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First Total Synthesis of Three Cembrene Diterpenoids

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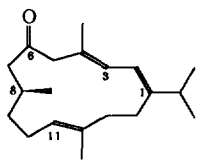
Abstract The first total synthesis of three diterpenoids of the cembrane class, is described. And the absolute stereochemistry of these natural products is assigned by synthesis.

Three cembrene diterpenoids, (+)-(1*E*,3*E*,11*E*)-1,3,11-cembratrien-6-one **1** and its olefin geometrical isomers (+)-(1*E*,3*Z*,11*E*)-1,3,11-cembratrien-6-one **2**, (+)-(1*Z*,3*Z*,11*E*)-1,3,11-cembratrien-6-one **3**, were first isolated in 1991 from the Caribbean sea whip *Eunicea calyculata* along with other four cubitane diterpenoids[1]. The co-occurrance of both the cubitane and cembrane skeletons supports the theory that the cembranoid carbon skeleton is a logical biosynthetic precursor to the irregular isoprenoid cubitane ring system[2]. Most important is the conversion of (+)-**1** into the calyculones and two other geometrical isomers by a photochemically induced 1,3-acyl migration. It is the first example of a 1,3-acyl migration in natural products and the first ring contraction involving the cembrane skeleton. The geometric structure of these compounds has been finally confirmed by spectral methods, but the absolute configuration at C-8 was not determined[1]. Their irregular reactivity, challenging structural features and unknown absolute stereochemistry promoted our search for a practical synthesis. Herein we report the first total synthesis of these cembrene diterpenoids (−)-**1**, (−)-**2** and (−)-**3**.



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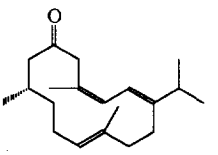

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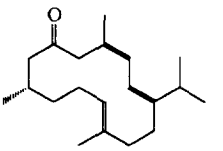

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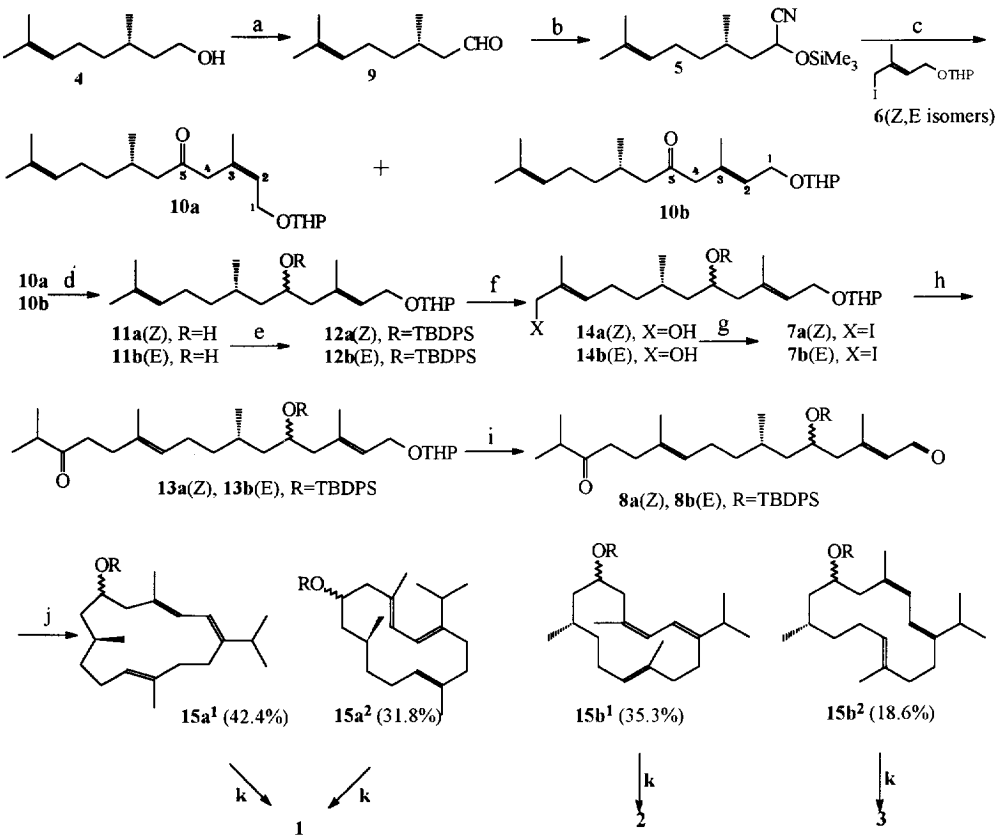
Our synthetic route starting from optically active citronellol **4** involves three key steps: 1) The alkylation reaction of the cyanohydrin trimethylsilyl ether **5** with halides **6**. 2) The high regioselective alkylation of methyl isopropyl ketone with halides **7**. 3) Intramolecular macrocyclization of **8** induced by Ti(0).

According to Jongheon's inference, the cembrenes have been interconverted to the calyculones whose configurations were confirmed as 1*S*,10*S*, the stereochemistry at C-8 in **1** is identical with that at C-1 in the

calyculones[1]. This means the stereochemistry of **1** should be 8*S*. So we selected (*S*)-(-)-Citronellol as the starting material.



a)PCC, silica gel, NaOAc, dry CH_2Cl_2, r.t., 1h, 80.1%; b)Me_3SiCN, KCN/18-crown-6, 0°C, 30min, 100%; c)1.$LiN(SiMe_3)_2$, THF, 0°C, 20min then **6**, r.t., 2h, 28%; 2.n-$Bu_4N^+F^-$, 10% aq. THF, 25°C, 2h, 93%; d)$NaBH_4$, MeOH, 96%; e)TBDPSCl, imidazole, DMF, r.t., 2h, 94%; f)SeO_2, t-BuOOH, CH_2Cl_2, 15h, 71%; g)I_2, Ph_3P, imidazole, Et_2O/CH_3CN, 100%; h) $MeC(O)CHMe_2$, LDA, -78°C, 2h, 80%; i) 1.p-TsOH, MeOH, r.t., 2h; 2.MnO_2, n-hexane, r.t., 20h, 93%; j)Zn/$TiCl_4$, Py, DME, reflux 24h, 74%; k) 1. n-$Bu_4N^+F^-$ in THF(1M), r.t., 40h; 2.PCC, silica gel, NaOAc, CH_2Cl_2, r.t., 30min, 90%

The first stage of the synthesis is the construction of a 15-membered carbon chain possessing a carbonyl group at C-5. Although many papers have reported that sulfur-stabilized anions might be suitable as masked nucleophilic acylating equivalents to perform alkylation reactions[3-6], these methods seemed not be suitable here and therefore we selected canohydrin TMS ether as the acylating equivalent[7]. Citronellol was first oxidized by PCC in CH_2Cl_2[8] to Citronellal **9** which was then converted to cyanohybrin trimethylsilyl ether **5** by addition of Me_3SiCN in the presence of a catalytic amount of KCN/18-crown-6 complex[9]. **5** was treated with 1.25 equiv of $LiN(SiMe_3)_2$ in THF and then coupled with **6** to afford the desired cyanohydrin compound which was directly converted into ketone (**10a**(Z):**10b**(E)=4:6 by GC) using catalytic amount of *n*-$Bu_4N^+F^-$ in 10% aqueous THF without further purification. The geometric configuration of **10a** and **10b** were determined by the

chemical shift of C-2 proton and the coupling of C-4 protons. In their ^{1}HNMR spectra, C-2 proton appeared at δ 5.61ppm for **10a** and δ 5.47ppm for **10b**. (Z: δ=5.61ppm, E: δ=5.53ppm calculated by *Tobey-Simon* equality); C-4 protons appeared as AB quadrulet pattern at δ 3.20ppm (J=16.2Hz) for **10a** but one single line at δ 3.09 ppm for **10b**. It is obvious that steric hindrance in Z isomer cause C-4 protos to be nearer to substitute (-OTHP) in space which made two nuclei of C-4 nonequivalent, therefore C-4 protons appeared germinal HH coupling. In contrast, two nuclei of C-4 in E isomer are equivalent because there is no large hindrance and thus it appeared as a singlet. For above two reasons, we determined that **10a** is Z isomer and **10b** is E isomer. Fortunately, when **10** were reduced by $NaBH_4$ to the corresponding alcohols **11**, *Z* and *E* isomers can be seperated conveniently on TLC (this reaction is a stereoselective reduction, but diastereoisomers can not be seperated on TLC. *Z*(5*S*,7*S*):d.e.%=26.7; *E*(5*S*,7*S*):d.e.%=33.3 by 400MHz ^{1}HNMR). Then **11a,11b** was protected separately with TBDPSCl to afford silyl ether **12a,12b**[9].

The next step was the high regioselective alkylation of **12** prior to the transformation of **13** to the cyclization precursor. Oxidation of **12** with 70% t-BuOOH in the presence of 0.1equiv SeO_2 in CH_2Cl_2 at r.t. afforded **14** which was then converted to its corresponding iodide 7. Alkylation of 7 was carried out with 5 equiv Li-enolate of methyl isopropyl ketone in dry THF at -78°C under argon atmosphere, only the kinetic product was obtained in 80.1% yield[10]. Removal of THP protecting group from **13** with catalytic amount of p-TsOH in MeOH followed by oxidization with 20 equiv MnO_2 in *n*-hexane results in the formation of compound **8**.

The final crucial step was intramolecular macrocyclization induced by low valent titanium. The substrate highly diluted in 30mL dry DME was syringed slowly to the refluxing mixture of $TiCl_4$/Zn-DME over 20hrs in order to afford the intramolecular cyclization compound. It was unusual that the macrocyclization of **8** produced nearly equal amount of *Z,E* isomers in the alkene-forming reaction, and they can be easily seperated by TLC. After macrocyclization products **15** had been deprotected with 1M *n*-$Bu_4N^+F^-$ in THF[11] and then oxidized by PCC in CH_2Cl_2, title compounds **1**, **2** and **3** were obtained respectively as clear oil. It is noteworthy that *Z,E* isomers **15a**[1] and **15a**[2] undergoing deprotection and oxidation result the same compound **1**. This result is coincident with the fact that only three natural products were isolated lacking of (1*Z*,3*E*,11*E*) isomer. The reason of this phenomenon is unknown yet.

The spectral data of synthetic compounds **1**, **2** and **3** showed good agreement with those of natural products, but the specific rotation of synthetic compounds have the opposite orientation to the natural products ($[\alpha]_D^{20}$, Synthetic: **1** -149 (*c*=0.3 $CHCl_3$), **2** -204 (*c*=0.25 $CHCl_3$), **3** -88 (*c*=0.25 $CHCl_3$); natural: **1** +353 (*c*=0.6 $CHCl_3$), **2** +283 (*c*=0.8 $CHCl_3$), **3** +23 (*c*=0.1 $CHCl_3$)[1]). Therefore, our synthetic material may well be enantiomeric with the natural product. Since the stereogenic center of (*S*)-(-)-Citronellol was never affected in our synthetic route, the absolute stereochemistry of synthetic compounds should be 8*S* and therefore the absolute stereochemistry of the natural occurring material should be 8*R* configuration.

In summary, we have accomplished the total synthesis of three natural products in chiral form (*S*)-(-)-**1**, (*S*)-(-)-**2** and (*S*)-(-)-**3** in 12 steps with 6.6% overall yield from citronellol, and the absolute configuration of the natural products was assigned to be 8*R*.

Experimental Section:

General FT-IR spectra were recorded on a FT-170SX (film) spectrometer. 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 brakets. ^{1}HNMR spectra were obtained in $CDCl_3$ solutions at 400 MHz except otherwise stated and ^{13}CNMR spectra were recorded in $CDCl_3$ solutions at 100 MHz. All chemical shifts are reported with respect to internal TMS. Optical rotation measurements were carried out in $CHCl_3$ solutions on a Perkin-Elmer 141 polarimeter. 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 their layer chromatography (TLC) using silica gel GF_{254}. All extracted organic phase were washed with brine and dried over anhydrous $MgSO_4$, then filltered prior to rotary evaporation in vaccum. Products were purified either by distillation or flash column chromatography (FCG) on silica gel (200-300 mesh) made in *Qing Dao Marine Chemical Factory* eluting with mixture solvent of pet. ether and ethyl acetate. The starting material (S)-(-)-β-Citronellol was purchased from incorporation, its enantiomeric purity was 77% ($[\alpha]_D^{20}$ (neat) = -4.1 found; $[\alpha]_D^{20}$ (neat) = -5.3 reported by Aldrich co.)

(S)-(-)-Citronellal 9 To a suspension of pyridinium chlorochromate (5.4g, 25mmol), silica gel (2.7g) and NaOAc (0.41g, 5mmol) in anhydrous CH_2Cl_2 (70 mL) was added dropwise the solution of Citronellol (1.56g, 10mmol) in anhydrous CH_2Cl_2 (20 mL) with efficient stirring at room temperature. After stirring for 1h, the reaction mixture was diluted with ether (100mL) and filtered through a short column on silica gel. The clear filterate was evaporated in vaccum to give an oily residue which was purified by flash column chromatography eluting with pet. ether/ethyl acetate (v/v 10:1) to afford Citronellal **9** (1.23g, 80%).

(S)-Cyanohydrin trimethylsilyl ether 5 Catalytic amount of KCN and 18-crown-6 complex was first added to Citronellal (770mg, 5mmol) with stirring, then Me_3SiCN (743mg, 7.5mmol) was added dropwise to the suspension at 0°C under argon atmosphere. The reaction was complete within 30 min and it can be used *in situ* without further purification. ^{1}HNMR(80MHz,$CDCl_3$): δ(ppm) 0.24(s, 9H, $SiMe_3$), 0.95(d, 3H, CH_3), 1.66(d, 6H, $2CH_3$), 1.28-2.05(m, 7H, $3CH_2$, CH), 4.45(t, J=6.2Hz, 1H, CHCN), 5.09(t, J=6.9Hz, 1H, CH=)

2-Methyl-4-tetrahydropyranoxy-2-butenyl iodide 6 To a stirred clear solution of 2-methyl-4-tetrahydropyranoxy-2-buten-1-ol (930mg, 5mmol, mixture of Z,E isomers), triphenyl phosphine (1.97g, 7.5mmol) and imidazole (510mg, 7.5mmol) in a mixture solvent of acetonitrile (7.5mL) and ether (12.5mL)

was added iodine crystals (1.9g, 7.5mmol) portionwise at 0°C (ice-water bath) over 10 min. The resulting mixture was stirred for another 20 min, the reaction mixture was diluted with ether (100mL) and washed with saturated $Na_2S_2O_3$ *aq.* solution, water and brine, then dried. Evaporation of the solvent under reduced pressur at 30°C gave the crude labile iodide which was purified by flash column chromatography to afford clear oil **6**.

(7S)-3,7,11-Trimethyl-1-tetrahydropyranoxy-2Z,10E-dodecadienyl-5-one 10a and 2E,10E isomer 10b

A solution of n-BuLi in n-hexane (1.70N, 4mL, 6.8mmol) was syringed dropwise to a stirred solution of $HN(SiMe_3)_2$ (1.8mL, 9mmol) in anhydrous THF (10mL) at 0°C over 10 min. The reaction mixture was stirred for further 30min and a solution of cynohydrin **5** (5mmol) in anhydrous THF (10mL) was added dropwise at 0°C. After being stirred for an additional 40 min at that temperature, a solution of anhydrous THF (10mL) containing iodide **6** (5mmol) was added dropwise over 5 min. The resulting mixture was allowed to warm to room temperature gradually followed stirring for 2hrs. Then the reaction was quenched with saturated NH_4Cl *aq.* solution (5mL). The reaction mixture was diluted with ether (100mL) and the organic phase was washed with water, brine, then dried. Evaporation of the solvent in vaccum to give the crude residue which was dissolved in 10% aqueous THF (15mL) without further purification. Catalytic amount of n-$Bu_4N^+F^-$ was added to the solution and the reaction mixture was stirred for 8 hours. Extracted the resulting mixture with ether (3×30mL) and organic phase was washed with water, brine, then dried. The solvent was removed in vaccum and the crude oil was purified by chromatography on silica gel (pet.ether/ether acetate 20:1) to afford **10a** and **10b** mixture (420mg, 26%) as a clear oil. **10a**: $[\alpha]_D^{20}$ -10.58 (c=1.00, $CHCl_3$); IR: 2944, 2871, 1713(C=O), 1444, 1363, 1203, 1107, 1039, 1021, 957, 903cm^{-1}; m/z(EIMS): 322(M^+, 0.3), 304(0.6), 238(0.7), 220(4), 153(10), 109(26), 85(100), 69(48), 55(26), 41(61); ^{1}HNMR: δ(ppm) 0.89(d, J=6.6Hz, 3H, CH_3), 1.60(s, 3H, CH_3), 1.68(s, 3H, CH_3), 1.77(s, 3H, CH_3), 1.20-2.01(m, 11H, $5CH_2$,CH), 2.20-2.28(dd, J=16.2Hz, J=8.2Hz, 1H, $COCH_2$), 2.39-2.45(dd, J=16.4Hz, J=5.6Hz, 1H, $COCH_2$), 3.20(ABq, J=16.2Hz, 2H, $COCH_2C$=), 3.52(m, 1H, OCH_2), 3.87(m, 1H, OCH_2), 3.95-4.00(dd, J=12.1Hz, J=7.5Hz, 1H, OCH_2CH=), 4.19-4.24(dd, J=12.0Hz, J=6.5Hz, 1H, OCH_2CH=), 4.62(t, J=4.1Hz, 1H, OCHO), 5.08(t, J=6.9Hz, 1H, CH=), 5.61(t, J=7.1Hz, 1H, CH=); ^{13}CNMR: δ(ppm) 17.8, 19.6, 19.7, 24.3, 25.5(2C), 25.7, 28.8, 30.8, 36.9, 47.1, 49.6, 62.3, 63.3, 97.8, 124.3, 125.0, 131.5, 133.7, 207.8; **10b**: $[\alpha]_D^{20}$ -13.00 (c=1.25, $CHCl_3$); IR and EIMS are the same with **10a**; ^{1}HNMR: δ(ppm) 0.87(d, J=6.6Hz, 3H, CH_3), 1.58(s, 3H, CH_3), 1.67(s, 3H, CH_3), 1.68(s, 3H, CH_3), 1.15-1.97(m, 11H, $5CH_2$, CH), 2.21-2.27(dd, J=8.1Hz, J=16.2Hz, 1H, $COCH_2$), 2.38-2.44(dd, J=5.6Hz, J=16.1Hz, 1H, CH_2CO), 3.09(s, 2H, $COCH_2C$=), 3.51(m, 1H, OCH_2), 3.88(m, 1H, OCH_2), 4.03-4.08(dd, J=7.2Hz, J=12.1Hz, 1H, OCH_2CH=), 4.24-4.29(dd, J=6.3Hz, J=12.2Hz, 1H, OCH_2CH=), 4.62(t, J=3.9Hz, 1H, OCHO), 5.07(t, J=6.5Hz, 1H, CH=), 5.47(t, J=6.7Hz, 1H, CH=); ^{13}CNMR: δ(ppm) 16.7, 17.6, 19.5, 19.7, 25.4(2C), 25.6, 28.7, 30.6, 36.9, 49.3, 54.2, 62.3, 63.4, 97.9, 124.2, 125.8, 131.4, 133.5, 208.7

(7S)-3,7,11-Trimethyl-1-tetrahydropyranoxy-5-hydroxy-2Z,10E-dodecadiene 11a and 2E,10E isomer 11b To an ice-cooled solution of ketone **10** (400mg, 1.24mmol) in MeOH (5mL) was added $NaBH_4$ portionwise at 0°C with stirring until the reaction was complete. The resulting mixture was diluted with water and extracted with ether (4×30mL). The organic layer was washed with water and brine, and dried. Evaporation of the solvent in vaccum gave an oily residue, which was chromatographed on silica gel (pet. ether/ethyl acetate 10:1) to yield the alcohol **11a** (155mg, 38.4%) and **11b** (232mg, 57.6%) seperately. **11a**: $[\alpha]_D^{20}$ -3.79 (c=1.10, $CHCl_3$); IR: 3474(OH), 2924, 2871, 1667, 1448, 1379, 1117, 1076, 1023, 905, 869cm^{-1}; m/z(EIMS): 255(0.4), 239(42), 237(55), 223(100), 153(52), 137(50), 121(26), 97(74), 85(93), 69(67); ^{1}HNMR: δ(ppm) 0.91(d, J=6.5Hz, 3H, CH_3), 1.60(s, 3H, CH_3), 1.68(s, 3H, CH_3), 1.80(s, 3H, CH_3), 1.16-2.08(m, 13H, 6CH_2, CH), 1.97-2.08(m, 1H, CH_2C=), 2.37-2.45(m, 1H, CH_2C=), 3.50-3.54(m, 1H, OCH_2), 3.79(m, 1H, **CH**OH), 3.85-3.89(m, 1H, OCH_2), 3.93-4.01(dd, J=7.3Hz, J=11.4Hz, 1H, O**C**H_2CH=), 4.21-4.28(dd, J=7.1Hz, J=11.7Hz, 1H, O**C**H_2CH=), 4.68(dt, J=3.5Hz, 1H, OCHO), 5.10(t, J=6.2Hz, 1H, CH=), 5.62(t, J=6.7Hz, 1H, CH=); ^{13}CNMR: δ(ppm) 17.6, 19.2(2C), 23.9, 25.3(2C), 25.7, 28.9, 30.3, 37.8, 41.0, 45.4, 61.8, 63.1, 67.0, 98.2, 124.0, 124.8, 131.0, 139.2; **11b**: $[\alpha]_D^{20}$ +4.00 (c=1.00, $CHCl_3$); IR and EIMS are the same with **11a**; ^{1}HNMR: δ(ppm) 0.90(d, J=6.5Hz, 3H, CH_3), 1.59(s, 3H, CH_3), 1.67(s, 3H, CH_3), 1.71(s, 3H, CH_3), 1.15-1.98(m, 13H, 6CH_2, CH), 1.96-2.22(m, 2H, CH_2C=), 3.48-3.53(dt, J=4.7Hz, J=10.3Hz, 1H, OCH_2), 3.77-3.84(m, 1H, C**H**OH), 3.85-3.90(dt, J=4.8Hz, J=10.2Hz, 1H, OCH_2), 4.01-4.09(dd, J=7.1Hz, J=11.8Hz, 1H, O**C**H_2CH=), 4.22-4.28(dd, J=6.9Hz, J=11.7Hz, 1H, O**C**H_2CH=), 4.62(t, J=4.1Hz, 1H, OCHO), 5.09(t, J=6.3Hz, 1H, CH=), 5.46(t, J=6.7Hz, 1H, CH=); ^{13}CNMR: δ(ppm) 16.6, 17.6, 19.1, 19.5, 25.3, 25.4, 25.6, 28.9, 30.6, 37.8, 44.6, 48.6, 62.2, 63.5, 66.4, 98.1, 124.2, 124.7, 131.1, 137.0

(7S)-3,7,11-Trimethyl-1-tetrahydropyranoxy-5-*tert*-butyldiphenylsiloxyl-2Z,10E-dodecadiene 12a and 2E,10E isomer 12b To a stirred solution of alcohol **11** (140mg, 0.43mmol) and imidazole (73mg, 1.08mmol) crystals in dry DMF (2mL) was added dropwise *tert*-butyldiphenyl silyl chloride (130mg, 0.47mmol) under argon atmosphere. After the addition, the stirring was continued for a period of 2hrs. Extracted the reaction mixture with ether (3×20mL), then the combined ether extract was washed with water, brine and dried. After evaporation of the solvent, the oily residue was chromatographed on silica gel (pet. ether/ethyl acetate 30:1) to yield silyl ether **12** (227mg, 94%) as a colorless oil. **12a**: $[\alpha]_D^{20}$ +12.83 (c=1.50, $CHCl_3$); IR: 2931, 2857, 1669, 1590, 1461, 1428, 1379, 1111, 1024, 906, 869, 739, 703, 611, 506cm^{-1}; m/z(FAB): 563(M^++1); ^{1}HNMR: δ(ppm) 0.60(d, J=6.5Hz, 3H, CH_3), 1.07(s, 9H, $C(CH_3)_3$), 1.57(s, 3H, CH_3), 1.62(s, 3H, CH_3), 1.70(s, 3H, CH_3), 1.13-1.94(m, 13H, 6CH_2, CH), 2.16-2.37(m, 2H, CH_2C=), 3.52-3.54(dt, J=11.0Hz, J=5.0Hz, 1H, OCH_2), 3.85-3.97(m, 3H, OCH_2, CHOR, O**C**H_2CH=), 4.19(dd, J=11.3Hz, J=6.2Hz, 1H, O**C**H_2CH=), 4.61(t, J=4.1Hz, 1H, OCHO), 5.08(t, J=7.4Hz, 1H, CH=), 5.37(t, J=8.1Hz, 1H, CH=), 7.38-7.76(m, 10H, 2Ph); ^{13}CNMR: δ (ppm) 17.6, 18.9, 19.5, 23.8, 25.4, 25.5(2C), 25.7, 27.0(3C), 28.3, 30.6, 37.8,

41.2, 44.6., 62.0, 63.6, 70.0, 97.9, 123.6, 124.9, 127.5, 129.4, 134.5(2C),136.0(8C), 137.3(2C); **12b**: $[\alpha]_D^{20}$ +9.23 (c=1.30, $CHCl_3$); IR and FABMS are the same with **12a**; ^{1}HNMR: δ(ppm) 0.63(d, J=6.5Hz, 3H, CH_3), 1.06(s, 9H, $C(CH_3)_3$), 1.59(s, 3H, CH_3), 1.62(s, 3H, CH_3), 1.70(s, 3H, CH_3), 1.09-1.93(m, 13H, $6CH_2$, CH), 2.20(m, 2H, CH_2), 3.51(m, 1H, OCH_2), 3.89(m, 2H, OCH_2, CHOR), 3.94-3.99(dd, J=7.5Hz, J=12.3Hz, 1H, OCH_2CH=), 4.12-4.21(dd, J=7.3Hz, J=12.0Hz, 1H, OCH_2CH=), 4.59(t, J=4.1Hz, 1H, OCHO), 5.06(t, J=7.2Hz, 1H, CH=), 5.30(t, J=6.9Hz, 1H, CH=), 7.37-7.75(m, 10H, 2Ph); ^{13}CNMR: δ(ppm) 16.1, 17.6, 19.3, 19.5, 25.4, 25.5(2C), 25.7, 27.0(3C), 28.4, 30.6, 37.7, 44.1, 48.7, 62.1, 63.2, 69.8, 97.5, 123.5, 124.9, 127.4, 129.4, 134.3(2C), 136.0(8C), 137.1(2C)

(6S)-2,6,10-Trimethyl-8-*tert*-butyldiphenylsiloxyl-12-tetrahydropyranoxy-2E,10Z-dodecadienyl-1-ol 14a and 2E,10E isomer 14b To a stirred clear solution of SeO_2 (5mg, 0.04mmol) and *tert*-butyl hydroperoxide (70%, 0.11mL, 0.8mmol) in CH_2Cl_2 (4mL) was added silyl ether **12** (210mg, 0.37mmol) dissolved in CH_2Cl_2 (2mL) dropwise at 0°C over 10min. After being stirred at room temperature for 15hrs, the reaction mixture was diluted with ether (100mL) and washed sequentially with 10% KOH *aq.* solution, water and brine, then dried. Evaporation of the solvent followed by purification on silica gel (pet. ether/ethyl acetate 10:1) to yield the allylic alcohol **14** (152mg, 71%) as clear oil. **14a**: $[\alpha]_D^{20}$ +11.88 (c=0.80, $CHCl_3$); IR: 3414(OH), 2931, 2856, 1670, 1589, 1428, 1111, 1024, 821, 738, 704, 507cm^{-1}; m/z(EIMS): 477(M^+-OTHP, 1), 475(1), 437(1), 419(5), 351(9), 239(5), 199(48), 153(54), 135(57), 85(100); ^{1}HNMR: δ(ppm) 0.59(d, J=6.5Hz, 3H, CH_3), 1.04(s, 9H, $C(CH_3)_3$), 1.62(s, 3H, CH_3), 1.66(s, 3H, CH_3), 1.16-1.97(m, 13H, $6CH_2$, CH), 2.12-2.18(dd, J=13.7Hz, 5.2Hz, 1H, CH_2C=), 2.32-2.39(dd, J=14.2Hz, 4.6Hz, 1H, CH_2C=), 3.50-3.53(dt, J=6.1Hz, 1H, OCH_2), 3.84-3.94(m, 3H, OCH_2, CHOR, OCH_2CH=), 3.97(s, 1H, CH_2OH), 3.98(s, 1H, CH_2OH), 4.15-4.20(dd, J=6.6Hz, 12.2Hz, 1H, OCH_2CH=), 4.59(t, J=4.0Hz, 1H, OCHO), 5.28-5.34(m, 2H, 2CH=), 7.37-7.73(m, 10H, 2Ph); ^{13}CNMR: δ(ppm) 13.6, 18.9, 19.4, 23.7, 24.6, 25.0, 25.4(2C), 27.0(3C), 28.4, 30.6, 37.3, 41.0, 44.0, 62.1, 63.6, 70.1, 97.9, 123.5, 126.5, 127.5, 129.5, 134.3(2C), 136.0(8C), 137.1(2C); **14b**: $[\alpha]_D^{20}$ +19.53 (c=0.70, $CHCl_3$); IR and EIMS are the same with **14a**; ^{1}HNMR: 0.62(d, J=6.8Hz, 3H, CH_3), 1.04(s, 9H, $C(CH_3)_3$), 1.62(s, 3H, CH_3), 1.66(s, 3H, CH_3), 1.09-1.97(m, 13H, $6CH_2$, CH), 2.14-2.18(m, 2H, CH_2C=), 3.50(m, 1H, OCH_2), 3.83-3.88(m, 2H, OCH_2, CHOR), 3.92-4.01(m, 1H, OCH_2CH=), 3.98(d, J=4.2Hz, 2H, CH_2OH), 4.10-4.15(dd, J=6.4Hz, 12.4Hz, 1H, OCH_2CH=), 4.56-4.60(dt, J=4.0Hz, 1H, OCHO), 5.27-5.32(m, 2H, 2CH=), 7.36-7.72(m, 10H, 2Ph); ^{13}CNMR: δ(ppm) 13.6, 16.2, 19.1, 19.5, 24.7, 25.0, 25.4(2C), 27.0(3C), 28.4, 30.6, 37.3, 44.2, 48.9, 62.1, 63.3, 69.8, 97.6, 123.5, 126.7, 127.5, 129.4, 134.4(2C), 136.0(8C), 137.1(2C)

(10S)-2,6,10,14-Tetramethyl-12-*tert*-butyldiphenylsiloxyl-16-tetrahydropyranoxy-6E,14Z-hexzdeca dienyl -3-one 13a and 6E,14E isomer 13b To a stirred clear solution of alcohol **14** (140mg, 0.24mmol), triphenyl phosphine (95mg, 0.36mmol) and imidazole (25mg, 0.36mmol) in a mixture solvent of acetonitrile

(1.8mL) and ether (3.2mL) was added iodine crystals (92mg, 0.36mmol) portionwise at 0°C over 5min. Then the resulting mixture was stirred for 10min before ether (20mL) was added. The extracted organic phase was washed with saturated $Na_2S_2O_3$ *aq.* solution, water and brine, and then dried. Evaporation of the solvent in vaccum at 30°C gave the crude labile iodide which was purified on silica gel. The pure iodide 7 was taken up in anhydrous THF (2mL) and used for the followed *procedure*: A solution of freshly distilled anhydrous diisopropylamine (0.25mL, 1.7mmol) in THF (10mL) was cooled to -20°C under argon atmosphere and a n-hexane solution of n-BuLi (1.6N, 0.9mL, 1.44mmol) was introduced by a dry syringe. The resulting mixture is stirred for 0.5h at that temperature and cooled to -78°C. After stirred at -78°C for 10min, the solution of methyl isopropyl ketone (0.12mL, 1.2mmol) in anhydrous THF (5mL) was syringed dropwise and the reaction mixture was stirred at -78°C for further 40min. Then the above solution of allylic iodide in THF (5mL) was added dropwise with efficient stirring. The stirring was continued for 2hrs at that temperature, then the reaction mixture was allowed to warm gradually to room temperature overnight. The reaction was quenched by the addition of saturated NH_4Cl *aq.* solution and ether (30mL), the combined organic phases were washed with water and brine, dried and concentrated. The resulting oil was purified by flash column chromatography on silica gel (pet. ether/ethyl acetate 20:1) to afford the ketone **13** (124mg, 80%) as a yellowish oil. **13a**: $[\alpha]_D^{20}$ +8.48 (c=1.10, $CHCl_3$); IR: 2988, 2857, 1715(C=O), 1590, 1428, 1110, 1024, 905, 869, 737, 707cm^{-1}; m/z(EIMS): 589(M^+-CMe_3, 10), 505(12), 487(18), 437(8), 419(15), 283(18), 221(100), 199(100), 135(36), 85(100); ^{1}HNMR: δ(ppm) 0.64(t, J=6.6Hz, 3H, CH_3), 1.04(s, 9H, $C(CH_3)_3$), 1.11, 1.12(d, J=6.7Hz, 6H, $2CH_3$), 1.55(s, 3H, CH_3), 1.66(s, 3H, CH_3), 1.27-2.52(m, 20H, 2CH, $9CH_2$), 3.50(m, 1H, OCH_2), 3.85(m, 3H, OCH_2, CHOR, OCH_2CH=), 4.15(m, 1H, OCH_2CH=), 4.58(m, 1H, OCHO), 5.06(dt, J=7.3Hz, 1H, CH=), 5.31(m, 1H, CH=), 7.38-7.71(m, 10H, 2Ph); ^{13}CNMR: δ(ppm) 16.0, 18.2, 18.8, 19.5, 23.9, 25.5(3C), 26.0, 27.0(3C), 28.6, 30.9, 33.5, 36.6, 37.9, 41.2, 42.5, 44.6, 62.1, 63.8, 70.0, 98.0, 123.7, 125.4, 127.4, 129.5, 134.5(2C), 136.0(8C), 137.3(2C), 214.2; **13b**: $[\alpha]_D^{20}$ +12.35 (c=1.12, $CHCl_3$); IR and EIMS are the same with **13a**; ^{1}HNMR: δ(ppm) 0.62(brs, 3H, CH_3), 1.03(s, 9H, $C(CH_3)_3$), 1.10, 1.11(d, J=6.7Hz, 6H, $2CH_3$), 1.55(s, 3H, CH_3), 1.65(s, 3H, CH_3), 1.15-2.21(m, 17H, $8CH_2$, CH), 2.47-2.51(m, 3H, CH_2COCH), 3.48(m, 1H, OCH_2), 3.84(m, 2H, OCH_2, CHOR), 3.93(m, 1H, OCH_2CH=), 4.10(m, 1H, OCH_2CH=), 4.55(m, 1H, OCHO), 5.05(m, 1H, CH=), 5.26(t, J=6.9Hz, 1H, CH=), 7.36-7.69(m, 10H, 2Ph); ^{13}CNMR: δ(ppm) 16.2, 18.2(2C), 19.1, 19.4, 25.0, 25.1, 25.5, 26.0, 27.0(3C), 28.6, 30.7, 33.5, 37.9, 38.7, 40.8, 44.1, 48.6, 62.2, 63.3, 69.8, 97.6, 123.7, 125.3, 127.4, 129.4, 133.5(2C), 136.0(8C), 137.1(2C), 214.5

(7S)-3,7,11,15-Tetramethyl-5-*tert*-butyldiphenylsiloxyl-14-oxy-2Z,10E-hexzdecadienal 8a and 2E,10E isomer 8b A mixture of ketone **13** (100mg, 0.15mmol) and catalytic amount of p-TsOH in dry MeOH (2mL) was stirred at r.t. for 2hrs, then extracted the reaction mixture with ether (3×30mL). The ether layer was washed with water, brine and dried. Evaporation of the solvent in vaccum gave the crude oil of alcohol, which without further purification was dissolved in anhydrous n-hexane (5mL). Active manganese dioxide

(261mg, 3mmol) was added to the resulting solution. The suspension mixture was stirred for 20hrs at room temperature and then diluted with ether (20mL). The mixture was filtered through a short column on silica gel and the resulting filterate was concentrated on a rotary evaporator in vaccum to give the crude oil which was purified on silica gel (pet. ether/ethyl acetate 15:1) to yield siloxyl enal **8** (78mg, 93%) as a clear oil. **8a**: $[\alpha]_D^{20}$ +9.26 (c=1.08, $CHCl_3$); IR: 2931, 2857, 1710(C=O), 1676(C=O), 1466, 1427, 1381, 1109, 1047, 936, 739, 705cm^{-1}; m/z(EIMS): 560(M^+, 1), 503(2), 419(6), 341(2), 265(41), 199(100), 187(37), 135(69), 71(64), 43(52); ^{1}HNMR: δ(ppm) 0.63(d, J=6.4Hz, 3H, CH_3), 1.03(s, 9H, $C(CH_3)_3$), 1.07, 1.11(d, J=7.1Hz, 6H, $2CH_3$), 1.57(s, 3H, CH_3), 1.65(s, 3H, CH_3), 1.55-2.74(m, 14H, $6CH_2$, 2CH), 3.95(m, 1H, CHOR), 5.03(m, 1H, CH=), 5.82(d, J=8.2Hz, 1H, =CHCHO), 7.36-7.72(m, 10H, 2Ph), 9.76(d, J=8.2Hz, 1H, CHO); ^{13}CNMR: δ(ppm) 16.0, 18.1(2C), 19.2, 23.4, 25.1, 26.9(3C), 28.6, 29.0, 33.5, 36.9, 38.9, 41.1, 44.5, 49.6, 70.1, 124.8, 127.6, 129.7, 133.6(2C), 135.9(10C), 160.3, 190.7, 214.2; **8b**: $[\alpha]_D^{20}$ +19.09 (c=1.40, $CHCl_3$); IR and EIMS are the same with **8a**; ^{1}HNMR: δ(ppm) 0.64(d, J=6.4Hz, 3H, CH_3), 1.03(s, 9H, $C(CH_3)_3$), 1.08,1.09(d, J=6.6Hz, 6H, $2CH_3$), 1.55(s, 3H, CH_3), 1.80(s, 3H, CH_3), 1.25-2.63(m, 14H, $6CH_2$, 2CH), 3.95(m, 1H, CHOR), 5.03(m, 1H, CH=), 5.75(d, J=8.2Hz, 1H, =CHCHO), 7.36-7.71(m, 10H, 2Ph), 9.86(d, J=8.2Hz, 1H, CHO); ^{13}CNMR: δ(ppm) 16.0, 18.2(2C), 19.3, 23.1, 25.1, 26.9(3C), 28.5, 29.0, 33.5, 37.2, 39.0, 40.8, 44.5, 49.2, 69.7, 125.0, 127.6, 129.5, 133.7(2C), 135.9(10C), 160.4, 190.7, 214.2

(8S)-6-*tert*-Butyldiphenylsiloxyl-1E,3E,11E-1,3,11-cembratriene 15a[1], 1Z,3E,11E isomer 15a[2], 1E,3Z,11E isomer 15b[1], 1Z,3Z,11E isomer 15b[2] To an anhydrous DME (30mL) was added by a dry syringe dropwise titanium tetrachloride (1mL, 19mmol) carefully at -78°C with efficient stirring over 5 min. After removal of the cooling bath, to the resulting suspension of TiCl4•DME complex was added zinc powder (1.27g, 9mmol) and followed by the addition of pyridine (0.2mL). The suspension mixture was then refluxed for 2.5hrs, to which was syringed slowly a dilute solution of siloxyl ether **8a** (75mg, 0.13mmol) or equivalent **8b** in anhydrous DME (30mL) for 20hrs. After the addition, the reaction mixture was refluxed for an additional 3hrs, then cooled to room temperature and 20% K_2CO_3 *aq.* solution (10mL) was added. The resulting suspension was extracted with ether (5×40mL), and the organic phase was washed with water, brine, then dried. Removal of the solvent and purification of the crude residue by flash column chromatography (eluting with pet. ether) afforded the cyclized silyl ether **15a[1]** and **15a[2]** (or corresponding **15b[1]** and **15b[2]**) as colorless oil (**15a[1]**: 30mg, 42.4% and **15a[2]**: 23mg, 31.8%; **15b[1]**: 25mg, 35.3% and **15b[2]**: 13mg, 18.6%). **15a[1]** : $[\alpha]_D^{20}$ -17.95 (c=0.74, $CHCl_3$); IR: 2958, 2927, 2855, 1597, 1462, 1457, 1427, 1378, 1109, 1041, 939, 821, 737, 703cm^{-1}; m/z(EIMS): 528(M^+, 9), 471(2), 377(1), 335(16), 293(25), 199(66), 183(14), 136(100), 135(55), 121(46), 93(17), 41(14); ^{1}HNMR: δ(ppm) 0.99(d, J=6.8Hz, 3H, CH_3), 1.04, 1.05(d, J=6.9Hz, 6H, $2CH_3$), 1.07(s, 9H, $C(CH_3)_3$), 1.55(s, 3H, CH_3), 1.69(s, 3H, CH_3), 1.23-2.57(m, 14H, $6CH_2$, 2CH), 4.00(m, 1H, CHOR), 5.05(t, J=7.0Hz, 1H, CH=), 5.88-5.98(ABq, J=11.4Hz, 2H, trans =CH-CH=), 7.36-7.69(m, 10H,

2Ph); ^{13}CNMR: δ(ppm) 15.7, 18.1, 19.1, 21.7, 23.1, 24.5, 25.9, 26.9, 27.1(3C), 29.5, 33.4, 37.8, 38.7, 40.3, 46.4, 71.4, 118.7, 126.6, 127.4, 129.5, 134.7(2C), 136.0, 136.1(10C), 146.6; **15a**^{2}: $[\alpha]_D^{20}$ -31.83 (c=1.00, $CHCl_3$); IR and EIMS are the same with **15a**^{1}; ^{1}HNMR: δ(ppm) 0.67(d, J=6.7Hz, 3H, CH_3), 1.06, 1.07(d, J=7.0Hz, 6H, $2CH_3$), 1.07(s, 9H, $C(CH_3)_3$), 1.58(s, 3H, CH_3), 1.76(s, 3H, CH_3), 1.20-2.41(m, 14H, $6CH_2$, 2CH), 3.98(m, 1H, CHOR), 4.95(t, J=6.6Hz, 1H, CH=), 5.88(d, J=11.6Hz, 1H, CH=), 6.05(d, J=11.3Hz, 1H, CH=), 7.35-7.70(m, 10H, 2Ph); ^{13}CNMR: δ(ppm) 17.6, 17.7, 19.2, 22.1, 22.9, 24.4, 25.4, 26.4, 27.1(3C), 28.7, 33.8, 38.0, 38.8, 43.1, 47.1, 70.6, 119.0, 126.6, 127.4, 129.5, 134.7(2C), 136.0(11C), 146.1; **15b**^{1}: $[\alpha]_D^{20}$ -11.11 (c=0.45, $CHCl_3$); IR and EIMS are the same with **15a**^{1}; ^{1}HNMR: δ(ppm) 0.75(d, J=6.6Hz, 3H, CH_3), 1.04(s, 9H, $C(CH_3)_3$), 1.05, 1.07(d, J=6.5Hz, 6H, $2CH_3$), 1.55(s, 3H, CH_3), 1.71(s, 3H, CH_3), 1.23-2.64(m, 13H, $6CH_2$, CH), 3.01(m, 1H, CH), 4.00(m, 1H, CHOR), 5.15(t, J=7.3Hz, 1H, CH=), 5.89(d, J=11.5Hz, 1H, CH=), 5.97(d, J=11.1Hz, 1H, CH=), 7.36-7.70(m, 10H, 2Ph); ^{13}CNMR: δ(ppm) 16.5, 20.2, 21.2, 22.0, 23.0, 24.3, 25.9, 27.0(3C), 27.1, 28.9, 33.5, 37.8, 38.9, 43.2, 46.4, 71.6, 119.8, 125.5, 127.5, 129.5, 133.3, 134.7(2C), 136.1(10C), 146.7; **15b**^{2} : $[\alpha]_D^{20}$ -12.67 (c=0.60, $CHCl_3$); IR and EIMS are the same with **15a**^{1}; ^{1}HNMR: δ(ppm) 0.67(d, J=6.9Hz, 3H, CH_3), 1.03(d, J=6.1Hz, 6H, $2CH_3$), 1.06(s, 9H, $C(CH_3)_3$), 1.58(s, 3H, CH_3), 1.73(s, 3H, CH_3), 1.20-2.50(m, 13H, $6CH_2$, CH), 2.96(m, 1H, CH), 4.05(m, 1H, CHOR), 4.94(t, J=7.3Hz, 1H, CH=), 5.93(d, J=11.3Hz, 1H, CH=), 6.07(d, J=11.5Hz, 1H, CH=), 7.08-7.69(m, 10H, 2Ph); ^{13}CNMR: δ(ppm) 15.7, 19.2, 21.1, 21.6, 24.4, 24.7, 25.8, 26.4, 27.1(3C), 28.2, 29.1, 35.9, 37.5, 43.1, 47.0, 71.2, 119.0, 122.7, 126.6, 129.5, 133.9, 134.5(2C), 136.1(10C), 147.8

(8S)-(1E,3E,11E)-1,3,11-Cembratrien-6-one 1 and (1E,3Z,11E) isomer 2, (1Z,3Z,11E) isomer 3 Silyl ether **15a**^{1} (25mg, 0.047mmol) or equivalent **15a**^{2}, **15b**^{1}, **15b**^{2} was dissolved in a solution of n-$Bu_4N^+F^-$ in THF (1N, 1.5mL) at room temperature. The mixture was stirred under argon atmosphere for 40hrs, then the resulting mixture was extracted with ether (4×10mL) and washed with water, brine and then dried. Removal of the solvent by rotary evaporation gave the crude oil which then was dissolved in 2mL anhydrous CH_2Cl_2 without further purification. Pyridinium chlorochromate (15mg, 0.07mmol), silica gel (7mg) and NaOAc (1mg) was added to the solution. The stirring was continued for 1h prior to the removal of the solvent in vaccum. The crude residue was purified by flash column chromatography on silica gel (pet. ether/ethyl acetate 10:1) to afford the title compound **1** (12mg, 90%) or corresponding **2** and **3** as colorless oil. **1**: $[\alpha]_D^{20}$ -149 (c=0.3, $CHCl_3$); IR: 2958, 2925, 2854, 1706(C=O), 1457, 1379, 1082, 861cm^{-1}; m/z(EIMS): 288(M^+, 9), 273(2), 245(2), 177(5), 161(4), 136(63), 121(100), 109(22), 93(62), 67(26); ^{1}HNMR: δ(ppm) 0.87(d, J=6.6Hz, 3H), 1.07(d, J=6.8Hz, 3H), 1.12(d, J=6.9Hz, 3H), 1.25(m, 1H), 1.48(m, 1H), 1.57(s, 3H), 1.65(m, 1H), 1.71(s, 3H), 2.00-2.13(m, 4H), 2.21-2.25(m, 2H), 2.39(m, 1H), 2.54(m, 1H), 2.65(dd, J=12.5Hz, J=4.1Hz, 1H), 2.88(d, J=12.6Hz, 1H), 3.19(d, J=12.7Hz, 1H), 5.10(t, J=7.1Hz, 1H), 6.07(d, J=11.2Hz, 1H), 6.23(d, J=11.2Hz, 1H); ^{13}CNMR: δ(ppm) 16.4, 18.2, 20.0, 21.8, 22.9, 24.7, 28.5, 29.8, 33.5, 37.3, 37.9, 48.8, 54.4,

118.7, 125.9, 126.8, 128.5, 136.1, 148.6, 211.5; **2**: $[\alpha]_D^{20}$ -204 (c=0.25, $CHCl_3$); IR and EIMS are the same with **1**; ^{1}HNMR: δ(ppm) 0.86(d,J=6.6Hz,3H), 1.04(s,3H), 1.09(s,3H), 1.15(m,1H),1.40(m,1H), 1.61(m,1H), 1.62(s,3H), 1.71(s, 3H), 1.90-2.25(m, 6H), 2.31(m, 1H), 2.57(m, 1H), 2.63(m, 1H), 2.72(m, 1H), 3.71(d, J=13.7Hz, 1H), 4.73(d, J=9.6Hz, 1H), 6.08(d, J=10.7Hz, 1H), 6.14(d, J=10.2Hz, 1H); ^{13}CNMR: δ(ppm) 16.1, 20.4, 21.1, 23.6(2C), 24.5, 27.2, 27.9, 32.8, 37.3, 38.5, 46.1, 48.0, 119.2, 125.5, 127.3, 128.3, 132.8, 147.9, 212.1; **3**: $[\alpha]_D^{20}$-88(c=0.25,$CHCl_3$); IR and EIMS are the same with **1**; ^{1}HNMR: δ(ppm) 0.84(d, J=6.3Hz, 3H), 1.04,1.06(d, J=7.2Hz, 6H), 1.21-1.25(m, 2H), 1.60(s, 3H), 1.76(s, 3H), 2.02-2.31(m, 9H), 3.05(d, J=6.7Hz, 1H), 3.18(d, J=12.6Hz, 1H), 3.21(d, J=14.3Hz, 1H), 5.09(dd, J=7.0Hz, J=7.3Hz, 1H), 5.91(d, J=11.3Hz, 1H), 6.29(d, J=11.4Hz, 1H); ^{13}CNMR: δ(ppm) 15.4, 19.5, 21.2, 21.8, 24.1, 24.6, 27.3, 27.7, 29.5, 35.9, 36.9, 46.1, 50.6, 119.5, 123.7, 126.3, 128.9, 134.2, 145.3, 210.7

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