:6), which were separated by HPLC using silica gel column. The stereochemistry of the epoxide ring in **14** and **15** was determined from the coupling constants between H-13 and H-14 (**14**; $J=2.2$ Hz, **15**; $J=4.4$ Hz).

The *trans*-epoxide **14** thus obtained was treated with *n*-butyllithium in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) under high dilution conditions.[2e] Purification of the crude product by column chromatography on alumina gave the cyclized product **16** in 45% yield. Although it was readily recognized by simple analysis of the proton nuclear magnetic resonance (^{1}H-NMR) spectra that the cyclization had taken place, extensive ^{1}H-NMR analysis of **16** and the corresponding ketone **18** revealed the arrangement of protons shown in Fig. 1, indicating the formation of a 13-membered ring. The *cis*-epoxide **15** was similarly treated with *n*-butyllithium to afford the cyclized product **17** in 65% yield. In the ^{1}H-NMR spectrum of **17**, the signals due to isopropyl methyls (δ 0.90 and 0.98 ppm) and a carbinyl proton (δ 3.64 ppm) were collapsed on irradiation of the multiplet at *ca.* 1.88 ppm [$-C\underline{H}(CH_3)_2$] leading to the same partial structure as **16** (Fig. 1). The relative configurations of the phenylthio group and hydroxybutyl side chain in **16** and **17** could not be clarified because of the flexibility of the molecules. Thus, both epoxides afforded 13-membered ring compounds, and the formation of a 14-membered ring product was not observed in either case.

We believe that the prefered formation of the 13-membered ring is due to steric hindrance at the reacting site in the transition state to the 14-membered ring. In general, the regioselectivity in these intramolecular cyclization would mainly be controlled by two factors in the transition state; local steric hindrance at the reacting sites, and angular strain distributed over the whole molecule. However, since the 10-, 12-, and 14-membered rings are readily formed by similar anionic cyclization,[2] the angular strain is unlikely to be involved in the present cases (**14** and **15**). On the other hand, the local steric hindrance would be larger in the attack at C-14 than C-13 owing to the presence of the isopropyl group on the former carbon. This may explain why the *trans*- and *cis*-epoxides (**14** and **15**) both failed to cyclize at C-14.

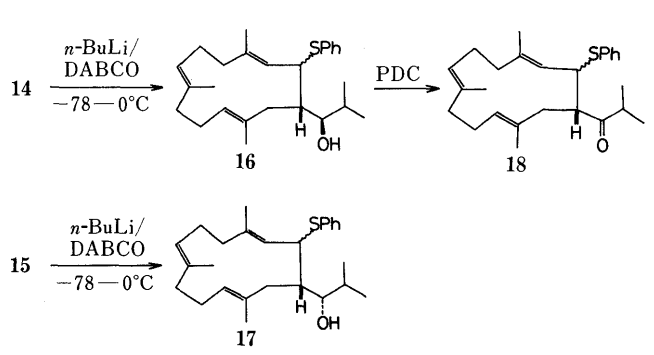

Chart 4

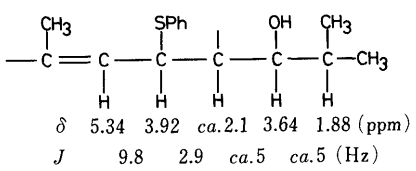

Fig. 1

Experimental

General ^{1}H-NMR spectra were recorded on a JEOL FX-90Q or GX-400 instrument in $CDCl_3$ solution with $(CH_3)_4Si$ as an internal standard. Infrared spectra (IR) were taken on a Shimadzu IR-27G spectrometer as a liquid film. Mass spectra (MS) were measured on a Shimadzu LKB-9000 spectrometer. High-resolution mass spectra (HRMS) were obtained on a JEOL HX-100 spectrometer. Column chromatography was performed on silica gel (Merck SG-60) or neutral alumina (Merck Aluminum oxide 90, activity grade II—III).

Tetrahydrofuran (THF) was dried on benzophenone ketyl radical. Ether, dichloromethane, and toluene were distilled from calcium hydride. DABCO was sublimed prior to use.

3-Methyl-2-oxobutyl Benzoate (5) Benzoyl chloride (3.79 g, 27 mmol) was added to an ice-cooled solution of the hydroxy-ketone **4** (2.50 g, 24.5 mmol) in pyridine (7 ml). After being stirred at room temperature overnight, the reaction mixture was poured into water and extracted with hexane. The organic layer was washed with aqueous $NaHCO_3$ and water, and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* followed by short column chromatography of the residue on silica gel (hexane–EtOAc, 20:1) afforded the benzoate **5** (4.79 g, 95%) as a colorless oil. IR: 1730, 1603, 1588, 1280 cm^{-1}. ^{1}H-NMR δ: 1.07 (6H, d, $J=6.8$ Hz). 2.65 (1H, m), 4.89 (2H, s), 7.2-8.1 (5H, m). MS *m/z*: 206 (M^+), 163 (base peak), 135, 106, 105, 86, 84, 77, 71.

2,2-Dimethoxy-3-methylbutyl Benzoate (6) A solution of the ketone **5** (8.0 g, 39 mmol), methyl orthoformate (22 ml), and *p*-TsOH (250 mg) in MeOH (150 ml) was stirred at 50 °C for 13 h. After addition of $NaHCO_3$, MeOH was evaporated off *in vacuo*. The residue was dissolved in water and the solution was extracted with ether. The organic layer was washed with saturated $NaHCO_3$ and brine, and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–EtOAc, 20:1) to give the acetal (8.26 g, 84%) as a colorless oil. IR: 1727, 1600, 1581, 1264 cm^{-1}. ^{1}H-NMR δ: 1.05 (6H, d, $J=7.0$ Hz), 2.19 (1H, sep, $J=7.0$ Hz), 3.28 (6H, s), 4.38 (2H, s), 7.3—7.7 (8H, m), 7.9—8.1 (2H, m). *Anal.* Calcd for $C_{14}H_{14}O_4$; C, 66.63; H, 7.99. Found: C, 66.44; H, 7.86.

(6*E*,10*E*)-2,6,10-Trimethyl-12-phenylthio-1,6,10-dodecatrien-3-ol (8) Aluminium isopropoxide (3 g, 14 mmol) was added to a solution of the epoxide **7** (4.6 g, 14 mmol) in anhydrous toluene (300 ml) under argon, and the mixture was heated at reflux for 12 h. The reaction was monitored by thin-layer chromatography (TLC) (hexane–EtOAc, 10:1). When the starting material had disappeared, ether (100 ml) and water (5 ml) were added and the mixture was stirred vigorously for 30 min. Then anhydrous $MgSO_4$ and celite were added. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–EtOAc, 10:1) to yield the allylic alcohol **11** (3.8 g, 82%) as a colorless oil. IR: 3400, 1660, 1596, 902 cm^{-1}. ^{1}H-NMR δ: 1.59 (6H, br s), 1.71 (3H, s), 3.53 (2H, d, $J=7.7$ Hz), 4.02 (1H, t, $J=6.3$ Hz), 4.82 (1H, br s), 4.92 (1H, br s), 5.13 (1H, m), 5.31 (1H, br t, $J=7.7$ Hz), 7.1—7.4 (5H, m). MS *m/z*: 330 (M^+), 221, 203, 135, 109, 107, 93 (base peak), 81. HRMS *m/z*: 330.2012 (Calcd for $C_{21}H_{30}OS$, 330.2016).

Claisen Rearrangement Using 6 and 8 A solution of the allylic alcohol **8** (3.15 g, 9.53 mmol), the acetal **6** (7.2 g, 29 mmol), and 2,4-dinitrophenol (184 mg, 1 mmol) in anhydrous toluene (70 ml) was heated gradually to 125 °C over 3 h and heating was continued for 30 h, during which time volatile materials were distilled off. The reaction mixture was passed through a short column of silica gel using benzene as an eluant. The eluate was further purified by column chromatography on silica gel (hexane–EtOAc, 20:1) to furnish two α-benzoyloxy-ketones, **9** (2.98 g, 60%) and **10** (0.6 g, 13%). **9** (Colorless oil). IR: 1730, 1603, 1594, 1278, 1105 cm^{-1}. ^{1}H-NMR δ: 1.08 (3H, d, $J=6.8$ Hz), 1.21 (3H, d, $J=6.8$ Hz), 1.52 (3H, s), 1.57

(3H, s), 1.71 (3H, s), 2.91 (1H, sep, $J=6.8$ Hz), 3.54 (2H, d, $J=7.7$ Hz), 5.00 (1H, br m), 5.29 (2H, br m), 5.52 (1H, dd, $J=8.8$, 9.5 Hz), 7.1—7.7 (8H, m), 7.9—8.1 (2H, m). MS *m/z*: 518 (M^+), 105 (base peak). HRMS *m/z*: 518.2849 (Calcd for $C_{33}H_{42}O_3S$, 518.2852). *Anal.* Calcd for $C_{33}H_{42}O_3S$: C, 76.41; H, 8.17. Found: C, 76.15; H, 8.16. **10** (Colorless oil). IR: 1727, 1602, 1586, 1275 cm^{-1}. ^{1}H-NMR δ: 1.21 (6H, s), 1.59 (9H, s), 3.55 (2H, d, $J=7.5$ Hz), 5.12 (2H, s), 5.0—5.6 (3H, m), 7.1—7.6 (8H, m), 7.9—8.2 (2H, m). MS *m/z*: 518 (M^+), 105 (base peak). HRMS *m/z*: 518.2852 (Calcd for $C_{33}H_{42}O_3S$, 518.2852).

(6*E*,10*E*,14*E*)-3-Hydroxy-2,6,10,14-tetramethyl-16-phenylthio-6,10,14-hexadecatrien-4-yl Benzoate (11) A solution of **9** (1.0 g, 1.93 mmol) in MeOH (30 ml) was treated with $NaBH_4$ (73 mg, 1.9 mmol) at 0 °C. After being stirred at room temperature for 30 min, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* yield the alcohol **11** (1.04 g, 100%) as a mixture of diastereomers. This mixture was used in the next step without separation. IR: 3550, 1733, 1610, 1595, 1280 cm^{-1}. MS *m/z*: 520 (M^+), 105 (base peak). HRMS *m/z*: 520.2989 (Calcd for $C_{33}H_{44}O_3S$, 520.3009).

(6*E*,10*E*,14*E*)-2,6,10,14-Tetramethyl-16-phenylthio-3-tetrahydropyranyloxy-6,10,14-hexadecatrien-4-ol (12) A solution of **11** (520 mg, 1 mmol), 3,4-dihydropyran (0.4 ml), and *p*-TsOH (20 mg) in CH_2Cl_2 (15 ml) was stirred at room temperature for 4 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ and then dried ($MgSO_4$). Evaporation of the solvent and column chromatography on silica gel (hexane–EtOAc, 15:1) afforded the tetrahydropyranyl ether of **11** (650 mg, 95%) as a mixture of diasteromers. IR: 1733, 1610, 1595, 1280 cm^{-1}. MS *m/z*: 604 (M^+), 85 (base peak).

The product was dissolved in MeOH (15 ml) and aqueous 2 N NaOH solution was added. The mixture was heated under reflux for 24 h. MeOH was evaporated off *in vacuo* and the residue was extracted with EtOAc. The organic layer was washed with water and dried ($MgSO_4$). Evaporation of the solvent yielded **12** (520 mg, 94%) as a colorless oil. IR: 3550, 1595 cm^{-1}. ^{1}H-NMR δ: 0.89 (3H, d, $J=6.6$ Hz), 0.97 (3H, d, $J=6.6$ Hz), 1.58 (6H, br s), 1.65 (3H, s), 3.55 (2H, d, $J=7.7$ Hz), 5.08 (1H, m), 5.27 (1H, m), 5.31 (1H, t, $J=7.5$ Hz), 7.1—7.4 (5H, m). MS *m/z*: 500 (M^+), 392, 189, 135, 121, 87, 85, 83 (base peak).

(6*E*,10*E*,14*E*)-4-Mesyloxy-2,6,10,14-tetramethyl-16-phenylthio-6,10,14-hexadecatrien-3-ol (13) A solution of the alcohol **12** (520 mg, 1 mmol) in dry pyridine (15 ml) was treated with MsCl (100 μl, 1.3 mmol) at 0 °C. After being stirred at 0 °C for 4 h, the reaction mixture was worked up as usual. The crude product was chromatographed on silica gel to give the mesylate (580 mg, 96%) as a colorless oil. IR: 1590, 1350, 1170, 1130, 1030, 905 cm^{-1}. HRMS *m/z*: 578.3091 (Calcd for $C_{32}H_{50}O_5S_2$, 578.3097).

A solution of the mesylate (1.9 g, 3.3 mmol) and PPTS (50 mg) in EtOH (60 ml) was stirred at room temperature for 48 h. After the addition of $NaHCO_3$ powder, ethanol was evaporated off *in vacuo*. The residue was diluted with water and extracted with EtOAc. The extract was evaporated *in vacuo* and the residue was chromatographed on silica gel (hexane–EtOAc, 5:1) to give **13** (950 mg, 60%) as a mixture of diastereomers. IR: 3550, 1585, 1350, 1170, 905, 590 cm^{-1}. MS *m/z*: 494 (M^+), 43 (base peak). HRMS *m/z*: 494.2523 (Calcd for $C_{27}H_{42}O_4S_2$, 494.2522).

(2*E*,6*E*,10*E*)-*trans*- and *cis*-13,14-Epoxy-3,7,11,15-tetramethyl-1-phenylthio-2,6,10-hexadecatrienes (14 and 15) Anhydrous K_2CO_3 (400 mg, 2.9 mmol) was added to a solution of the mesylate **13** (261 mg, 0.53 mmol) in MeOH (20 ml). After being stirred vigorously for 30 min at room temperature, the reaction mixture was filtered through Celite. The filtrate was evaporated *in vacuo* and the residue was extracted with EtOAc after dilution with water. Evaporation of the solvent yielded the epoxide (204 mg, 97%) as a mixture of *cis*- and *trans*-isomers. This was separated by HPLC (Chemcosorb 5-Si; hexane–EtOAc, 20:1). The ratio of **14** and **15** was approximately 4:6. **14** (Colorless oil). ^{1}H-NMR δ: 0.96 (3H, d, $J=7.3$ Hz), 1.01 (3H, d, $J=6.6$ Hz), 1.59 (6H, s), 1.67 (3H, s), 2.26 (1H, dd, $J=5.9$, 13.9 Hz), 2.47 (1H, dd, $J=2.2$, 7.3 Hz), 2.77 (1H, td, $J=2.2$, 5.9 Hz), 3.55 (2H, d, $J=7.3$ Hz), 5.08 (1H, br t, $J=5.9$ Hz), 5.22 (1H, br t, $J=6.6$ Hz), 5.31 (1H, br t, $J=6.6$ Hz), 7.1—7.4 (5H, m). HRMS *m/z*: 398.2628 (Calcd for $C_{26}H_{38}OS$, 398.2641). **15** (Colorless oil). ^{1}H-NMR δ: 0.95 (3H, d, $J=6.6$ Hz), 1.10 (3H, d, $J=6.6$ Hz), 1.58 (3H, s), 1.60 (3H, s), 1.70 (3H, s), 2.18 (1H, dd, $J=7.1$, 15.4 Hz), 2.23 (1H, dd, $J=5.1$, 15.4 Hz), 2.59 (1H, dd, $J=4.4$, 9.5 Hz), 3.04 (1H, ddd, $J=4.4$, 5.1, 15.4 Hz), 3.56 (2H, d, $J=8.1$ Hz), 5.08 (1H, br t, $J=6$ Hz), 5.24 (1H, br t, $J=6.6$ Hz), 5.32 (1H, br t, $J=6$ Hz), 7.1—7.3 (5H, m). HRMS *m/z*: 398.2614 (Calcd for $C_{26}H_{38}OS$, 398.2621).

Cyclization (1) From **14**: The *trans*-epoxide **14** (176 mg, 0.44 mmol) was placed in a well dried three-necked flask and the flask was evacuated for 1 h. DABCO (50 mg, 0.45 mmol) was added and evacuation was continued for an additional 20 min. Anhydrous THF (150 mg) was added and the mixture was cooled with dry ice-MeOH bath. Stirring was continued for 40 min at the same temperature, then *n*-butyllithium (0.9 ml of 15% hexane solution, 0.45 mmol) was added. The deep yellow solution was stirred at the same temperature for 2 h and then the cooling bath was replaced with an ice-water bath. Stirring was continued for an additional 2 h, then the reaction was quenched by the addition of water (2 ml). Most of the THF was evaporated *in vacuo* and the residue was diluted with water and extracted with EtOAc. The organic layer was washed successively with aqueous $NaHCO_3$, water, and brine, and dried ($MgSO_4$). The solvent was evaporated off *in vacuo*, and the residue was chromatographed on alumina (hexane–EtOAc, 10:1) to afford **16** (79 mg, 45% based on the consumed **14**) as a colorless oil. IR: 3475, 1580, 1440, 1020, 840, 690 cm^{-1}. ^{1}H-NMR δ: 0.95 (3H, d, $J=7.3$ Hz), 1.01 (3H, d, $J=6.6$ Hz), *ca.* 1.88 (1H, m), 3.44 (1H, dd, $J=3.7$, 8.1 Hz), 4.36 (1H, dd, $J=2.9$, 10.3 Hz), 4.88 (1H, br t, $J=7$ Hz), 5.04 (1H, br m), 5.24 (1H, d, $J=10.3$ Hz), 7.2—7.3 (5H, m). MS *m/z*: 398 (M^+), 43 (base peak). HRMS *m/z*: 398.2629 (Calcd for $C_{26}H_{38}OS$, 398.2641).

(2) From **15**: The *cis*-epoxide **15** (245 mg, 0.62 mmol) was similarly treated with *n*-butyllithium to yield **17** (122 mg, 65% based on the consumed **15**) as a colorless oil. IR: 3475, 1580, 1440, 1380, 1020, 840, 690 cm^{-1}. ^{1}H-NMR δ: 0.90 (3H, d, $J=6.8$ Hz), 0.98 (3H, d, $J=6.4$ Hz), 1.30 (3H, s), 1.56 (3H, s), 1.64 (3H, s), 1.88 (1H, m), 2.28 (2H, br d, $J=5.9$ Hz), 3.64 (1H, br t, $J=5$ Hz), 3.92 (1H, dd, $J=2.9$, 9.8 Hz), 4.90 (1H, t, $J=7.3$ Hz), 5.03 (1H, t, $J=6.4$ Hz), 5.34 (1H, d, $J=9.8$ Hz), 7.2—7.4 (5H, m). MS *m/z*: 398 (M^+), 43 (base peak). HRMS *m/z*: 398.2636 (Calcd for $C_{26}H_{38}OS$, 398.2641).

(3*E*,7*E*,11*E*)-4,8,12-Trimethyl-1-(2-methylpropanoyl)-2-phenylthio-3,7,11-cyclotridecatriene (18) Pyridinium dichromate (PDC) (75 mg, 0.2 mmol) was added to a solution of **16** (17 mg, 0.043 mmol) in CH_2Cl_2 (5 ml), and the mixture was stirred at room temperature overnight. After being diluted with ether, the reaction mixture was filtered through a Celite pad. The filtrate was evaporated *in vacuo* and the residue was chromatographed on alumina (ether) to yield the ketone **18** (10 mg, 58%) as a colorless oil. IR: 1715 cm^{-1}. ^{1}H-NMR δ: 1.08 (6H, d, $J=6.6$ Hz), 1.47 (3H, s), 1.54 (3H, s), 1.55 (3H, s), 2.36 (1H, dd, $J=8.8$, 5.0 Hz), 2.53 (1H, br d, $J=15.0$ Hz), 2.84 (1H, m), 3.14 (1H, m), 4.15 (1H, dd, $J=4.2$, 9.3 Hz), 4.93 (1H, br t, $J=5$ Hz), 5.05 (1H, br m), 5.56 (1H, d, $J=8.8$ Hz), 7.18—7.34 (5H, m). HRMS *m/z*: 396.2522 (Calcd for $C_{26}H_{36}OS$, 396.2485).

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