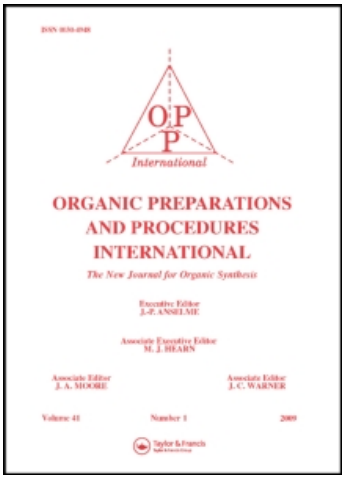

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A CONVERGENT SYNTHESIS OF (±)-SARCOPHYTOL-A BENZYL ETHER

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To cite this Article Li, Weidong , Mao, Jianmin , Li, Ying and Li, Yulin(1994) 'A CONVERGENT SYNTHESIS OF (±)-SARCOPHYTOL-A BENZYL ETHER', Organic Preparations and Procedures International, 26: 4, 445 — 457
To link to this Article: DOI: 10.1080/00304949409458035
URL: http://dx.doi.org/10.1080/00304949409458035

ORGANIC PREPARATIONS AND PROCEDURES INT., 26 (4), 445-457 (1994)

A CONVERGENT SYNTHESIS OF (±)-SARCOPHYTOL-A BENZYL ETHER

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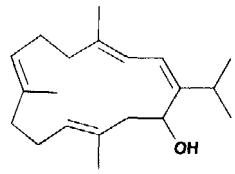
A large number of cembrane-type diterpenoid natural products characterized by the presence of a fourteen-membered carbocycle have been isolated from terrestrial plants, insects and animals and especially from marine sources in recent years.[1] Interest in the chemistry of this type of natural product has been prompted as a result of their remarkably wide-range of biological activities and challenging structural features.[2] Over the past decade, though synthetic studies in the field have made great progress, the lack of a general and efficient method for the construction of fourteen-membered rings has made the cembranes and cembrenoids an attractive problem for total syntheses.[3] Among the macrocyclization methodologies reported in the literature, the titanium-induced intramolecular reductive coupling of dicarbonyl precursors developed by *McMurry* and co-workers[4] is an extraordinarily general and effective means for preparing carbocyclic rings of all sizes; in this way, some total syntheses of naturally occurring antitumor cembrenoids, i. e. sarcophytol-B,[5] (±)-crassin and (±)-isolobophytolide[6] have been achieved. By employing the versatile macrocyclization method in our previous synthetic studies on cembrane diterpenoids, we have accomplished the total syntheses of cembrene-C,[7] (±)-cembrene-A[8] and isosarcophytol-A.[9] In order to extend the application of this macrocyclization method, sarcophytol-A was chosen as our next target molecule for total synthesis.

Sarcophytol-A (**1**), a cembrane diterpenoid first isolated by *Mitsuhashi*[10] in 1979 from a marine soft coral (*Sarcophyton glaucum*) and later from other kinds of soft coral (*Nephthea Sp.*[11] and *Lobophytum Sp.*[12]), has been shown to inhibit the activity of the powerful tumor promoter teleocidin[13] and to exhibit potent antitumor activity.[14] Its structure was established as (1*Z*,3*E*,7*E*,11*E*,14*S*)-cembra-1,3,7,11-tetraen-14-ol, an isomer of isosarcophytol-A (**2**)[15] whose total synthesis has been recently completed in our laboratory.[9] We now describe in detail our synthetic studies on (±)-sarcophytol-A (**1**) and the total synthesis of its benzyl ether (**3**) starting from available 4-hydroxy-2-butanone and geraniol in twelve steps.

Our convergent synthetic strategy is outlined in *Scheme* 1 which involves the construction of the fourteen-membered carbocyclic ring along with the formation of the *Z*-form conjugated double bond meanwhile by the titanium-induced macrocyclization of the hydroxy-protected dicarbonyl



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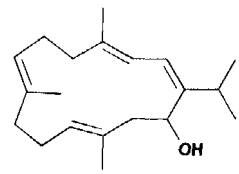

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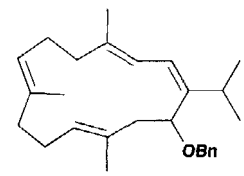
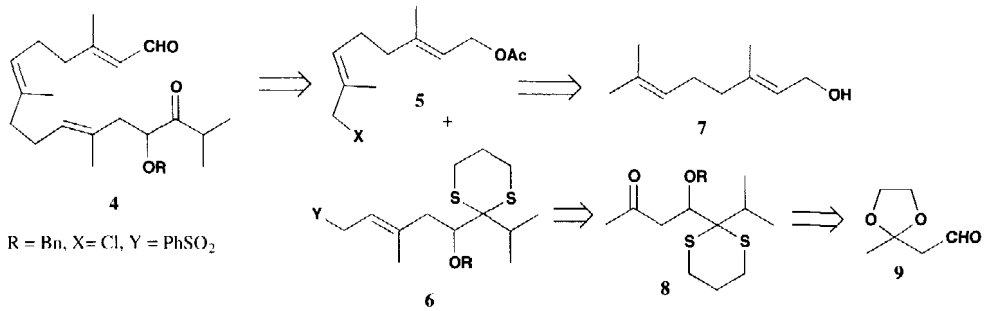


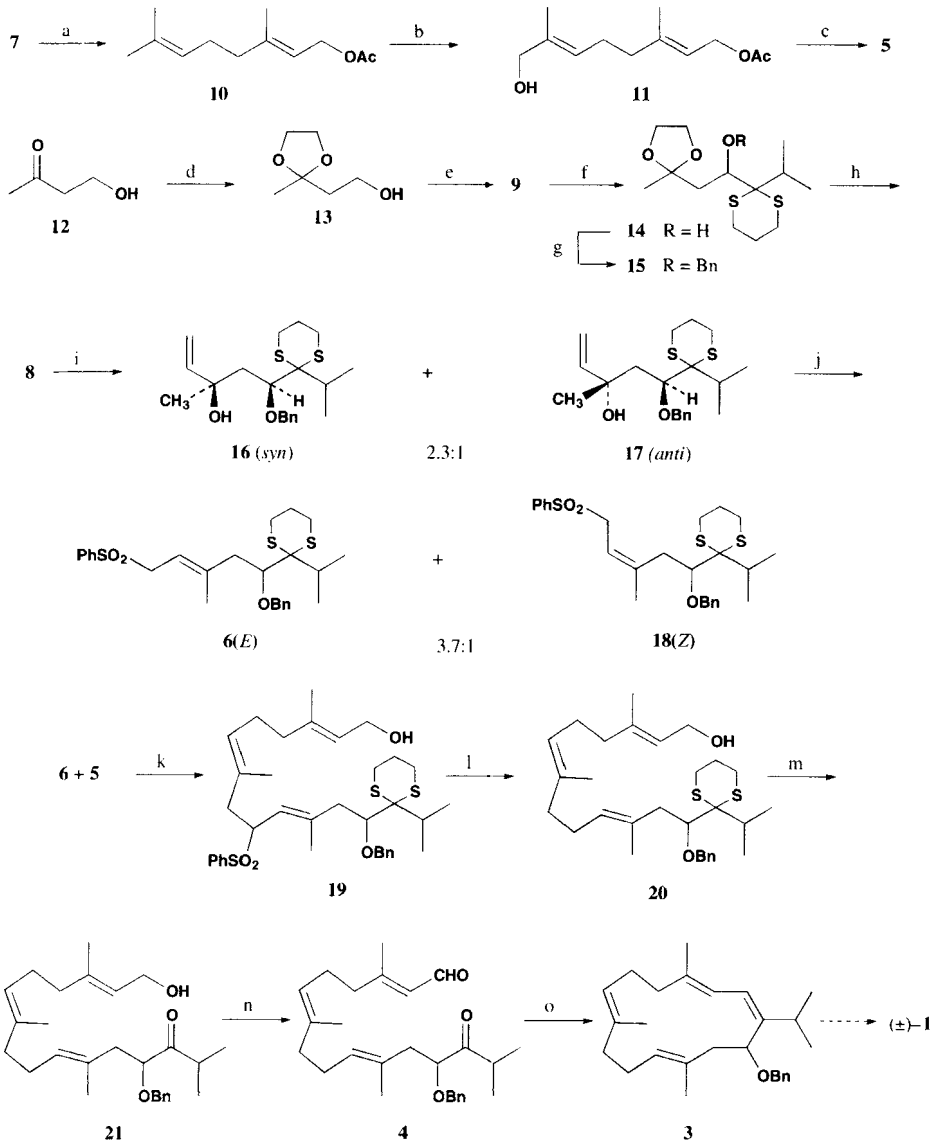
3

precursor **4** prepared by the phase-transfer catalytic coupling of allylic phenylsulfone **6** with allylic chloride **5**. The allylic chloride **5** which supplies two *E* double bonds of the target molecule is readily derived [16] from commercially available geraniol (**7**). The key intermediate in the synthesis *E*- allylic phenylsulfone **6**, is synthesized from the ketal-protected aldehyde **9** in five steps by employing the *Grignard* reaction of ketone **8** with vinylmagnesium bromide and, following double bond migration during bromination of the resulting tertiary allylic alcohol, establishing the third double bond at the same time.



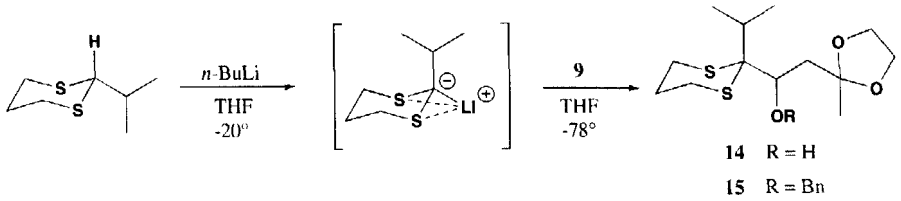
Scheme 1

Thus, the total synthetic route is detailed in *Scheme* 2. 4-Hydroxy-2-butanone (**12**) prepared[17] by the condensation of acetone with formaldehyde was employed as the starting material. It was protected as its glycol ketal **13** by reflux with ethylene glycol in dry benzene catalyzed by pyridinium *p*-toluenesulfonate (PPTs) and then oxidized with pyridinium chlorochromate (PCC) in the presence of sodium acetate to give the ketal-protected aldehyde **9** in 36% overall yield from ketone **12.** Nucleophilic addition of 2-lithio-2-isopropyl-1,3-dithiane (derived from 2-isopropyl-1,3-dithiane by treatment with *n*-butyllithium at -20°) to aldehyde **9** at -78° in tetrahydrofuran afforded the desired adduct alcohol **14** in 62% yield; the free hydroxy of **14** was then protected as its corresponding benzyl ether **15** in 76% yield by usual method (NaH/DMSO, BnCl, rt). The stable conformation of the adducts **14** and **15** was presumed[18] to be kinetically-controlled (Eq. 1) in which the isopropyl group located in the axial substitution in the chair-form conformation of the 1,3-dithiane as a result of the preferable conformation of 2-lithio-2-isopropyl-1,3-dithiane required that the lithium ion be held in the equatorial position by the cooperative effect of the carbanion with an unshared electron pairs of each of the two sulfur atoms.



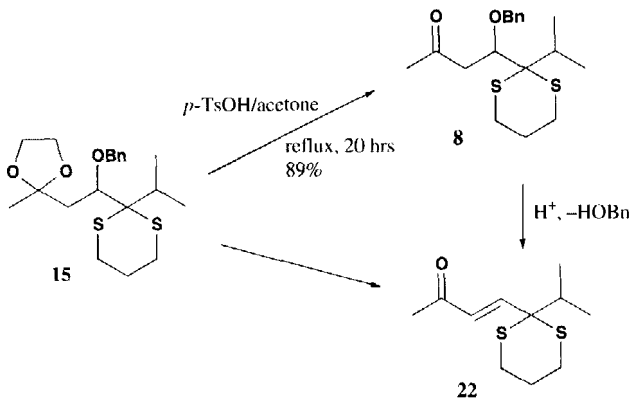
Scheme 2

a) Ac_2O/Py, rt (100%); b) 1. SeO_2/*t*-BuOOH, CH_2Cl_2, rt; 2. $NaBH_4$/MeOH, rt (64%); c) CCl_4/PPh_3, reflux(87%); d) ethylene glycol/PPTs, PhH, reflux (52%); e) PCC/NaOAc, silica gel, CH_2Cl_2, rt (70%); f) 2-lithio-2-isopropyl-1,3-dithiane/THF, -78°~rt (62%); g) NaH/DMSO, BnCl, rt (76%); h) acetone/*p*-TsOH(cat.), rt (80%); i) CH_2=CHMgBr/THF, 0°~45° (91%); j) 1. PBr_3/Py, pet. ether, -20~0°; 2. $NaSO_2Ph$/DMF, rt; k) 1. 50% NaOH/TBAB, rt; 2. K_2CO_3/MeOH, rt (88%); l) 6% Na(Hg)/Na_2HPO_4, MeOH, 0° (47%); m) $HgCl_2$/$CaCO_3$, 95% MeOH-H_2O, reflux (85%); n) 4-acetoxy-2,2,6,6-tetramethyl-piperidine-1-oxoammonium perchlorate/CH_2Cl_2, rt (79%); o) $TiCl_3$•$AlCl_3$ (3:1)/Zn-Cu, THF, reflux, 30 hrs (62%).



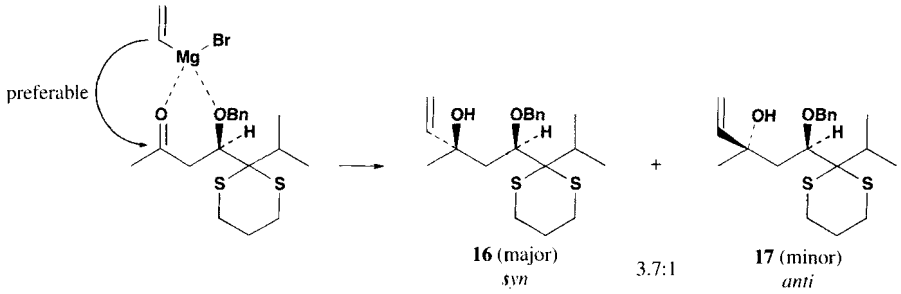
(1)

This was confirmed by their ^{1}H NMR spectral data in which the methyl of the bulky isopropyl appeared as two doublets (2d) due to the restricted rotation and the vicinal proton of the benzyl group as double doublet (dd). Selective hydrolysis of the glycol ketal protective group of compound **15** by treatment with a catalytic amount of *p*-TsOH in wet acetone at room temperature gave the desired deprotected ketone **8** in good yield (80%). It is noteworthy that when the same reaction mixture was heated under reflux for a long time (20 hrs), a more polar product was obtained in 89% yield; structure was confirmed as that of *trans* enone **22** by its spectral data [υ_{max} 1696, 1674 cm^{-1}; δ_H 6.57 ppm (ABq, J = 16.5Hz); M^+ 230 and base peak 187. (M-43)]. The pathway for its generation outlined in Eq. 2 involves the deprotection of the ketal protective group of **15** and the following elimination of the β-benzyloxy of the carbonyl group in the ketone catalyzed by acid.



(2)

Grignard reaction of ketone **8** with vinylmagnesium bromide in tetrahydrofuran at 0° and followed by heating at 50° to complete the reaction afforded a pair of stereoisomers of *syn* product **16** and *anti* isomer **17** in 91% combined yield with a ratio of 3.7:1 after flash column chromatography on silica gel. In the light of Cram's rule,[19] the addition of vinylmagnesium bromide to the carbonyl group of ketone **8** was conducted through the stable transition state conformation of six-membered ring in which the oxygen atom of the benzyloxy group acted as a coordinated atom (Eq. 3), thus favoring the *syn* product **16** along with the minor *anti* product **17**. The intramolecular hydrogen bond between the tertiary free hydroxy and the β-benzyloxy is present in the major *syn* product **16**, which is less polar than its isomer **17** (**16**, R_f 0.32; **17**, R_f 0.22, developed by a solvent mixture of pet. ether/ethyl acetate 6:1) and is responsible for a greater difference in the chemical shifts of the two protons of the benzyloxy group than that of isomer **17** (δOCH_2Bn (dd): **16**, 5.40 and 4.67 ppm; **17**, 5.25 and 4.71 ppm).



(3)

Bromination of the isomeric mixture of **16** and **17** with phosphorous tribromide in the presence of a small amount of dry pyridine in light petroleum ether gave the double bond migrated allylic bromides (*cis* and *trans*), which then were subjected to nucleophilic substitution with sodium benzenesulfinate in dimethylformamide to yield the key intermediate *E*-form allylic phenylsulfone **6** as main product along with its Z-form isomer **18** in 64% combined yield with a ratio of ca. 2.3:1 after flash chromatography on silica gel. When *syn* **16** or *anti* **17** was used as an alternative substrate for the above procedures (bromination and substitution), the same isomer ratio of **6** and **18** (ca. 2.3:1) was obtained. The chemical shift of vinyl methyl protons in *E*-form **6** is at higher field than that of its Z-isomer **18** (δCH_3 (*E*):1.56 ppm and (δCH_3 (*Z*): 1.83 ppm) as a result of the closer proximity of the strongly electron-withdrawing allylic phenylsulfone.[20]

The phase-transfer catalytic coupling of *E*-form allylic sulfone **6** with the readily available allylic chloride **5**[16] was conducted by employing *Sato's* procedure[21] using *n*-tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst at ambient temperature in 50% sodium hydroxide aqueous solution. The coupled product **19** was obtained in 88% yield after further cleavage of the acetyl group by treatment with potassium carbonate in methanol. Reductive cleavage of the phenylsulfonyl group by treatment with 6% sodium amalgam in the presence of sodium hydrogen phosphate in dry methanol at 0° gave product **20** in 47% yield. Hydrolysis of the dithioketal protective group of **20** in the usual way ($HgCl_2/CaCO_3$, wet methanol, reflux), followed by oxidation of the corresponding hydroxyketone **21** with 4-acetoxy-2,2,6,6-tetramethylpiperidine-1-oxoammonium perchlorate[22] in methylene chloride afforded the desired dicarbonyl precursor **4** as a colorless oil in 75% overall yield from **20**.

The intramolecular cyclization of precursor **4**, the key step of the synthesis, was carried out by slowly syringing a dilute solution of **4** in anhydrous tetrahydrofuran to the refluxing low valent titanium slurry (prepared[7] *in situ* by the reduction of $TiCl_3 \cdot AlCl_3$ (3:1) with a Zn-Cu couple) in THF over a period of 26 hrs. Reflux was continued for an additional 4 hrs. After the usual workup and careful flash column chromatography on silica gel, the title compound **3** was obtained in moderate yield (62%). Its structure was confirmed by its spectral data and further conversion of **3** to (±)-sarcophytol-A is in progress in our laboratory.

EXPERIMENTAL SECTION

Melting points were determined on a Kofler apparatus and were uncorrected. FT-IR spectra were recorded on a FT-5DX or a FT-170SX spectrometer. ^{1}H NMR spectra were reported in δ (ppm) units with TMS as the internal standard; Mass spectra (MS) were measured on a ZAB-HS or a MAT-44S spectrometer at 70ev and signals given in *m/z* with relative intensity (%) in brackets. All solvents were purified and dried by standard techniques just before use. All reactions were routinely carried out under an inert atmosphere of Ar or N_2, and monitored by thin layer chromatography (TLC) using silica gel GF_{254}. Products were purified either by distillation or flash column chromatography (FCG) on silica gel (200~300mesh) made in *Qing Dao Marine Chemical Factory* by elution with solvent mixture of pet. ether and ethyl acetate or acetone, ether *et al.* All products were colorless oils except otherwise stated. All extracted organic phases were washed with brine and dried over anhydrous $MgSO_4$, then filtered prior to rotary evaporation *in vacuo*. Genanyl acetate (**22**) was prepared from commercially available geraniol (*Aldrich Co.*) by the usual acetylation with acetic anhydride/pyridine quantitatively.

3,7-Dimethyl-8-hydroxy-2*E*,6*E*-octadien-1-yl Acetate (11).- To a stirred solution of selenium dioxide (760 mg, 6.85 mmol) and of 75% *tert*-butyl hydroperoxide (3 mL, 25 mmol) in CH_2Cl_2 (25 mL) was added dropwise a solution of geranyl acetate **10** (2.6 g,13.3 mmol) in CH_2Cl_2 (10 mL) at room temperature. After the addition was complete, the reaction mixture was stirred for a period of 3 hrs and diluted with ether (30 mL); the organic layer was washed with water (20 mL) and brine (20 mL), then dried. After the solvent was removed *in vacuo*, the resulting residue was taken up in methanol (15 mL), to which was added sodium borohydride (390 mg, 10 mmol) portionwise at 0° with stirring. After being stirred for 0.5 hr, the solution was concentrated under reduced pressure to give a yellow oil which was dissolved in ether (30 mL) and washed with 2N HCl aqueous and water, brine (each 10 mL), then dried. Evaporation of the solvent gave a residue which was chromatographed on silica gel (pet. ether/acetone 4:1) to yield 11 (1.80 g, 64%) as a colorless oil. IR (film): 3437 (br, OH), 1738 (s, C=O), 1670, 1021 cm^{-1}; ^{1}H NMR (80 MHz): δ 1.68 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 2.04 (s, 3 H, $COCH_3$), 2.0~2.4 (m, 4 H, CH_2), 3.97 (s, 2 H, CH_2O), 4.59 (d, 2 H, J = 7.1 Hz,CH_2OAc), 4.9~5.3 (m, 2 H, CH=) ppm

3,7-Dimethyl-8-chloro-2*E*,6*E*-octadien-1-yl acetate (5).- To a solution of acetate **11** (1.2 g, 5.64 mmol) in dry carbon tetrachloride (20 mL) was added triphenylphosphine (1.7 g, 6.44 mmol) portion-wise under reflux over a period of 1 hr, then refluxed for an additional 1 hr. Light pet. ether (40 mL) was added and, after cooling, the mixture was filtered to remove the solid material. Evaporation of the filtrate *in vacuo* gave an oily residue, which was purified by FCG on silica gel (pet ether/ethyl acetate 10:1) to afford **5** (1.06 g, 81%) as a colorless oil. ^{1}H NMR (80 MHz): δ 1.71 (br s, 6 H, 2xCH_3), 2.02 (s, 3 H, CH_3), 2.1 (br m, 4 H, CH_2), 3.96 (s, 2 H, CH_2Cl), 4.55 (d, 2 H, J = 7.2 Hz, CH_2OAc), 5.0~5.4 (br m, 2 H, CH=) ppm

2-Methyl-2-(2-hydroxyethyl)-1,3-dioxolane (13).- A mixture of **12** (2.0 g, 22.7 mmol), ethylene glycol (3.0 g, 48.4 mmol) and PPTs (570 mg, 2.3 mmol) in anhydrous benzene (65 mL) was refluxed for a period of 2.5 hrs to remove water from the reaction mixture by azeotropic distillation. After the

reaction was complete (monitored by TLC), the reaction mixture was concentrated to remove most of the benzene and the resulting residue was diluted with ether (100 mL), washed successively with saturated sodium bicarbonate aqueous solution, water and brine (each 20 mL), then dried. Evaporation of the solvent under reduced pressure gave dioxolane **13** (1.56 g, 52%) as a colorless oil. IR (film): 3437 (s, OH), 1448, 1378, 1048 cm^{-1}; ^1H NMR (60 MHz, CCl_4/TMS): δ 1.34 (s, 3 H, CH_3), 1.91 (t, 2 H, *J* = 5.6 Hz, CH_2), 2.42 (br s, OH), 3.72 (t, 2 H, *J* = 5.6 Hz, CH_2OH), 3.97 (s, 4 H, OCH_2CH_2O) ppm

2-Methyl-2-(2-oxoethyl)-1,3-dioxolane (9).- To a suspension of dry PCC (25 g, 0.16 mmol), anhydrous sodium acetate (4.1 g, 50 mmol) and silica gel (200~300 mesh, 10 g) in methylene chloride (200 mL) was added dropwise a solution of methylene chloride (20 mL) containing alcohol **13** (8 g, 60.6 mmol) with efficient stirring during a period of 0.5 hr at room temperature. After being stirred for an additional 1.5 hrs, the reaction mixture was diluted with ether (300 mL) and filtered through a short column on silica gel. The clear filtrate was evaporated *in vacuo* to give an oily residue which then was purified by flash column chromatography eluting with pet. ether/acetone (v/v 10:1) to afford aldehyde **9** (5.5 g, 70%) as a yellow oil. IR (film): 2720, 2681 (w), 1726 (s, C=O), 1381, 1190, 1047 cm^{-1}; ^1H NMR (80 MHz): δ 1.50 (s, 3 H, CH_3), 2.68 (s, 2 H, CH_2), 3.99 (s, 4 H, OCH_2CH_2O), 9.73 (s, CHO) ppm.

2-Isopropyl-2-[1-hydroxy-3,3-(1,3-dioxocyclopentyl)butyl]-1,3-dithiane (14).- To a stirred solution of 2-isopropyl-1,3-dithiane (850 mg, 5.2 mmol) in anhydrous THF (20 mL) was added dropwise a hexane solution of *n*-BuLi (4.8 mL, 1.1 M, 5.2 mmol) at -20°. After being stirred for 2 hrs at that temperature, the reaction mixture was cooled to -78° by a dry ice-acetone bath, to which was added dropwise a solution of aldehyde **9** (650 mg, 5 mmol) in THF (5 mL). After the stirring was continued for 1.5 hrs at -78°, the reaction mixture was allowed to warm to room temperature gradually over a period of 1 hr, then saturated NH_4Cl aqueous solution (10 mL) and ether (30 mL) were added to quench the reaction, organic layer was separated and the aqueous phase was extracted with ether (2x15 mL). The combined Et_2O-THF extract was washed with water and brine (each 10 mL), then dried. Evaporation of the solvent gave an oily residue which was chromatographed flashly eluting with pet ether/ethyl acetate (v/v 5:1) to afford **14** (900 mg, 62%) as a colorless oil. IR (film): 3484 (s, OH), 1442, 1382, 1046 cm^{-1}; ^1H NMR (80 MHz): δ 1.16 (d, 3 H, *J* = 6.7 Hz, CH_3), 1.19 (d, 3 H, *J* = 6.7 Hz, CH_3), 1.44 (s, 3 H, CH_3), 3.99 (s, 4 H, OCH_2CH_2O), 1.70~2.30 (m, 5 H), 2.35~3.15 (m, 4 H, $2CH_2S$), 4.27 (t, 1 H, *J* = 6.1Hz, OCH) ppm; MS (EI): *m/z* = 292 (M^+, 1%), 277 (M-15, 1), 191 (2), 161 (100), 87 (54), 43 (32).

Anal. Calcd for $C_{13}H_{24}O_3S_2$: C, 53.39; H, 8.27. Found: C, 53.66; H, 8.21

2-Isopropyl-2-[1-benzoxy-3,3-(1,3-dioxocyclopentyl)butyl]-1,3-dithiane (15).- To a clear solution of freshly distilled DMSO (10 mL) was added portionwise sodium hydride (200 mg, 8.3 mmol) at room temp. with constant stirring. After being stirred for an additional 0.5 hr, alcohol 14 (1.17 g, 4 mmol) dissolved in dry DMSO (5 mL) was syringed dropwise to the reaction mixture at room temperature and stirred for another 0.5 hr, then freshly distilled dry benzyl chloride (1.4 g, 11.2 mmol) was introduced by a dry syringe and the stirring was continued for 2 hrs at ambient temperature to

complete the reaction. The reaction mixture was diluted with water (50 mL) and extracted with ether (4x30 mL) and the combined ether extract washed with water (4x8 mL) and brine (15 mL), then dried. Evaporation of the solvent gave an oily residue which was purified by flash column chromatography eluting with pet. ether/ethyl acetate (v/v 7:1) to afford benzyl ether 15 (1.01 g, 76%) as a colorless oil along with the recovery starting material **14** (150 mg). IR (film): 3088, 1603, 1458, 1378, 1111, 1053, 734, 698 cm^{-1}; ^1H NMR (80 MHz): δ 1.19 (d, 6 H, J = 6.3 Hz, $CH(CH_3)_2$), 1.40 (s, 3 H, CH_3), 1.50~2.30 (m, 5 H), 2.60~3.10 (m, 4 H, 2 CH_2S), 3.98 (s, 4 H, OCH_2CH_2O), 4.10 (m, 1 H, OCH), 4.73 (d, 1 H, J = 10.8 Hz), 5.00 (d, 1 H, J = 10.8 Hz), 7.26 (br s, 5 H, ArH) ppm; MS (EI): m/z = 382 (M^+, 1%), 367 (1), 339 (1), 281 (2), 221 (2), 161 (100), 91 (33), 87 (78).

Anal. Calcd for $C_{20}H_{30}O_3S_2$: C, 62.79; H, 7.90. Found: C, 62.45; H, 7.81

2-Isopropyl-2-(1-benzyloxy-3-oxobutyl)-1,3-dithiane (8).- A mixture of ether **15** (1.25 g, 3.3 mmol) and *p*-TsOH (100 mg, 0.6 mmol) in wet acetone (60 mL) was allowed to stir for a period of 5 hrs at room temperature. After removal of the acetone *in vacuo*, the resulting residue was taken up in ether (30 mL) and washed with saturated sodium bicarbonate aqueous solution, water and brine (each 10 mL), then dried. Evaporation of the solvent under reduced pressure gave an oily residue which was chromatographed flashly eluting with pet. ether/ethyl acetate (v/v 10:1) to yield ketone **8** (880 mg, 80%) as a colorless oil. IR (film): 1715 (vs, C=O), 1674, 1604, 1358, 1093, 1076, 737 cm^{-1}; ^1H NMR (80 MHz): δ 1.20 (d, 6 H, J = 6.3 Hz, $CH(CH_3)_2$), 2.17 (s, 3 H, CH_3), 1.70~2.10 (m, 3 H), 2.40~3.10 (m, 6 H, CH_2 and CH_2S), 4.50~4.70 (m, 1 H, OCH), 4.62 (d, 1 H, J = 11.2 Hz), 4.87 (d, 1 H, J = 11.2 Hz), 7.31 (br s, 5 H, ArH) ppm; MS (EI): m/z = 338 (M^+, 1%), 295 (2), 261 (100), 91 (64).

Anal. Calcd for $C_{18}H_{26}O_2S_2$: C, 63.87; H, 7.74. Found: C, 63.56; H, 7.65

***syn*- and *anti*-2-Isopropyl-2-(3-methyl-2-hydroxy-1-benzyloxy-4-pentenyl)-1,3-dithiane (16 and 17).**- To the cooled (0°) *Grignard* reagent prepared *in situ* from dry magnesium turnings (500 mg, 20.8 mmol) and vinyl bromide (2.0 g, 18.5 mmol) in anhydrous THF (20mL) at 40~50° was added dropwise a solution of **8** (1.63 g, 4.82 mmol) in anhydrous THF (10 mL) with efficient stirring during a period of 15 min. After the addition was complete, the reaction mixture was warmed to 40~50° and stirred for an additional 1 hr to complete the reaction, then allowed to cool to 0° gradually, to which was added saturated NH_4Cl aqueous solution and ether (30 mL) to quench the reaction, organic layer was separated and the aqueous phase extracted with ether (2x15 mL). The combined ether-THF extract was washed with water and brine(each 10 mL), then dried. After evaporation of the solvent, the oily residue was chromatographed carefully eluting with pet. ether/ethyl acetate (v/v 6:1) to afford the *syn*-adduct alcohol **16** (1.25 g, R_f 0.32, 71%) and the corresponding *anti*-adduct **17** (0.35 g, R_f 0.22, 20%) with a ratio of 3.7:1 (91% overall yield) as colorless oils. *syn*-Adduct **16**: IR (film): 3504 (s, OH), 1642 (m, C=C), 1602, 1453, 1372, 1087, 997, 737 cm^{-1}; ^1H NMR (80 MHz): δ 1.16~1.26 (m, 9 H, 3xCH_3), 1.70~2.25 (m, 5 H), 2.50~3.0 (m, 4 H, 2CH_2S), 4.15~4.35 (m, 1 H, OCH), 4.67 (d, 1 H, J = 10.4 Hz), 5.40 (d, 1 H, J = 10.4 Hz), 5.15~6.15 (m, 3 H, $CH=CH_2$), 7.30 (br s,5 H, ArH) ppm; MS (EI): m/z = 366 (M^+, 1%), 289 (1), 161 (100), 91 (83), 71 (14).

Anal. Calcd for $C_{20}H_{30}O_2S_2$: C, 65.53; H, 8.25. Found: C, 65.89; H, 8.20

Anti-isomer **17**: IR (film): 3452 (s, OH), 1641 (m, C=C), 1454, 1386, 1094, 1071, 698 cm^{-1}; ^1H NMR (80 MHz): δ 1.23 (d, 6 H, *J* = 6.3 Hz, $CH(CH_3)_2$), 1.37 (s, 3 H, CH_3), 1.70~2.30 (m, 5 H), 2.50~3.30 (m, 4 H, $2CH_2S$), 4.15~4.35 (m, 1H, OCH), 4.92~6.10 (m, 3 H, $CH=CH_2$), 4.71 (d, 1 H, *J* = 10.5 Hz), 5.25 (d, 1 H, *J* = 10.5 Hz), 7.30 (br s, 5 H, ArH) ppm; MS(EI): *m/z* = 351 (M-15, 1%), 161(100), 91(74), 71(11).

Anal. Calcd for $C_{20}H_{30}O_2S_2$: C, 65.52; H, 8.25. Found: C, 65.92; H, 8.18

2-Isopropyl-2-(3-methyl-1-benzyloxy-5-benzenesulfonyl-3*E*-pentenyl)-1,3-dithiane (6) and its-*Z*-isomer (18).- To a cooled (-20~15°) solution of **16** and **17** (850 mg, 2.32 mmol) and anhydrous pyridine (0.2 mL) in light pet. ether (30~60°, 30 mL) was added dropwise freshly distilled PBr_3 (0.3 mL, 3.16 mmol) dissolved in pet. ether (10 mL) with efficient stirring. After 2 hrs of stirring at ice temperature, ice water (20 mL) was added to the reaction mixture and organic layer was separated, the aqueous phase extracted with pet. ether (3x10 mL). The combined organic phases were washed with 15% Na_2CO_3 aq. solution (2x10 mL), water (10 mL) and brine (15 mL), then dried. Evaporation of the solvent under reduced pressure gave an oily residue which was taken up in dry DMF (20 mL) and dry powdered $NaSO_2Ph$ (1.5 g, 9.15 mmol) was added in one portion. The resulting solution was stirred vigorously for a period of 20 hrs in dark at ambient temperature. Addition of water (65 mL) was followed by extraction with ether (4x30 mL) and the combined ether extract was washed with water (3x15 mL), brine (20 mL), then dried. Evaporation of the solvent gave an oily residue which was purified by FCG (pet. ether/ethyl acetate 5:1) to yield **6** (440 mg, 45%) and its Z- isomer **18** (190 mg, 19%) in 64% combined yield. **6**, IR (film): 1664(C=C), 1305, 1149 (s, SO_2) cm^{-1}; ^1H NMR (80 MHz): δ 1.15 and 1.23 (2d, 6 H, *J* = 6.4 Hz, $CH(CH_3)_2$), 1.56 (s, 3 H, CH_3), 1.50~2.10 (m, 5 H), 2.45~3.10 (m, 4 H, $2CH_2S$), 3.75~4.05 (m, 1 H, CHO, 3.75 (d, 2 H, *J* = 7.5 Hz, CH_2SO_2), 4.48 and 4.79 (ABq, 2 H, *J* = 11.1 Hz, OCH_2Ar), 5.32 (t, 1 H, *J* = 7.5 Hz, CH=), 7.20~7.85 (m, 10 H, ArH) ppm; MS (EI): *m/z* = 447 (M-43, 1%), 349 (21), 161 (100), 91 (59).

Anal. Calcd. for $C_{26}H_{34}O_3S_3$: C, 63.63; H, 6.98. Found: C, 63.38; H, 6.91

18, colorless crystal, mp. 113.5~114.0°; IR (KBr): 1661 (C=C), 1307, 1149 (s, SO_2) cm^{-1}; ^1H NMR (80 HMz): δ 1.12 and 1.18 (2d, 6 H, *J* = 6.4 Hz, $CH(CH_3)_2$), 1.83 (s, 3 H, CH_3), 1.50~2.30 (m, 5H), 2.45~3.15 (m, 4 H, $2CH_2$), 3.75~4.10 (m, 3 H, CHO and CH_2SO_2), 4.32 and 4.48 (ABq, 2 H, *J* = 11Hz, OCH_2Ar), 5.33 (t, 1 H, *J* = 8.0 Hz, CH=), 7.18~7.88 (m, 10 H, ArH) ppm; MS (EI): *m/z* = 490(M^+, 1%), 383 (M-107, 11), 349 (M-171, 26), 329 (61), 281 (13), 187 (33), 161 (99), 91 (100).

Anal. Calcd. for $C_{26}H_{34}O_3S_3$: C, 63.63; H, 6.98. Found: C, 63.34; H, 6.89

2-Isopropyl-2-(1-benzyloxy-5-benzenesulfonyl-13-hydroxy-3,7,11-trimethyl-3*E*,7*E*,11*E*-trideca-trienyl)-1,3-dithiane (19).- A mixture of **6** (440 mg, 0.90 mmol) and **5** (250 mg, 1.0 mmol) in 50% NaOH aq. solution (10 mL) was stirred for 10 min, then *n*-tetrabutylammonium bromide (TBAB, 150 mg, 0.16 mmol) was added in one portion. The reaction mixture was stirred vigorously for a period of 5 hrs at ambient temperature. Addition of water (40 mL) was followed by extraction with ether (3x20 mL), and the combined organic phases were washed with water (3x10 mL), brine (15 mL), then dried. After evaporation of the solvent, the residue was dissolved in methanol (15 mL) and powdered dry

K_2CO_3 (150 mg, 1.09 mmol) was added to. The resulting mixture was stirred constantly for 1 hr at room temperature and followed by filtration, evaporation to give an oily residue, which was taken in ether (30 mL) and washed with water and brine each (10 mL), then dried. After the solvent was evaporated, the residue was subjected to chromatographic purification eluting with pet. ether/ethyl acetate (4:1) to yield coupled product **19** (500 mg, 88%) as a pale yellowish oil. IR (film): 3440 (s, OH), 1667 (C=C), 1304, 1144 (s, SO_2) cm^{-1}; ^1H NMR (80 MHz): δ 1.22 (d, 6 H, $CH(CH_3)_2$), 1.50~2.20 (m, 21 H), 2.40~3.0 (m, 4 H, $2CH_2S$), 3.75~4.75 (m, 6 H), 5.05~5.30 (m, 3 H, CH=), 7.27~7.80 (m, 10 H, ArH) ppm; MS(EI): *m/z* = 501(M-141, 1%), 483(4), 161(100), 91(66).

Anal. Calcd. for $C_{36}H_{50}O_4S_3$: C, 67.25; H, 7.84. Found: C, 67.49; H, 7.78

2-Isopropyl-2-(1-benzyloxy-13-hydroxy-3,7,11-trimethyl-3*E*,7*E*,11*E*-tridecatrienyl)-1,3-dithiane (20).- To a cooled (0°) mixture of **19** (500 mg, 0.78 mmol) and powdered dry Na_2HPO_4 (580 mg, 4 mmol) in anhydrous methanol (10 mL) was added 6% sodium amalgam (1.5 g, 3.75 mmol) portionwise with vigorous stirring over a period of 0.5 hr. After the addition was complete, the reaction mixture was stirred for an additional 1 hr and then filtered. The filtrate was evaporated *in vacuo* to give an oily residue, which was dissolved in ether (20 mL) and washed with water, brine (each 10 mL), and dried. Evaporation of the solvent under reduced pressure and purification by FCG eluting with pet. ether/ethyl acetate (8:1) afforded alcohol **20** (180 mg, 47%). IR (film): 3332 (s, OH), 1667 (C=C), 1028, 844 cm^{-1}; ^1H NMR (80 MHz): δ 1.18 and 1.27 (2d, 6 H, *J* = 7 Hz, $CH(CH_3)_2$), 1.64 (br s, 6 H, $2CH_3$), 1.72 (s, 3 H, CH_3), 1.80~2.20 (m, 13 H), 2.40~3.20 (m, 4 H, $2CH_2S$), 4.15 (d, 2 H, *J* = 7.1 Hz, CH_2O), 4.67 (br s, 1 H, CH), 4.58 and 4.85 (ABq, 2 H, *J* = 11.3 Hz, OCH_2Ar), 5.0~5.40 (m, 3H, CH=), 7.25~7.40 (m, 5 H, ArH) ppm; MS(EI): *m/z* = 459 (M-43, 1%), 411 (1), 323 (2), 161 (100), 91 (41).

Anal. Calcd. for $C_{30}H_{46}O_2S_2$: C, 71.66; H, 9.22. Found: C, 71.87; H, 9.11

3,7,11,15-Tetramethyl-13-benzyloxy-14-oxo-2*E*,6*E*,10*E*-hexaddecatrienol (21).- To a suspension of $HgCl_2$ (125 mg, 0.45 mmol) and $CaCO_3$ (50 mg, 0.5 mmol) in mixture solvent of 95% methanol-water (10 mL) was added a solution of **20** (100 mg, 0.2 mmol) in methanol (1 mL) with stirring. After a period of 10 min, the resulting reaction mixture was refluxed for ca. 1 hr to complete the reaction. The cooled reaction mixture was filtered and evaporated *in vacuo* to yield an oily residue, which was taken in ether (10 mL), washed with NH_4OAc aq. solution (5 M), water and brine (each 4 mL) and dried. After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel flashly to give alcohol **21** (80 mg, 95%) as a colorless oil. IR (film): 3360 (s, OH), 1715 (s, C=O), 1666 (C=C); ^1H NMR (80 MHz): δ 1.08 (d, 6 H, *J* = 6.7 Hz, $CH(CH_3)_2$), 1.51 (s, 3 H, CH_3), 1.60 and 1.69 (2s, each 3 H, $2xCH_3$), 1.90~2.10 (m, 12 H), 4.17 (d, 2 H, *J* = 7 Hz, CH_2O), 4.00~4.75 (m, 3 H, CHO and OCH_2Ar), 5.0~5.5 (m, 3 H, CH=), 7.33 (br s, 5 H, ArH) ppm.

Anal. Calcd. for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77. Found: C, 78.38; H, 9.65

3,7,11,15-Tetramethyl-13-benzyloxy-14-oxo-2*E*,6*E*,10*E*-hexadecatrienal (4).-To a stirred suspension of 4-acetoxy-2,2,6,6-tetramethyl-piperidine-1-oxoammonium perchlorate (70 mg, 0.23 mmol) in anhydrons CH_2Cl_2 (3 mL) was added dropwise a solution of CH_2Cl_2 (1 mL) containing alcohol **21**

(80 mg, 0.19 mmol) at ambient temperature. After being stirred for a period of 0.5 hr, the reaction mixture was diluted by the addition of ether (10 mL) and washed with water and brine (each 5 mL) and dried. Evaporation of the solvent under reduced pressure gave on oily residue which was purified by FCG eluting with pet. ether/ethyl acetate (10:1) to afford the desired dicarbonyl precursor **4** (55 mg, 79%) as a colorless oil. IR (film): 1713 (s, C=O), 1674 (s, C=O), 1632 cm^{-1}; ^1H NMR (80 MHz): δ 1.05 (d, 6 H, J = 6.8 Hz, $CH(CH_3)_2$), 1.60 (br s, 9 H, $3xCH_3$), 2.10~2.50 (m, 11 H), 4.01 (t, 1 H, J = 7.0 Hz, CHOBn), 4.36 and 4.53 (ABq, 2 H, J = 11 Hz, OCH_2Ar), 5.05~5.35 (m, 2 H, CH=), 5.93 (d, 1 H, J = 8.1 Hz, CH=), 7.38 (br s, 5 H, ArH), 9.97 (d, 1 H, J = 8.1 Hz, CHO) ppm; MS (EI): m/z = 339 (M-71, 14), 192 (3), 91 (100), 71 (19).

Anal. Calcd. for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33. Found: C, 78.69; H, 9.25

Synthesis of (±)-Sarcophytol-A Benzyl Ether (3).- A vigorously stirred mixture of $TiCl_3$•$AlCl_3$ (3:1,3.65 g) and Zn-Cu couple (4.0 g) in anhydrous THF (35 mL) was refluxed for a period of 3 hrs to complete the formation of a low valent titanium slurry, to which a solution of precursor **4** (50 mg, 0.122 mmol) in anhydrous THF (30 mL) was syringed slowly under argon atmosphere over a period of 28 hrs. After the addition was complete, the rectum mixture was refluxed for an additional 5 hrs and then cooled to ambient temperature, diluted by the addition of redistilled petroleum ether (60 mL) and stirred vigorously for 15 min. Filtration of the resulting mixture was followed by evaporation of the solvent *in vacuo* to give an oily residue, which was purification by flash column chromatography on silica gel eluting with *n*-hexane/ether (10:1) to afford the title compound **3** (30 mg, 60%). IR (film): 3029, 2957, 2856, 1652, 1606, 1384, 840, 698, 733 cm^{-1}; ^1H NMR (400 MHz): δ 1.10 and 1.15 (2d, 6 H, $CH(CH_3)_2$), 2.58 (sept, 1 H, J = 7 Hz, $CH(CH_3)_2$), 1.41, 1.59 and 1.74 (3s, each 3 H, $3xCH_3$), 2.0~2.3 (m, 10 H), 4.25 and 4.48 (ABq, 2 H, J = 12 Hz, OCH_2Ar), 4.36 and 4.38 (dd, 1 H, J = 6.5; 9.2 Hz, CHOBn), 4.93 (m, 1 H, CH=), 5.14 (t, 1 H, J = 7 Hz, CH=), 5.95 and 6.34 (ABq, 2 H, J = 11.5 Hz, *trans* =CH-CH=), 7.25~7.33 (m, 5 H, ArH) ppm; MS (EI): m/z = 378 (M^+, 20%), 335 (M-43, 2), 287 (M-91, 4), 272 (1), 227 (3), 137 (30), 109 (21), 91 (100), 77 (9), 43 (19)

Anal. Calcd for $C_{27}H_{38}O$: C, 85.66; H, 10.11. Found: C, 85.93; H, 10.34

2-Isopropyl-2-(3-oxo-1-butenyl)-1,3-dithiane (22).- A mixture of benzyl ether **15** (950 mg, 2.5 mmol) and *p*-TsOH (70 mg, 0.4 mmol) in wet acetone (20 mL) was refluxed for a period of 20 hrs. After removal of the acetone *in vacuo*, the residue was dissolved in ether (5 mL) and washed with saturated $NaHCO_3$ aqueous solution, water and brine (each 5 mL), then dried. After evaporation of the solvent, the residue was purified by flash column chromatography eluting with pet ether/ethyl acetate (v/v 8:1) to give enone **22** (510 mg, 89%) as a colorless oil. IR (film): 1696 (vs, C=O), 1674, 1615, 1424, 1387, 1170, 909 cm^{-1}; ^1H NMR (80 MHz): δ 1.10 (d, 6 H, J = 6.4 Hz, $CH(CH_3)_2$), 2.33 (s, 3 H, CH_3), 1.67~2.00 (m, 3 H), 2.60~2.90 (m, 4 H, $2CH_2S$), 6.57 (ABq, 2 H, J = 16.5 Hz, *trans* CH=CH) ppm; MS (EI): m/z = 230 (M^+, 8%), 215 (2), 187 (M-43, 100).

Anal. Calcd for $C_{11}H_{18}OS_2$: C, 57.34; H, 7.88. Found: C, 57.68; H, 7.81

Acknowledgement.- We thank the National Natural Science Foundation of China and the Special Research Grant for Doctoral Sites in Chinese Universities for financial support.

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(Received December 13, 1993; in revised form February 28, 1994)