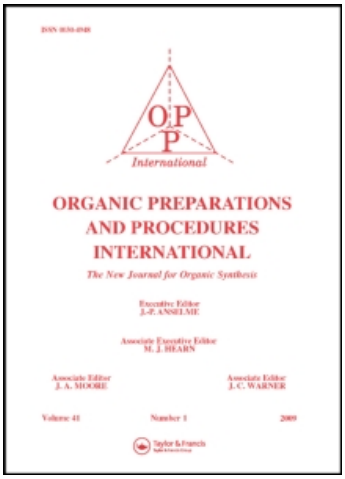

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A CONVERGENT AND STEREOSELECTIVE SYNTHESIS OF CEMBRENENE PRECURSOR-4,10-DIMETHYL-7-ISOPROPENYL-14-OXO-3Z,5E,10E-PENTADECATRIENAL

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A CONVERGENT AND STEREOSELECTIVE SYNTHESIS OF CEMBRENENE PRECURSOR-4,10-DIMETHYL-7-ISOPROPENYL-14-OXO-3Z,5E,10*E*-PENTADECATRIENAL†

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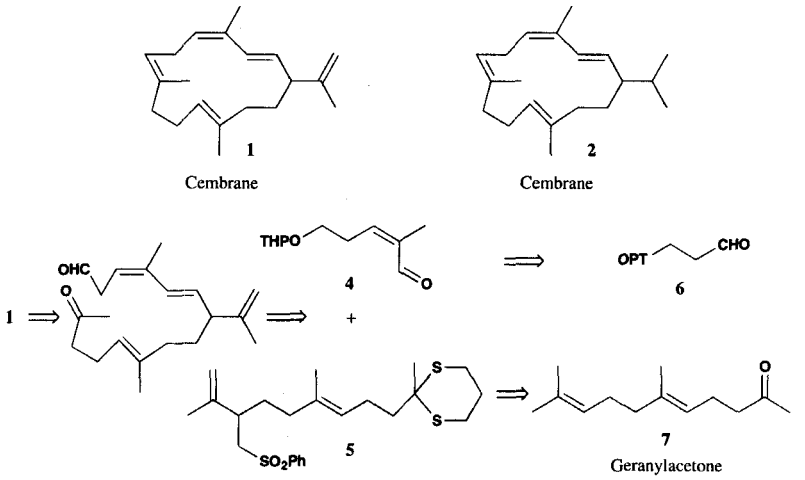
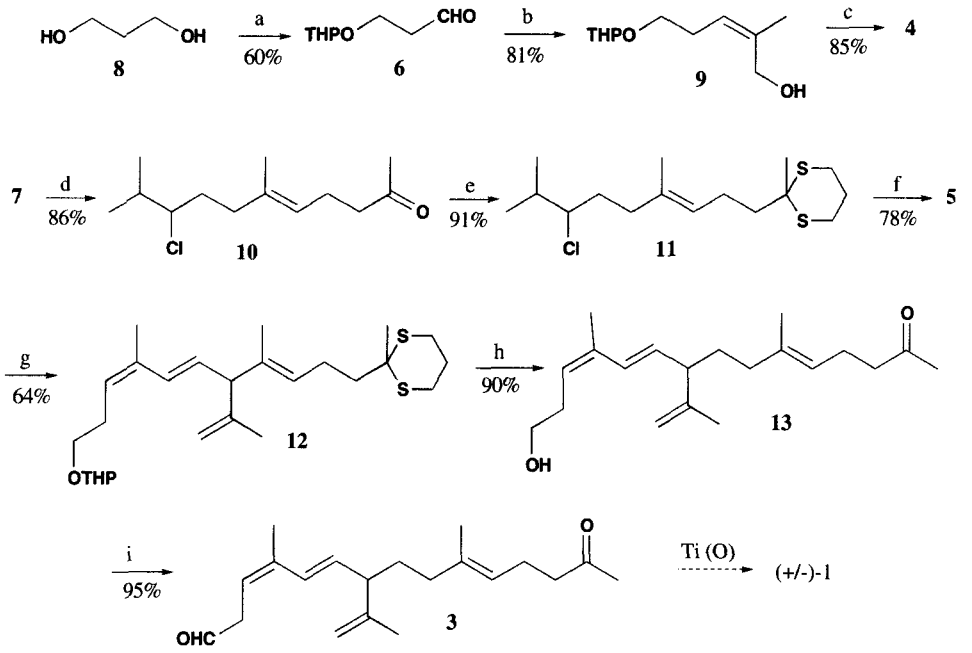
Cembrenene (**1**),[1] a hydrocarbon cembrane diterpene, was first isolated from marine soft coral (*Sinylaria mayi*) in 1981, which possess the same carbocyclic skeleton as cembrene (**2**),[2] the first naturally occurring cembranetype diterpene to be characterized. The challenging structural feature of the fourteen-membered carbocyclic ring offered an attractive target for the synthetic organic chemists. The first total synthesis of **2** was achieved by Dauben[3] and the synthesis of **1** has been reported by several research groups.[4] In our previous studies on the total synthesis of cembrane-type diterpenoids, employing titanium-induced intramolecular reductive coupling of dicarbonyl precursors developed by *McMurry*[5] as the key macrocyclization step, we have accomplished the total synthesis of cembrene-C,[6] (±) cembreneA[7] and (±)-isosarcophytol-A.[8] Herein we wish to describe the convergent and stereoselective synthesis of a cembrenene precursor, 4,10-dimethyl-7isopropenyl-14-oxo-3Z,5*E*,10*E*-pentadecatrienal (**3**). The retro-synthetic analysis is detailed in Scheme 1.



Scheme 1

Our synthetic strategy involves the titanium-induced intramolecular cyclization (yet to be accomplished) of dicarbonyl precursor **3** which was prepared by the stereospecific reductive elimination of the adduct of Z-form enal **4** with homoallylic phenyl sulfone **5** derived from *trans*-geranylacetone (**7**) through regioseleetive allylic chlorination and alkylation of secondary allylic chloride. The synthetic route is outlined in Scheme 2.



a) 1) DHP/*p*-TsOH, CH_2Cl_2, r.t.; 2) PCC/NaOAC, CH_2Cl_2, r.t.; b) 1) $Ph_3P{=}CHCH_3$/THF, -78°, 10 min; 2) *n*-BuLi (1.1 equiv.), -50° to 20°; 3) $(CH_2O)_n$, -20° to r.t.; 4) NH_4Cl-H_2O (10%); c) MnO_2/Na_2CO_3 (1.0 equiv.), CH_2Cl_2, r.t.; d) SO_2Cl_2/Na_2CO_3 (4.0 equiv.), CH_2Cl_2, -5° to 0°; e) $HS(CH_2)_3SH/BF_3{\bullet}Et_2O$, CH_2Cl_2, -20°- r.t.; f) $LiCH_2SO_2Ph$/THF-HMPA (*v/v* 4:1), -78° to r.t.; g) 1) *n*-BuLi/THF, -78°; 2) Enal **4**, -78°; 3) Ac_2O, -78° to r.t.; 4) 6% Na(Hg)/MeOH-EtOAc (*v/v* 1:1), 0°; H) 1) PPTs/MeOH, 50°; 2) $HgCl_2/CaCO_3$ (2.0 equiv.), 95% MeOH-H_2O, reflux; i) PCC/CH_2Cl_2, r.t.

Scheme 2

1,3-Propanediol was protected selectively as its monotetrahydropyranyl ether and followed by oxidation with PCC in CH_2Cl_2 in the presence of sodium acetate to give the aldehyde **6** in a combined yield of 60%. The modified Wittig reaction[9] of aldehyde **6** with the ylide of ethyltriphenylphosphonium iodide was carried out at -78° in THF. The resulting *Wittig* betain solution was treated with *n*-butyl lithium (1.1 equiv.) at -50°, followed by the addition of powdered paraformaldehyde (3 equiv.) initially at -20° and then warmed to room temperature overnight to afford the desired Z-form allylic alcohol **9** in 81% yield with the ratio of E/Z> 96:4 (determined by GC). Oxidation of allylic alcohol **9** with active managanese dioxide (MnO_2) in CH_2Cl_2 gave the Z-enal **4** in 41% overall yield from 1,3-propanediol. *trans*-Geranylacetone (**7**) was subjected to regioselective chlorination with

SO_2Cl_2 in the presence of 4 equivalents of anhydrous sodium carbonate in CH_2Cl_2 to give the terminal allylic chloride **10** which was then protected as its thioketal **11**[7] in 78% overall yield from **7**. Alkylation of the secondary allylic chloride **11** with the lithium carbanion of methyl phenyl sulfone in THF-HMPA (*v/v*, 4:1) solution from -78° to ambient temperature afforded the homoallylic sulfone **5** in 78% isolated yield (based on the consumed starting material). Addition of lithium carbanion of sulfone **5** to Z-enal **4** was conducted at -78° in THF. The reaction was quenched with acetic anhydride to give the corresponding β-acetoxy sulfone adduct which was subjected to the stereospecific reductive elimination by treatment with 6% sodium amalgam in a solvent mixture of methanol/ethyl acetate (*v/v*, 1:1) to afford the dithiane **12** in 64% overall yield with the formation of a *trans*-conjugated double bond.[10] Treatment of dithiane **12** with catalytic amount of pyridinium *p*-toluenesulfonate (PPTs) in methanol at 50° to remove the tetrahydropyranyl protecting group was followed by cleavage of the resulting thioketal in 95° methanol-water in the presence of mercuric chloride and calcium carbonate under reflux to give the ketol **13** in 90% yield. Compound **13** was oxidized with PCC in CH_2Cl_2 to afford the title keto aldehyde precursor **3** in an overall yield of 33% from *trans*-geranylacetone. The intramolecular reductive coupling of precursor **3** induced by low valent titanium (prepared *in situ* by $TiCl_3$/*Zn*-Cu[5] $TiCl_4$/Zn[8]) was carried out in THF or DME under reflux. However, in all attempts, a complicated mixture was obtained in which no any desired cyclized product was identified.

EXPERIMENTAL SECTION

FT-IR spectra were recorded on FT-170SX spectrometer. ^1H NMR spectra were obtained on a FT-80A or a *Brüker* AM 200 instruments in $CDCl_3$ solution, chemical shifts were reported in ppm units with TMS as the internal standard. Mass spectra (MS) were measured on a ZABHS spectrometer at 70 eV 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, and monitored by thin layer chromatography (TLC) using silica gel GF_{254}. Products were purified by flash column chromatography (FCG) on silica gel (200~300 mesh) made in *Qing Dao Marine Cehimical Factory* eluting with the solvent mixture of petroleum ether and ethyl acetate or acetone, ether *etc*. 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*. *trans*-Geranylacetone was purchased from *Aldrich Chenrical Co.*

3 Tetrahydropyranoxy-propionaldehyde (6).- To a stirred mixture of 1,3-propanediol (3.5 mL, 3.8 g, 50 mmol) and catalytic amounts of *p*-TsOH (20 mg) in CH_2Cl_2 (15 mL) was added dropwise dihydropyran (DHP, 4.2 g, 50 mmol) dissolved in CH_2Cl_2 (10 mL) over a period of 20 min at ambient temperature. After the addition was complete, the reaction mixture was allowed to stir for 0. 5 hr and then diluted with ether (40 mL), washed with 5% $NaHCO_3$ aqueous solution, water and brine (each 10 mL), and dried. Evaporation of the solvent was followed by chromatographic purification (pet. ether/acetone 6:1) to give the desired monoprotected alcohol (5.4 g, 67%) as a colorless oil. IR (film): ν_{max} = 3417 (s, OH), 2842, 1072, 1033 cm^{-1}; ^1H NMR (80 MHz): δ = 1.22 (t, 2 H, *J* = 7.0 Hz, CH_2), 1.30-1.70 (m, 2 H, CH_2), 1.83 (t, 2 H, *J* = 7.0 Hz, CH_2), 2.25 (br s, OH), 3.30 -4.00 (m, 6 H,

$3XCH_2O$), 4.56 (br s, 1 H, CHO_2) ppm.

Anal. Calcd for $C_8H_{16}O_3$ (160.2): C, 59.97; H, 10.07; Found: C, 59.81; H, 9.94

To a vigorously stirred suspension of PCC (450 mg, 2.2 mmol), sodium acetate (NaOAc, 36 mg, 0.44 mmol) and silica gel H (300 mg) in dry CH_2Cl_2 (5 mL) was added dropwise a solution of CH_2Cl_2 (2 mL) containing the above monoprotected alcohol (160 mg, 1 mmol) at room temperature. Stirring was continued for 0.5 hr, the mixutre was diluted by the addition of ether (10 mL), then filtered through a short column on silica gel. The resulting filtrate was concentrated *in vacuo* to give an oily residue, which was purified by FCG to yield aldehyde **6** (142 mg, 90%) as a colorless oil. IR (film): 2871, 1728 (s, C=O), 1121, 1074, 1035 cm^{-1}; ^1H NMR (80 MHz): δ 1.60-2.0 (m, 6H, $3XCH_2$), 2.66 (dt, 2H, J = 6.0 Hz, J_2 = 1.9Hz, CH_2CHO), 3.30-4.30 (m, 4H, $2XCH_3O$), 4.56 (brs, 1H, CHO_2), 9.80 (t, 1 H, J = 1.9 Hz, CHO) ppm.

Anal. Calcd for $C_8H_{14}NO_3$: C, 60.74; H, 8.92; Found: C, 60.59; H, 8.85

2-Methyl-5-tetrahydropyranoxy-2-pentenyl-l-ol (9).- To a well stirred suspension of ethyltriphenylphosphonium iodide (418 mg, 1 mmol) in anhydrous THF (10 mL) was added dropwise *n*-butyllithium (in *n*-hexane, 0.9 M, 1.2 mL, 1.1 mmol) at ice temperature (0°). After being stirred for 0.5 hr at room temperature, the resulting ylide solution was cooled to -78° by a dry ice-acetone bath and aldehyde **6** (160 mg, 1 mmol) disolved in THF (1 mL) was syringed dropwise with vigorous stirring. The stirring was continued for 0.5 hr at 78°, then the reaction mixture (*Wittig* betain solution) was allowed to warm to -50° and to which *n*-butyllithium (1.1 mmol) was introduced dropwise. After the mixture was warmed slowly to 20°, powdered anhydrous paraformnaldehyde (100 mg, 3.3 mmol) was added in one portion and allowed to warm gradually to room temperature with vigorous stirring for 4 hrs. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (4 mL), organic layer was separated, the aqueous phase extracted with ether (3X5 mL). The combined THF-Et_2O extract was washed with water and brine (each 8 mL), and dried. Evaporation of the solvent in vaccum gave an oily residue which was purified by FCG (pet. ether/ethyl acetate 6:1) to yield the desired Z-form allylic alcohol **9** (162 mg, 81%) as a colorless oil with the ratio of E/Z>96: 4 (determined by GC). IR (film): ν_{max} = 3384 (brs, OH), 1641, 1079, 1032, 813 cm^{-1}; ^1H NMR (80MHz): δ 1.35-1.72 (m, 6 H, $3XCH_3$), 1.81 (s, 3H, CH_3), 2.18 (s, OH), 2.25-2.40 (m, 2H, CH_2), 3.30-3.80 (m, 4 H, $2XCH_2O$), 4.08 (d, 2 H, J = 2.4 Hz, CH_2OH), 4.55 (br s, 1 H, CHO_2), 5.35-5.50 (m, 1 H, CH=) ppm; MS (EI): m/z = 201 (M+1, 6%), 199 (M-1, 7), 85 (100).

Anal.. Calcd for $C_{11}H_{20}O_3$. C, 65.97; H, 10.07. Found: C, 65.62; H, 9.91

2-Methyl-5-tetrahydropyranoxy-2-pentenal (4).- To a suspension of active MnO_2 (2 g, 23 mmol) and powdered anhydrous NA_2CO_3 (50 mg, 0. 47 mmol) in anhydrous CH_2Cl_2 mL) was added dropwise a solution of CH_2Cl_2 (1 mL) containing Z-enol **9** (120 mg, 0.6 mmol) with vigorous stirring. After being stirred for 2 hrs at room temperature, ether mL) was added and the reaction mixture was filtered. Evaporation of the resulting fillrate in vacuum gave an oily residue, which was purified by FCG (or subjected to GC analysis directly) (pet. ether/ethyl acetate 9:1) to yield Z-enal **4** (100 mg, 85%) as a colorless oil. IR (film): ν_{max} = 2870, 1667 (s, C=O), 1644, 1076, 1034, 814 cm^{-1}; ^1H NMR

(80 MHz): δ 1.30-1.70 (m, 6H, $3XCH_2$), 1.76 (d, 3H, J = 1.3 Hz, CH_3), 2.502.95 (m, 2H, CH_2), 3.50-3.95 (m, 4H, $2XCH_2O$), 4.59 (brs, 1H, CHO_2), 6.55 (dr, 1 H, J = 7.3 and 1.3 Hz, CH=), 9.42 (s, 1 H, Z-CH=), 10.14 (s, 1 H,*E*-CH=) ppm; MS (E1): *m/z*=198 ($M^{+\bullet}$, 2%), 85 (100).

Anal. Calcd for $Cl_1H_{18}O_3$: C, 66.64; H, 9. 15. Found: C, 66.35; H, 9.33

(E)-5,10-Dimethyl-9-chloro-6,10-undecadienyl-2-one (10).- To a mixture of *trans*-geranylacetone **7** (200 mg, 1 mmol) and powdered anhydrous Na_2CO_3 (425 mg, 4 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise a solution of SO_2Cl_2 (0.1 mL, 1.15 mmol) in $CHICl_2$ (1 mL) at -5° with efficient stirring. After being stirred for a period of 1 hr at -5°-0° the reaction was quenched by the addition of water (2 mL) and ether (15 mL). The organic layer was separated and the aqueous phase was extracted with ether (2 X 5 mL). The combined Et_2O-CH_2Cl_2 extract was washed with water and brine (each 8 mL), then dried. Evaporation of the solvent *in vaccuo* was followed by chromatographic purification on silica gel (pet. ether/acetone 25:1) to give the terminal chlorinated product **10** (172 mg, as a colorless oil. IR (film): ν_{max} = 3081, 1717, (s, C=O), 1647, 1160, 907, 790, 776 cm^{-1}; ^1H NMR (200MHz): δ 1.62 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.90-2.10 (m, 2H, CH_2), 2.47 (t, 2H, J = 7.0 Hz, CH_2), 4.37 (t, 1 H, J = 7.0 Hz, CHCl), 4.90 and 4.99 (2Xs, each 1 H, C=CH_2), 5.16 (t, 1 H, J = 7.2 Hz, CH=) ppm; MS (EI): *m/z* = 228 ($M^{+\bullet}$, 3%), 194 (M-Cl, 8).

Anal. Calcd for $C_{13}H_{21}ClO$: C, 68.24; H, 9.25. Found: C, 68.47; H, 9.10

(E)-2-Methyl-2-(7-chloro-4,8-dimethyl-3,8-nonadienyl)-1,3-dithiane (11).- To a mixture of **10** (460 mg, 2 mmol) and 1,3-propanedithiol (0. 22 mL, 2.2 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise a solution of CH_2Cl_2 (1 mL) containing 47% BF_3•Et_2O (0.1 mL, 0.9 mmol) at -15° with efficient stirring. After being stirred for 0.5 hr at that temperature, the reaction mixture was allowed to warm to ambient temperature over a period of 5 hrs, then ether (20 mL) was added and the resulting mixture washed with 10% aqueous KOH and brine (each l0 mL), and dried. Evaporation of the solvent gave a residue which was subjected to purification by FCG (pet. cther/acctone 60:1) to give dithiokctal **11** (590 mg, 91%) as a colorless oil. IR (film): ν_{max} = 3078, 1646 (C=C), 1447, 1372, 907 (s) cm^{-1}; ^1H NMR (200 Mhz):δ 1.62 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 1.90-2.25 (m, 10 H, CHD, 2.80-2.95 (m, 4 H, $2CH_3S$), 4.35 (t, 1 H, J =7.2 Hz, CHCl), 4.90 and 5.00 (2Xs, each 1 H, C=CH_2), 5.19 (br t, 1 H, , J= 6.8 Hz, CH=) ppm; MS (El): *m/z=318* ($M^{+\bullet}$, 6%), 283 (M-Cl, 55), 175 (57), 133 (100), 95 (47).

Anal. Calcd for $CH_{27}ClS_2$: C, 60.27; H, 8.54. Found: C, 59.88; H, 8.71

(E) -2-Methyl-2-C4-methyl-7-isopropenyl-8-phenylsulfonyl-3-octenyl-3-1,3-dithiane (5).- To a stirred solution of methyl phenyl sulfone (CH_3SO_2Ph, 1.4 g, 9 mmol) in anhydrous THF/HMPA (*v/v* 4:1, 15 mL) was added dropwise *n*-butyllithium (in *n*-hexane, 1.8 M, 5 mL, 9 mmol) at -78° over a period of 10 min. The resulting solution was stirred for 2 hrs at that temperature. A solution of allylic chloride **11** (1.27 g, 4 mmol) in THF/HMPA (*v/v*: 4:1, 4 mL) was added dropwise with constant stirring. After being stirred for a period of 2 hrs at -78°, the reaction mixture was allowed to warm to ambient temperature overnight. Saturated aqueous NH_4Cl solution (10 mL) and ether (50 mL) was added to the reaction mixture. The organic layer was separated, the aqueous phase extracted with

ether (3 X 20 mL), then the combined organic phase was washed with water (3 X 10 rnL), then brine (10 mL), and dried. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel (pet. ether/ethyl acetate 6:1) to yield homoallyl sulfone **5** (990 mg, 78°/00) as a colorless oil along with the recovery starting material **11** (350 mg). IR (film): ν_{max} = 079, 1646, 1147 (s, SOD, 909 cm^{-1}; ^1H NMR (200 MHz): δ 1.52 (s, 3H, CH_3), 1.55 (s, 3H, CHa), 1.59 (s, 3H, CH_3), 1.73-2.20 (m, 10H, CH_2), 2.60 (br m, 1 H), 2.83 (br m, 4 H, $2CH_2S$), 3.11 (m, 2 H, Cjt]2SC)2), 4- 65 and 4.74 (2Xs, each 1 H, C:CH_2), 5.05 (t, I H, ,1-6.4 Hz, CH-), 7.44-7.90 (m, 5 H, ArH) ppm; MS(El): *n-./,:=438* ($M^{+'}$, 9°f00), 363(27), 297(10), 283(15), 189(48), -47(61), 133(100).

Anal. Calcd for $C_{23}H_{34}O_2S_3$: C, 62.97; H, 7.81; Found: C, 62.73; H, 7.95

2-Methyl-2-(4,10-dimethyl-7-isopropenyl-1,3,4-tetrahydropyranoxy-3E,8E,10E-tridecatrienyl)-l,3-dithiane (12).- To a stirred solution of homoallylsulfone 5 (450 mg, 1.03 mmol) in anhydrous THF (10 mL) was added dropwise *n*-butyllithium (in *n*-hexane, 0.8 M, 1.3 mL, 1.04 mmol) at -78° within 5 min. After being stirred for a period of 2 hrs at that temperature, a solution of (Z)-enal 4 (200 mg, 1 mmol) dissolved in THF (2 mL) was syringed over 5 min, then the mixture was stirred for an additional 2 hrs at -78°. Acetic anhydride (0.5 mL) was added and the mixture was allowed to warm gradually to ambient temperature over 1 hr. Addition of saturated aqueous NH_4Cl solution (50 mL) was followed by separation and extraction work-up, then evaporation to yield an oily crude residue which, without further purification, was dissolved in MeOH and EtOAc *(v/v* 1: 1, 15 mL) and cooled to 0° under argon. To the above solution was added 6% sodium amalgam (500 mg, 1.30 mmol) portionwise with vigorous stirring over 0. 5 hr. After an additional 0. 5 hr, water (5 mL) was added, the organic layer was separated and the aqueous solution extracted with ether (3 X 10 mL). The combined organic phase was washed with water and brine (each 10 mL), and dried. Evaporation of the solvent was followed by chromatographic purification (pet. ether/ethyl acetate 20:1) to yield compound **12** (300 mg, 64°) as a colorless oil. IR (film): ν_{max} = 927, 1643, 1606, 1121, 1073, 1034, 907cm^{-1}; ^1H NMR (200MHz): δ 1.59 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 1.65-2.10 (m, 10 H), 2.20-2.45 (m, 6 H), 2.64 (m, 1 H), 2.87 (br m, 4 H, $2CH_2S$), 3.35-3.65 (m, 4H, $2CH_2O$), 4.56 (brs, 1H), 4.77 (brs, 2H, C=CH_2), 5.15 (t, 1H, J= 6.8 Hz, CH=), 5.30 (t, 1 H, J = 7.5 Hz, CH=), 5.62 (dd, 1 H, J = 15.3, 7.0 Hz, CH=), 6.45 (d, 1 H, *J* = 15.2 Hz, CH=) ppm; MS (El): *m/z* = 478 ($M^{+\bullet}$, 1°)), 463 (4), 437 (2), 393 (11), 345 (8), 261 (21), 133 (100), 85 (82).

Anal. Calcd for $C_{25}H_{46}S_2O_2$: C, 70. 24; H, 9.68. Found: C, 70.51; H, 9.75

6,12 Dimethyl-9-isopropenyl-15-hydroxy-5E,10E,12Z-pentadecatrienyl-2-one (13).- A solution of **12** (170 mg, 0.36 mmol) and pyridinium *p*-toluenesulfonate (20 mg) in methanol (8 mL) was heated to 50° and stirred constantly for a period of 2 hrs. The cooled reaction mixture was concentrated *in vacuo* to give an oily residue, which was taken up in ether (15 mL), washed with water, brine (each 5 mL), and dried. Evaporation of the solvent under reduced pressure gave the crude product which, without further purification, was dissolved in 95% MeOH H_2O (3 mL) and added dropwise to a suspension of $HgCl_2$ (100 mg, 0.37 mmol) and $CaCO_3$ (40 mg, 0. 4 mmol) in 95% MeOH-H_2O with vigorous stirring. The reaction mixture was then refluxed for 0. 5 hr to complete the reaction, filtered

and evaporated to afford a slurry which was token in ether (15 mL) and washed with 1N HCl aqueous, water and brine (each 5 mL), and dried. After evaporation of the solvent, the resulting oily residue was chromatographed on silica gel (pet. ether/ether 5:1) to yield the deprotected product **1a** (97 mg, 90%) as a colorless oil. IR (film): ν_{max} = 3374, 1716, 1639, 1609, 1074 cm^{-1}; ^1H NMR (200 MHz): δ 1.59 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 1.84 (s, 3 H, CH_3), 1.80-2.00 (br m, 2 H), 2.13 (s, 3 H, CH_3CO), 2.15-2.55 (m, 8H), 2.65 (m, 1H), 3.66 (t, 2H, , J = 6.7 Hz, CH_2O), 4.74 (brs, 2H, C=CH_2), 5.06 (brm, 1 H, CH=), 5.28 (t, 1 H, J = 6.9Hz, CH=), 5.58 (dd, 1 H, J = 15.6; 7.2 Hz, CH-=),6.42 (d, 1H, J = 15.6 Hz, CH=) ppm; MS (EI): *m/z* = 304 ($M^{+\cdot}$, 0.5%), 303 (1), 286 (3), 261 (5), 137 (18), 81 (40), 43 (100).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.57; H, 10.50

4,10-Dimethyl-7-isopropenyl-14-oxo-3E,5E,10Z-pentadecatrienal (3).- To a suspension of anhydrous PCC (120 mg, 0.53 mmol) and silica gel (200 mg) in anhydrous CH_2Cl_2 (5 mL) was added a solution of CH_2Cl_2 (1 mL) containing **13** (60 mg, 0. 197 mmol) at room temperature with constant stirring. After a period of 0. 5 hr, the reaction mixture was diluted with ether (10 mL) and filtered through a short column on silica gel. The flitrate was evaporated *in vacuo* to give a crude oil, which was purified by FCG (pet. ether/ether 8:1) to yield the keto aldehyde precursor **3** (55 mg, 93%) as a colorless oil. IR (film): ν_{max} = 2868, 2819, 1716, 1643, 1607, 1121, 1031 cm^{-1}; ^1H NMR (200MHz): δ 1.57 (s, 3 H, CH_3), 1.66 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 2.13 (s, 3H, CH_3CO), 1.80-2.00 (m, 2H), 2.15-2.53 (m, 6H, CH_2), 2.64 (m, 1H), 3.29 (dd, 2H, *J* = 6.9; 1.3 Hz, CH_2CHO), 4.75 (br s, 2 H, C=CH_2), 5.05 (br t, 1 H, J = 6.8 Hz, CH=), 5.43 (t, 1H, ,1.6.9Hz, CH=), 5.66 (rid,1 H, *J* = 15.3; 7.3Hz, CH-); 6.28 (d, 1 H, J = 15.3 Hz, CH=) ppm; MS(El): *m/z* = 302 ($M^{+\cdot}$, 1H), 301 (1), 287 (3), 261 (2), 259 (5), 163 (11), 139 (8), 81 (41), 43 (100).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10. 00. Found: C, 79.16; H, 10. 15

A Typical Procedure for the Macrocyclizafion of Compound 3.- A mixture of $TiCl_3$ (1.85 g, 12 mmol) and Zn-Cu alloy powder (2.34 g, 36 mmol) in anhydrous THF (35 mL) containing anhydrous Et_3N (0.2 mL) was refluxed for 2.5 hrs under argon atmosphere to afford a low valent titanium slurry, to which precursor **3** (45 mg, 0. 15 mmol) was added slowly by a syringe as a dilute solution in dry THF (30 mL) over a period of 20 hrs. After the addition was complete, the reaction mixture was refluxed for an additional 3 hrs and then cooled to ice temperature and diluted by the addition of K_2CO_3 aqueous solution (10%, 20 mL) and *n*-hexane (50 mL). The resulting mixture was separated and followed by extractive workup, then the combined organic phase was washed with water (20 mL) and brine (20 mL), and dried. Evaporation of the solvent under reduced pressure gave a crude oil, which was purified by flash column chromatography eluted with hexane and no any desired cyclized product was obtained, but a complicated mixture.

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