A New, Ring Closing Metathesis-based Synthesis of (-)-Fumagillol

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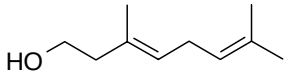
Supporting information

3(*E*)-3,7-dimethyl-octa-3,6-dien-1-ol (isogeraniol) **1**.



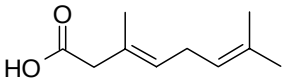
Butyn-1-ol (5 mL, 66 mmol) was slowly added (ca. 1h) to a cold (0°C) solution containing Cp_2ZrCl_2 (7.5 g, 25 mmol) in 1,2-dichloroethane (150 mL) and $AlMe_3$ (2M in toluene, 100 mL, 200 mmol). The mixture was stirred at 20°C for 24 h and THF (100 mL) was added, followed by 4-bromo-2-methyl-2-butene (8.3 mL, 72.6 mmol, 1.1 eq) and palladium tetrakistriphénylphosphine (770 mg, 0.66 mmol). Stirring was continued for 24 h and the mixture was poured slowly at 0°C, with vigorous stirring, into 1 M hydrochloric acid. The mixture was extracted twice with ether (250 mL), the organic layers were combined, washed with brine, dried, and the solvent was evaporated to afford a 9 :1 mixture of isogeraniol and **1'**. This mixture, dissolved in a 9 :1 mixture of DMF and water containing cuprous chloride (1 g, 10.8 mmol) and $PdCl_2(CH_3CN)_2$ (140 mg, 0.54 mmol) was stirred under an oxygen atmosphere, at 30°C, for 48 h. After standard work-up, the residue was chromatographed through a short pad of silicagel (eluent : cyclohexane / AcOEt 8/2) to afford 6.65 g (65%) of isogeraniol.

bp 74-75 °C (P = 1.8 mbar)

^{1}H-NMR (250 MHz, $CDCl_3$) : 5.21 (m, *J* = 7.1, 1H, C*H*CH_2CH=CMe_2) ; 5.08 (m, *J* = 7.2, 1H, $CHCH_2C$*H*=CMe_2) ; 3.64 (m, 2H, C*H*$_2$OH) ; 2.70 (t, *J* = 6.9, 2H, CHC*H*$_2$CH=CMe_2) ; 2.23 (t, *J* = 6.3, 2H, $HOCH_2CH_2$) ; 1.67 (d, *J* = 1.0, 3H, CH_3) ; 1.64 (s, 3H, C*H*$_3$) ; 1.61 (s, 3H, C*H*$_3$) ; 1.55 (s, 1H, O*H*).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 131.6, 131.0, 126.5, 122.7, 60.0, 42.5, 27.0, 25.5, 17.6, 15.6.

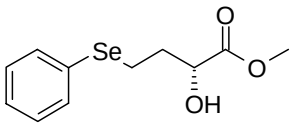
3(*E*)-3,7-dimethyl-octa-3,6-dienoic acid (isogeranic acid) **3**.



A cool (0 °C) solution of CrO_3 (7.8 g, 78 mmol) in water (22.7 mL) and sulfuric acid (7.2 mL) was added to a cold (0 °C) solution of isogeraniol (4.0 g, 26 mmol) in acetone (300 mL) at a rate such that the temperature was maintained at 0 °C. After completion of the addition, the mixture was stirred for 15 min at 0 °C and water (250 mL) was added. Extraction with ether (2 x 250 mL) and filtration through a short pad of silicagel (eluent : cyclohexane / AcOEt 75/25) provided pure isogeranic acid as a colorless oil (1.50 g, 35%)

^{1}H-NMR (250 MHz, $CDCl_3$) : 10-7.5 (s, 1H, COO*H*) ; 5.31 (m, *J* = 7.2, 1H, C*H*CH_2CH=CMe_2) ; 5.09 (m, *J* = 7.2, 1H, $CHCH_2$C*H*=CMe_2) ; 3.01 (s, 2H, HOOCCH_2) ; 2.72 (t, *J* = 7.2, 2H, CHCH_2CH=CMe_2) ; 1.73 (d, *J* = 0.6, 3H, CH_3) ; 1.68 (d, *J* = 1.0, 3H, CH_3) ; 1.62 (s, 3H, CH_3).
^{13}C-NMR (62.9 MHz, $CDCl_3$) : 178.7, 132.0, 128.8, 127.4, 122.2, 44.7, 27.1, 25.6, 17.6, 16.2.

Methyl 2-(*R*)-2-hydroxy-4-phenylselenylbutanoate **5**.



A solution of diphenyldiselenide (29 g, 93 mmol) in DMF (150 mL) was added slowly to a suspension of sodium borohydride (7.04 g, 186 mmol) in DMF (100 mL). The mixture was stirred at 20°C until light yellow and the temperature was raised to 80°C. A solution of (*R*)-(+)-α-hydroxybutyrolactone (9.50 g, 93 mmol) in DMF (25 mL) was added slowly and stirring was continued for 2 h at 80°C. Excess aqueous HCl (1M) was added and the reaction mixture was partitioned between water and ether. The

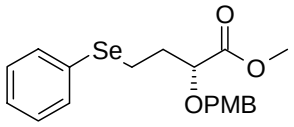
organic layer was dried and concentrated *in vacuo* to afford a residue which was dissolved in ether (100 mL) and treated with excess diazomethane. The progress of the ester formation was followed by TLC (cyclohexane/AcOEt 1/1). Upon completion of the reaction and work-up, the resulting oil was chromatographed (SiO_2, eluent : cyclohexane/AcOEt 7/3) to afford pure **5** : 18.7 g, 74%.

$[\alpha]_D^{20}$ = + 6 ° ($CHCl_3$, *C* = 1.18)

^{1}H-NMR (250 MHz, $CDCl_3$) : 7.49 (m, 2H, Ar*H*) ; 7.26 (m, 3H, Ar*H*) ; 4.32 (ddd, *J* = 8.0, 5.3, 4.0, 1H, C*H*OH) ; 3.77 (s, 3H, OCH_3) ; 3.01 (dd, *J* = 8.0, 7.2, 2H, SeCH_2) ; 2.79 (d, *J* = 5.3, 1H, O*H*) ; 2.16 & 2.03 (m, 2H, CH_2).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 175.0, 132.4, 129.6, 129.0, 126.8, 69.7, 52.5, 34.5, 22.6.

Methyl 2-(*R*)-2-*p*-methoxybenzyloxy-4-phenylselenylbutanoate **6**.



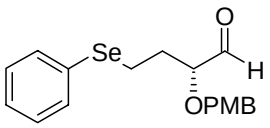
Camphorsulfonic acid (3.2 g, 13.7 mmol) was added to a solution of **5** (18.7 g, 68.5 mmol) and freshly prepared *p*-methoxybenzyl trichloroacetimidate (38.7 g, 137 mmol) in dichloromethane (150 mL). The mixture was stirred at 20°C for 24 h and quenched with a saturated solution of $NaHCO_3$. The mixture was partitioned between ethyl acetate and water and the organic layer was dried and concentrated *in vacuo*. The residue was chromatographed (SiO_2, eluent :cyclohexane/AcOEt 8/2) to afford pure **6** : 18.94 g, 70%.

$[\alpha]_D^{20}$ = + 67 ° ($CHCl_3$, *C* = 1.0)

^{1}H-NMR (250 MHz, $CDCl_3$) : 7.47 (m, 2H, Ar*H*) ; 7.26 (m, 5H, Ar*H*) ; 6.86 (d, *J* = 8.5, 2H, Ar*H*) ; 4.62 & 4.29 (2d, *J* = 11.0, 2H, OCH_2Ar) ; 4.10 (dd, *J* = 4.5, 8.0, 1H, C*H*COOMe) ; 3.80 (s, 3H, OCH_3) ; 3.75 (s, 3H, COOCH_3) ; 2.97 (m, 2H, SeCH_2) ; 2.10 (m, 2H, $SeCH_2CH_2$).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 172.9, 159.4, 132.6, 129.7, 129.3, 129.0, 126.9, 113.7, 76.6, 72.1, 55.2, 51.9, *33.4, 23.3.*

2-(*R*)- 2-*p*-methoxybenzyloxy-4-phenylselenylbutanal **7**.



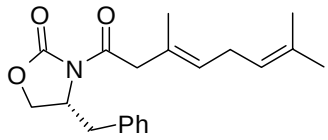
A solution of DIBAH in toluene (20.4 mL, 1.5 M, 30.6 mmol) was added at -78 °C to a solution of ester **7** (7.8 g, 19.8 mmol) in toluene (50 mL). After stirring for 20 min at -78 °C, methanol (10 mL) was added cautiously. The cold bath was removed and the temperature was allowed to reach 20°C. A saturated solution of sodium tartarate (0.5 mL) was added, followed by ethyl acetate (100 mL) and anhydrous $MgSO_4$ (1g). The mixture was stirred at 20°C for 1h and filtered. The solid was washed with ethyl acetate (3 x 100mL) and the combined filtrates were concentrated *in vacuo*. The residue was chromatographed (SiO_2, eluent :cyclohexane/AcOEt 8/2) to afford pure **7** : 6.75 g, 94%.

$[\alpha]_D^{20}$ = + 30 ° ($CHCl_3$, *C* = 1.55)

^{1}H-NMR (250 MHz, $CDCl_3$) : 9.64 (d, 1H, *J* = 1.6, C*H*O) ; 7.48 (m, 2H, Ar*H*) ; 7.25 (m, 5H, Ar*H*) ; 6.88 (d, *J* = 8.7, 2H, Ar*H*) ; 4.48 & 4.44 (2d, *J* = 11.2, 2H, OCH_2Ar) ; 3.93 (ddd, *J* = 7.0, 5.2, 1.6, 1H, C*H*CHO) ; 3.80 (s, 3H, OCH_3) ; 2.99 (m, 2H, SeCH_2) ; 2.02 (m, 2H, $SeCH_2CH_2$) .

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 203.0, 159.5, 132.7, 129.7, 129.1, 129.0, 127.0, 113.9, 82.2, 72.3, 55.2, 30.6, 22.8.

4-(*R*)-4-benzyl-3-[3(*E*)-(3,7-dimethylocta-3,6-dienoyl)-oxazolidin-2-one **8.**



Pivaloyl chloride (99 mg, 101 µL, 0.82 mmol) was added to a cold (-78°C) solution of (*E*)-isogeranic acid (138 mg, 0.82 mmol) and triethylamine (99 mg, 137 µL, 0.98 mmol) in THF (2 mL). The mixture was stirred for 15 min at -78°C then 15 min at 0°C. In parallel, 0.56 mL (0.90 mmol, 1.1 eq) of a 1.6 M BuLi solution in hexanes was added at -78°C to a solution of (*R*)-(+)-4-benzyl-2-oxazolidinone (159 mg, 0.90 mmol)

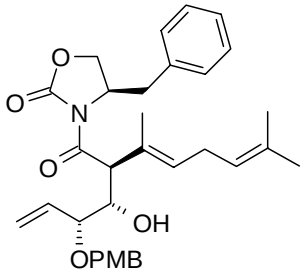
in THF (3 mL). The mixture was stirred for 15 min at -78 °C, then, added to the mixed anhydride, at -78°C *via* cannula. Stirring was continued for 20 min, the cold bath was removed and the mixture was allowed to reach 20°C in the course of ca. 1 h. The reaction was quenched by adding saturated ammonium chloride (1mL). The mixture was extracted with CH_2Cl_2, and the residue obtained after evaporation of the solvent was chromatographed (SiO_2, eluent :cyclohexane/AcOEt 8/2) to afford pure **8** (188 mg, 70 %).

$[\alpha]_D^{20}$ = - 48 ° ($CHCl_3$, *C* = 1.0)

^{1}H-NMR (250 MHz, $CDCl_3$) : 7.36-7.26 (m, 3H, Ar*H*) ; 7.24-7.19 (m, 2H, Ar*H*) ; 5.29 (tm, *J* = 7.0, 1H, C*H*CH_2CH=CMe_2) ; 5.11 (tm, *J* = 7.1, 1H, C*H*=CMe_2) ; 4.67 (dddd, *J* = 3.5, 3.5, 7.0, 10.0, 1H, C*H*N) ; 4.16 (ABX, 2H, CH_2O) ; 3.63 (AB, 2H, COCH_2) ; 3.31 (dd, *J* = 3.1, 13.2, 1H, C*H*Ph) ; 2.76 (dd, *J* = 9.8, 13.1, 1H, C*H*Ph) ; 2.76 (t, *J* = 7.0, 2H, CHCH_2CH=CMe_2) ; 1.75 (s, 3H, CH_3) ; 1.69 (s, 3H, CH_3) ; 1.63 (s, 3H, CH_3).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 171.5, 153.3, 135.2, 131.8, 129.3, 128.9, 128.5, 127.8, 127.2, 122.4, 66.0, 55.2, 45.2, 37.8, 27.1, 25.6, 17.7, 16.6.

4-(*R*)-4-benzyl-3-{2(*S*)-2-[(1*S*, 2*R*)-1-hydroxy-2-*p*-methoxybenzyloxy-but-3-enyl]-3,7-diméthyloct-3,6-dienoyl}-oxazolidin-2-one **9**.



A solution of oxazolidinone **8** (5.1 g, 15.6 mmol) in THF (10 mL) was added to a solution of LDA (15.6 mmol) in THF (10 mL) and hexane (16 mL). The mixture was stirred for 45 min at -78° and a solution of aldehyde **7** (6.7 g, 18.4 mmol) in THF (10 mL) was added. The mixture was stirred for a further 45 min, quenched (ammonium chloride), and partitioned beween water and ether to give a residue which was dissolved in chloroform (150 mL). Tetrabutylammonium periodate (16 g, 36.9 mmol) was added and the mixture was stirred at 60°C for 2 h. Work-up and chromatography

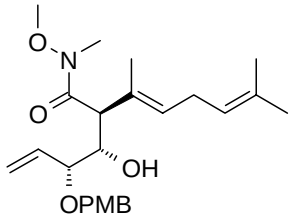
(SiO_2, eluent :cyclohexane/AcOEt 8/2) afforded successively unreacted **8** (752 mg) and **9** (4.61g, 55%)

$[\alpha]_D^{20}$ = - 121 ° ($CHCl_3$, *C* = 0.82)

^{1}H NMR (250 MHz, $CDCl_3$) : 7.33-7.20 (m, 5H, Ar*H*) ; 7.12 (d, *J* = 7.7, 2H, Ar*H*) ; 6.83 (d, *J* = 8.5, 2H, Ar*H*) ; 5.91 (ddd, *J* = 8.1, 10.3, 17.2, 1H, C*H*=CH_2) ; 5.54 (tm, *J* = 7.1, 1H, MeC=C*H*) ; 5.42 & 5.34 (2dm, *J* = 10.3, & *J* = 17.1, 2H, CH_2=CH) ; 5.06 (tm, *J* = 7.1, 1H, C*H*=CMe_2) ; 4.77 (d, *J* = 8.6, 1H, NCOC*H*C=C) ; 4.54 (d, *J* = 10.8, 1H, CH_2pC_6H_4OMe) ; 4.42 (m, 1H, C*H*N) ; 4.31 (ddd, *J* = 3.5, 6.3, 8.6, 1H, C*H*OH) ; 4.25 (d, *J* = 10.8, 1H, CH_2pC_6H_4OMe) ; 4.05-3.93 (AB, 2H, NCOOCH_2) ; 3.74 (m, 1H, C*H*OPMB) ; 3.69 (s, 3H, OCH_3) ; 3.07 (dd, *J* = 3.2, 13.3, 1H, C*H*Ph) ; 2.73 (t, *J* = 7.1, 2H, C=CCH_2C=C) ; 2.21 (d, *J* = 3.7, 1H, O*H*) ; 1.86 (dd, *J* = 10.8, 13.3, 1H, C*H*Ph) ; 1.76 (s, 3H, CH_3) ; 1.66 (s, 3H, CH_3) ; 1.59 (s, 3H, CH_3).

^{13}C NMR (62.9 MHz, $CDCl_3$) : 171.8, 159.2, 152.7, 135.8, 135.7, 132.1, 131.8, 130.1, 129.9, 129.6, 129.3, 128.8, 127.0, 122.1, 120.1, 113.7, 83.2, 72.2, 70.4, 65.6, 55.9, 55.0, 53.7, 37.0, 27.3, 25.6, 17.7, 14.7.

2-(*S*)-2-[(1*S*, 2*R*)-1-hydroxy-2-*p*-methoxybenzyloxy-but-3-enyl]-3,7-dimethyloct-3,6-dienoic acid methoxy-methyl-amide **10**.



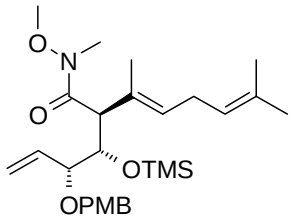
A solution of trimethylaluminium in toluene (2 M, 15.05 mL, 30.1 mmol) was added to a cold (0 °C) suspension of *N,O*-dimethylhydroxylamine hydrochloride (2.93 g, 30.1 mmol) in THF (10 mL). The mixture was stirred at 20°C for 45 min, then cooled to 0°C. A solution of oxazolidinone **9** (4.61 g, 8.6 mmol) in THF (10 mL) was added, and stirring was continued overnight. The mixture was then poured slowly onto a cold aqueous solution of tartaric acid (15%, 150 mL). Extraction with ethyl acetate and chromatography (SiO_2, eluent :cyclohexane/AcOEt 8/2) afforded pure **10** (2.58 g, 71%) as a colorless oil.

$[\alpha]_D^{20}$ = - 133 ° ($CHCl_3$, *C* = 1.02)

^{1}H-NMR (400 MHz, $CDCl_3$, 330K) : 7.23 & 6.85 (2d, *J* = 8.8, 4H, Ar*H*) ; 5.89 (ddd, *J* = 8, 10.4, 17.6, 1H, C*H*=CH_2) ; 5.36 (m, 2H, MeC=C*H*, & CH_2=CH) ; 5.27 (dm, *J* = 17.4, 1H, CH_2=CH) ; 5.10 (tm, *J* = 7.2, 1H, C*H*=CMe_2) ; 4.52 & 4.28 (2d, *J* = 11.2, 2H, CH_2pC_6H_4OMe) ; 4.18 (dt, *J*=2, 6.4,1H, C*H*OH) ; 3.81 (m, 1H, C*H*OPMB) ; 3.79 (s, 3H, ArOCH_3) ; 3.66 (m, 1H, NCOC*H*C=C) ; 3.60 (s, 3H, NOCH_3) ; 3.18 (sl, 1H, O*H*) ; 3.11 (s, 3H, NCH_3) ; 2.75 (t, *J* = 7.2, 2H, C=CCH_2C=C) ; 1.76 (s, 3H, CH_3) ; 1.72 (s, 3H, CH_3) ; 1.62 (s, 3H, CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$, 330K) : 159.3, 135.7, 131.9, 130.9, 130.3, 130.0, 129.2, 122.5, 119.0, 113.9, 81.5, 73.2, 69.9, 61.0, 55.3, 51.8, 32.6, 27.3, 25.5, 17.7, 15.2.

2-(*S*)-2-[(1*S*,2*R*)-2-*p*-methoxybenzyloxy-1-trimethylsilyloxy-but-3-enyl]-3,7-dimethyloct-3,6-dienoic acid methoxy-methyl-amide **11**.



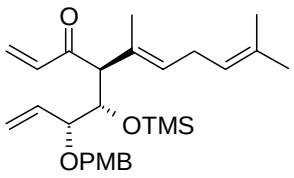
TMSCl (455 µL, 3.59 mmol) was added to a solution of amide **10** (1.0 g, 2.39 mmol), triéthylamine (1.65 mL, 11.97 mmol,) and DMAP (438 mg, 3.59 mmol) in THF (10 mL). The mixture was stirred for 2 h at 20°C. After quenching (ammonium chloride), extraction (dichloromethane) and chromatography (SiO_2, eluent :cyclohexane/AcOEt 8/2), 1.16g (100%) of **11** were obtained.

$[\alpha]_D^{20}$ = - 103 ° ($CHCl_3$, *C* = 1.18)

^{1}H NMR (250 MHz, $CDCl_3$) : 7.24 & 6.84 (2d, *J* = 8.7, 4H, Ar*H*) ; 5.90 (ddd, *J* = 8.5, 10.3, 17.3, 1H, C*H*=CH_2) ; 5.37 (tm, *J* = 7.1, 1H, MeC=C*H*) ; 5.31 & 5.15 (2dm, *J* = 10.3, & *J* = 17.3, 2H, CH_2=CH) ; 5.08 (tm, *J* = 7.2, 1H, C*H*=CMe_2) ; 4.44 & 4.31 (2d, *J* = 11.2, 2H, CH_2pC_6H_4OMe) ; 4.41 (dd, *J* = 2.4, 10.1, 1H, C*H*OTMS) ; 3.79 (s, 3H, ArOCH_3) ; 3.73 (dd, *J* = 2.4, 8.5, 1H, C*H*OPMB) ; 3.58 (s, 3H, NOCH_3) ; 3.37 (broad signal, 1H, NCOC*H*C=C) ; 3.09 (s, 3H, NCH_3) ; 2.71 (t, *J* = 7.1, 2H, C=CCH_2C=C) ; 1.70 (s, 3H, CH_3) ; 1.65 (s, 3H, CH_3) ; 1.60 (s, 3H, CH_3) ; 0.03 (s, 9H, CH_3Si).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 173.3 , 158.7 , 135.3 , 131.3 , 131.1 , 130.9 , 129.2 , 128.1 , 122.7 , 119.5 , 113.4 , 82.9 , 75.3 , 69.8 , 61.0 , 55.2 , 52.9 , 32.3 , 27.2 , 25.6 , 17.7 , 15.9 , 0.51.

(4*S*,5*E*)-4-[(1*S*,2*R*)-2-*p*-methoxybenzyloxy-1-trimethylsilyloxy-but-3-enyl]-5,9-dimethyl-deca-1,5,8-trienone **12**.



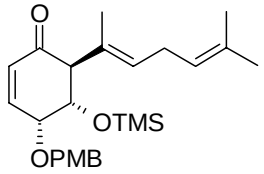
To a cold (0°C) solution of amide **11** (477 mg, 0.97 mmol) in THF (3 mL), were added 6 mL of vinylmagnesium bromide (1M in THF, 6.0 mmol). After stirring at 20°C for 12h, the mixture was canulated into 5 mL of a 2 :1 (V/V) mixture of saturated ammonium chloride and THF. After extraction (ether) and chromatography (SiO_2, eluent :cyclohexane/AcOEt 95/5), pure **12** was obtained (387 mg, 87%).

$[\alpha]_D^{20}$ = - 214 ° ($CHCl_3$, *C* = 1.0)

^{1}H-NMR (250 MHz, CD_2Cl_2) : 7.24 & 6.85 (2d, *J* = 8.7, 4H, Ar*H*) ; 6.33 (dd, *J* = 10.2, 17.4, 1H, CH_2=C*H*CO) ; 6.14 (dd, *J* = 1.4, 17.4, 1H, CH_2=CHCO) ; 5.83 (ddd, *J* = 8,5, 10.3, 17.4, 1H, C*H*=CH_2) ; 5.65 (dd, *J* = 1.4, 10.2, 1H, CH_2=CHCO) ; 5.32 (m, 2H, MeC=C*H* ; CH_2=CH) ; 5.10 (dm, *J* = 17.4, 1H, CH_2=CH) ; 5.09 (tm, *J* = 7.2, 1H, C*H*=CMe_2) ; 4.43 & 4.25 (2d, *J* = 11.3, 2H, CH_2pC_6H_4OMe) ; 4.40 (dd, *J* = 3.2, 9.3, 1H, C*H*OTMS) ; 3.78 (s, 3H, ArOCH_3) ; 3.57 (dd, *J* = 3.2, 8.5, 1H, C*H*OPMB) ; 3.39 (d, *J* = 9.3, 1H, COC*H*C=C) ; 2.71 (t, *J* = 7.2, 2H, C=CCH_2C=C) ; 1.67 (s, 3H, CH_3) ; 1.60 (2s, 6H, CH_3) ; 0.05 (s, 9H, SiCH_3).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 198.6, 158.8, 135.8, 135.5, 131.7, 130.8, 130.7, 129.7, 129.2, 127.6, 122.3, 119.8, 113.5, 82.5, 74.0, 69.7, 61.9, 55.1, 27.4, 25.6, 17.7, 14.9, 0.5.

(4*R*,5*S*,6*S*)-4-*p*-methoxybenzyloxy-5-trimethylsilyloxy-6-[(*E*)-1,5-dimethyl-hex-1,4-dienyl]-cyclohex-2-enone **13**.



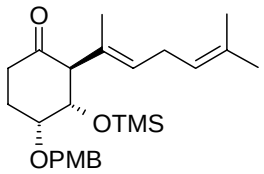
$Ti(OiPr)_4$ (12 µl) was added to a solution of dienone **12** (40 mg) in dichloromethane (1mL). The mixture was stirred for 30 min at 30°C and Grubbs's complex **1** (9 mg) was added. The mixture was placed in a tightly stoppered flask, heated to 55°C and stirred for 10 h, at which time more Grubbs's complex (9 mg) was added. The reaction was allowed to proceed for a further 14 h. After standard work-up and preparative TLC (SiO_2, eluent :cyclohexane/AcOEt 8/2), cyclohexenone **13** was obtained as a colorless oil (20 mg, 53%).

$[\alpha]_D^{20}$ = - 92 ° ($CHCl_3$, *C* = 0.8)

^{1}H-NMR (250 MHz, $CDCl_3$) : 7.28 & 6.88 (2d, *J* = 8.5, 4H, Ar*H*) ; 6.75 (ddd, *J* = 1.0, 4.0, 10.1, 1H, CH=C*H*CHOPMB) ; 6.04 (dd, *J* = 1.2, 10.1, 1H, C*H*=CHCHOPMB) ; 5.15 (tm, *J* = 7.1, 1H, MeC=C*H*) ; 5.03 (tm, *J* = 7.2, 1H, C*H*=CMe_2) ; 4.70 & 4.57 (2d, *J* = 11.8, 2H, OCH_2pC_6H_4OMe) ; 4.23 (ddd, *J* = 1.0, 3.1, 7.1, 1H, C*H*OTMS) ; 4.12 (ddd, *J* = 1.3, 3.1, 4.0, 1H, C*H*OPMB) ; 3.81 (s, 3H, ArOCH_3) ; 3.31 (d, *J* = 7.3, 1H, COC*H*C=C) ; 2.70 (t, *J* = 7.2, 2H, C=CCH_2C=C) ; 1.66 (s, 3H, CH_3) ; 1.59 (2s, 6H, CH_3) ; 0.11 (s, 9H, SiCH_3).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 199.5, 159.3, 145.5, 131.7, 130.8, 130.0, 129.4, 129.1, 128.9, 122.3, 113.8, 72.8, 71.9, 71.7, 61.7, 55.2, 27.1, 25.6, 17.7, 15.3, 0.3.

(2*S*,3*S*,4*R*)-2-[(*E*)-1,5-dimethyl-hex-1,4-dienyl]-4-*p*-methoxybenzyloxy-3-trimethylsilyloxy-cyclohexanone **14**.



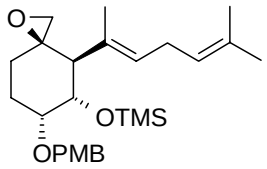
Under vigorous stirring, 25 drops of a 50% suspension of RaNi in water were added to a cold (0°C) solution of cyclohexenone **13** (375 mg, 0.87 mmol) in THF (5 mL). After 1h, ether (10 mL) was added, and the mixture was extracted with ethyl acetate. Chromatography (SiO_2, eluent :cyclohexane/AcOEt 85/15) afforded pure **14** (colorless oil, 306 mg, 83%)

$[\alpha]_D^{20}$ = - 18 ° ($CHCl_3$, *C* = 1.10)

^{1}H-NMR (250 MHz, $CDCl_3$) : 7.31 & 6.88 (2d, *J* = 8.6, 4H, Ar*H*) ; 5.17 (tm, *J* = 6.7, 1H, MeC=C*H*) ; 5.09 (tm, *J* = 7.1, 1H, C*H*=CMe_2) ; 4.72 & 4.61 (2d, AB, *J* = 11.8, 2H, OC*H*$_2$pC_6H_4OMe) ; 3.94 (dd, *J* = 2.5, 9.7, 1H, C*H*OTMS) ; 3.82 (m, 1H, C*H*OPMB) ; 3.81 (s, 3H, ArOC*H*$_3$) ; 3.37 (d, *J* = 9.8, 1H, COC*H*C=C) ; 2.73 (t, *J* = 7.1, 2H, C=CC*H*$_2$C=C) ; 2.58 (m, 1H, CH_2axCO) ; 2.24-2.05 (m, 2H, CH_2eqCO & CH_2eqCHOPMB) ; 1.66 (s, 3H, C*H*$_3$) ; 1.60-1.52 (m, 1H, CH_2axCHOPMB) ; 1.60 (s, 3H, C*H*$_3$) ; 1.55 (s, 3H, C*H*$_3$).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 209.5, 159.1, 131.2, 130.6, 129.5, 129.1, 129.0, 122.7, 113.6, 75.3, 73.7, 71.4, 64.1, 55.2, 35.5, 27.1, 25.6, 24.3, 17.7, 14.3, 0.3.

(3*R*,4*S*,5*S*,6*R*)-4-[(*E*)-1,5-dimethyl-hex-1,4-dienyl]- 6-*p*-methoxybenzyloxy-5-trimethylsilyloxy-1-oxaspiro [2,5] octane **15**.



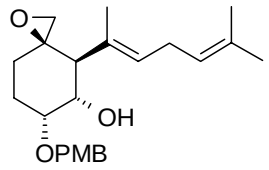
To a suspension of NaH (28 mg, 1.16 mmol) in DMSO/THF (1 :1 V/V, 1 mL) was added trimethylsulfoxonium iodide (385 mg, 1.74 mmol). The mixture was stirred at 20°C for 1 h and LiI (186 mg, 1.39 mmol) was added. Stirring was continued for 40 min, and the cyclohexanone **14** (50 mg, 0.116 mmol) dissolved in DMSO/THF (1 :1 V/V, 1 mL), was added and stirring was continued for 30 min. The mixture was partitioned between ether and a pH7 buffer. Chromatography (SiO_2, eluent :cyclohexane/AcOEt 85/15) afforded pure **15** (colorless oil, 27 mg, 53%).

$[\alpha]_D^{20}$ = - 73 ° ($CHCl_3$, *C* = 1.25)

^{1}H-NMR (250 MHz, $CDCl_3$) : 7.30 & 6.86 (2d, *J* = 8.6, 4H, Ar*H*) ; 5.23 (tm, *J* = 7.5, 1H, MeC=C*H*) ; 5.05 (tm, *J* = 7.1, 1H, C*H*=CMe_2) ; 4.62 & 4.52 (2d, AB, *J* = 11.8, 2H, OC*H*$_2$pC_6H_4OMe) ; 4.02 (dd, *J* = 2.8, 10.5, 1H, C*H*OTMS) ; 3.80 (s, 3H, ArOC*H*$_3$) ; 3.73 (dt, *J* = 2.3, 4.7, 1H, C*H*OPMB) ; 2.91 (d, *J* = 10.4, 1H, C*H*CMe=CH) ; 2.65 (tm, *J* = 6.8, 2H, C=CC*H*$_2$C=C) ; 2.58 & 2.42 (2d, *J* = 5.0, 2H, OC*H*$_2$ époxyde) ; 2.13 (m, 1H, C*H*axCH_2CHOPMB) ; 1.94 (m, 1H, C*H*$_2$eqCHOPMB) ; 1.67 (m, 1H, C*H*axCHOPMB) ; 1.66 (s, 3H, C*H*$_3$) ; 1.59 (s, 3H, C*H*$_3$) ; 1.56 (s, 3H, C*H*$_3$) ; 1.05 (dt, *J* = 13.6, 4.0, 1H, C*H*eqCH_2CHOPMB).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 158.9, 131.1, 130.6, 129.1, 128.7, 122.9, 113.5, 76.8, 73.4, 71.1, 60.2, 55.2, 51.2, 50.4, 28.3, 26.9, 25.6, 25.0, 17.6, 15.3, 0.6.

(3*R*,4*S*,5*S*,6*R*)-4-[(*E*)-1,5-dimethyl-hex-1,4-dienyl]- 5-hydroxy-6-*p*-methoxybenzyloxy-1-oxaspiro [2,5] octane **16**.



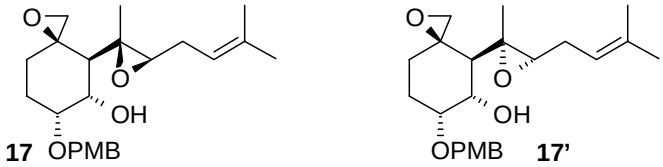
To a solution of epoxide **15** (136 mg) in THF (5mL) containing water (0.2 mL) was added *p*-toluenesulfonic acid (4 mg) and the mixture was stirred for 30 min at 20°C. Saturated $NaHCO_3$ in water (2mL) was added and the mixture was partitioned between water and ether. Chromatography (SiO_2, eluent :cyclohexane/AcOEt 7/3) afforded pure **16** (colorless oil, 85 mg, 75%)

$[\alpha]_D^{20}$ = - 108 ° ($CHCl_3$, *C* = 0.95)

^{1}H-NMR (250 MHz, $CDCl_3$) : 7.28 & 6.88 (2d, *J* = 8.6, 4H, Ar*H*) ; 5.21 (tm, *J* = 7.0, 1H, MeC=C*H*) ; 5.06 (tm, *J* = 7.1, 1H, C*H*=CMe_2) ; 4.63 & 4.45 (2d, AB, *J* = 11.3, 2H, OC*H*$_2$pC_6H_4OMe) ; 3.95-3.89 (m, 2H, C*H*OPMB & C*H*OH) ; 3.81 (s, 3H, ArOC*H*$_3$) ; 2.78 (d, *J* = 10.8, 1H, COC*H*C=C) ; 2.70 (t, *J* = 7.1, 2H, C=CC*H*$_2$C=C) ; 2.61 & 2.45 (2d, *J* = 5.0, 2H, OC*H*$_2$ époxyde), 2.18 (dt, *J* = 4.2, 13.6, 1H, C*H*axCH_2CHOPMB) ; 2.12-2.01 (m, 2H, C*H*$_2$*eq*CHOPMB & O*H*) ; 1.72 (tdd, *J* = 13.8, 4.0, 1.9, 1H, C*H*$_2$*ax*CHOPMB) ; 1.67 (s, 3H, C*H*$_3$) ; 1.62 (s, 3H, C*H*$_3$) ; 1.60 (s, 3H, C*H*$_3$) ; 1.05 (ddd, *J* = 2.6, 4.4, 13.5, 1H, C*H*eqCH_2CHOPMB).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 159.2, 131.7, 131.1, 130.6, 129.9, 129.2, 122.7, 113.8, 76.4, 70.9, 70.9, 60.6, 55.2, 51.0, 50.9, 28.2, 26.9, 25.6, 24.4, 17.7, 14.1.

Mixture of (3*R*, 4*S*, 5*S*, 6R)- 4-[(1*R*, 2*R*)-1,2-epoxy-1,5-dimethyl-hexen-1,4-dienyl]-5-hydroxy-6-*p*-methoxybenzyloxy -1-oxaspiro[2,5]octane **17** and (3*R*, 4*S*, 5*S*, 6R)- 4-[(1*S*, 2*S*)-1,2-epoxy-1,5-dimethyl-hexen-1,4-dienyl]-5-hydroxy-6-*p*-methoxybenzyloxy -1-oxaspiro[2,5]octane **17'**.



17 **17'**

$Ti(OiPr)_4$ (63 µL, 0.215 mmol) was added to a cold (- 25 °C) solution of epoxide **16** (40 mg, 0.107 mmol) in dichloromethane (1.5 mL). The mixture was stirred for 15 min and *tert*-butyl hydroperoxide (5.5 M in decane, 78 µL, 0.430 mmol) was added. The reaction was allowed to proceed for 12 h and 2 mL of a 10 % solution of tartaric acid was added. After work-up and extraction as above, preparative TLC (SiO_2, eluent :cyclohexane/AcOEt 7/3) afforded a ca 1 :1 mixture of **17** and **17'** (27 mg).

Epoxide **17** :

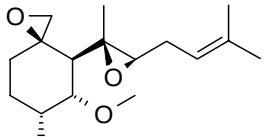
^{1}H-NMR (250 MHz, $CDCl_3$) : 7.26 & 6.87 (2d, *J* = 8.6, 4H, ArH) ; 5.18 (tm, *J* = 7.3, 1H, MeC=C*H*) ; 4.58 & 4.47 (2d, AB, *J* = 11.3, 2H, OCH_2pC_6H_4OMe) ; 4.04 (dt, *J* = 3.0, 11.0, 1H, C*H*OH) ; 3.92 (m, 1H, C*H*OPMB) ; 3.80 (s, 3H, ArOCH_3) ; 2.88 (d, *J* = 4.3, 1H, OCH_2 epoxide) ; 2.57 (t, *J* = 6.5, 1H, OC*H*CH_2 epoxide) ; 2.52 (d, *J* = 4.3, 1H, CH_2 epoxide) ; 2.47 (d, *J* = 10.0, 1H, O*H*) ; 2.40–1.97 (m, 4H, CH_2CH=, C*H*axCH_2CHOPMB, CH_2eqCHOPMB) ; 1.87 (d, *J* = 11, 1H, HOCHC*H*CMe) ; 1.73 (s, 3H, CH_3) ; 1.64 (s, 3H, CH_3) ; 1.70 (m, 1H, CH_2axCHOPMB) ; 1.26 (s, 3H, CH_3) ; 0.97 (m, 1H, C*H*eqCH_2CHOPMB).

Mixture **17** and **17**'

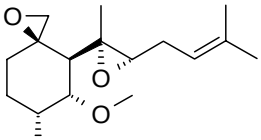
^{1}H-NMR (250 MHz, $CDCl_3$) :

:7.26 & 6.87 (4d, *J* = 8.6, 4H, ArH) ; 5.18 (2tm, *J* = 7.3, 1H, MeC=C*H*) ; 4.63-4.40 (4d, 2AB, *J* = 11.3, 2H, OC*H*$_2$pC_6H_4OMe) ; 4.04 (dt, *J* = 3.0, 11.0, 0.5H, C*H*OH **17**) ; 3.90 (m, 1H, C*H*OPMB) ; 3.85 (m, 0.5H, C*H*OH **17'**) ; 3.80 (2s, 3H, ArOC*H*$_3$) ; 3.17 (d, *J* = 4.5, 0.5H, OC*H*$_2$ epoxide **17'**) ; 2.88 (d, *J* = 4.3, 0.5H, OC*H*$_2$ epoxyde **17**) ; 2.74 (t, *J* = 6.5, 0.5H, OC*H*CH2 epoxide **17'**) ; 2.57 (t, *J* = 6.5, 0.5H, OC*H*CH2 epoxide **17**) ; 2.52 (d, *J* = 4.3, 0.5H, C*H*$_2$ epoxide **17**) ; 2.50-1.93 (m, 6H, C*H*$_2$CH=, C*H*axCH$_2$CHOPMB, CHO*H*, OC*H*$_2$ epoxide **17',** HOCHC*H*CMe **17',** C*H*$_2$eqCHOPMB) ; 1.87 (d, *J* = 11, 0.5H, HOCHC*H*CMe **17**) ; 1.73 & 1.70 (2s, 3H, C*H*$_3$) ; 1.70 (2m, 1H, C*H*$_2$axCHOPMB) ; 1.64 & 1.61 (2s, 3H, C*H*$_3$) ; 1.29 & 1.27 (2s, 3H, C*H*$_3$) ; 0.99 (2m, 1H, C*H*eqCH$_2$CHOPMB).

(3*R*, 4*S*, 5*S*, 6R)- 4-[(1*R*, 2*R*)-1,2-epoxy-1,5-dimethyl-hexen-1,4-dienyl]-5-hydroxy-6-*p*-methoxybenzyloxy -1-oxaspiro[2,5]octane **18** and (3*R*, 4*S*, 5*S*, 6R)- 4-[(1*S*, 2*S*)-1,2-epoxy-1,5-dimethyl-hexen-1,4-dienyl]-5-hydroxy-6-*p*-methoxybenzyloxy -1-oxaspiro[2,5]octane **18'**.



18



18'

Methyl iodide (0.25 mL, 4.12 mmol), was added to a solution of the above 1/1 mixture of epoxides **17** and **17'** (52 mg, 0.134 mmol) in cold (0°C) THF. NaH (60% in oil, 6.5 mg, 0.162 mmol) was added and the mixture was stirred for 15 min. DMF (1 mL) was added and stirring was continued for 8h at 20°C. Diethyl ether (2 mL) and saturated ammonium chloride (1 mL) were added. The residue obtained after extraction (ethyl acetate) and evaporation of the solvent was chromatographed on preparative TLC plates (eluent :cyclohexane/AcOEt 7/3) to provide **18** (26 mg) and **18'** (26 mg).
Overall yield 97 %.

Bis epoxide**18 :**

$[\alpha]_D^{20}$ = - 61° ($CHCl_3$, *C* = 0.85)

R_f = 0.30 (cyclohexane / AcOEt 75/25)

^{1}H-NMR (250 MHz, $CDCl_3$) : 7.30 & 6.86 (2d, *J* = 8.6, 4H, Ar*H*) ; 5.19 (tm, *J* = 7.4, 1H, C*H*=CMe_2) ; 4.65 & 4.57 (2d, AB, *J* = 12, 2H, OC*H*$_2$pC_6H_4OMe) ; 4.07 (dt, *J* = 2.3, 4.4, 1H, C*H*OPMB) ; 3.79 (s, 3H, ArOC*H*$_3$) ; 3.55 (dd, *J* = 2.4, 11.0, 1H, C*H*OMe) ; 3.37 (s, 3H, OC*H*$_3$) ; 2.94 (d, *J* = 4.3, 1H, OC*H*$_2$ epoxide) ; 2.55 (t, *J* = 6.4, 1H, OC*H*CH_2 epoxide) ; 2.50 (d, *J* = 4.3, 1H, OC*H*$_2$ epoxide) ; 2.34 (m, 1H, C*H*$_2$'CH=C) ; 2.21-2.08; (m, 2H, C*H*$_2$'CH=C & C*H*axCH_2CHOPMB) ; 2.11 (d, *J* = 11.0, 1H, C*H*CHOMe) ; 1.95 (m, 1H, C*H*$_2$eqCHOPMB) ; 1.72 (s, 3H, C*H*$_3$) ; 1.64 (s, 3H, C*H*$_3$) ; 1.60 (tdd, *J* = 13.7, 4.3, 2.2, C*H*$_2$axCHOPMB) ; 1.19 (s, 3H, C*H*$_3$) ; 0.98 (ddd, *J* = 3.1, 4.0, 13.5, 1H, C*H*eqCH_2CHOPMB).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 158.9, 134.6, 131.0, 129.2, 118.8, 113.6, 81.3, 70.9, 70.1, 60.8, 59.9, 58.5, 56.4, 55.2, 50.9, 47.5, 29.2, 27.4, 25.7, 25.3, 18.0, 14.1.

Bis epoxide **18'**

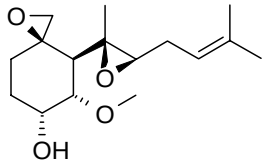
$[\alpha]_D^{20}$ = - 92 ° ($CHCl_3$, *C* = 1.0)

R_f = 0.45 (cyclohexane / AcOEt 75/25)

^{1}H-NMR (250 MHz, $CDCl_3$) : 7.28 & 6.86 (2d, *J* = 8.6, 4H, Ar*H*) ; 5.19 (tm, *J* = 7.0, 1H, C*H*=CMe_2) ; 4.59 (s, 2H, OC*H*$_2$pC_6H_4OMe) ; 4.05 (m, 1H, C*H*OPMB) ; 3.80 (s, 3H, ArOC*H*$_3$) ; 3.43 (dd, *J* = 2.6, 11.0, 1H, C*H*OMe) ; 3.31 (s, 3H, OC*H*$_3$) ; 3.28 (d, *J* = 4.5, 1H, OC*H*$_2$ epoxide) ; 2.74 (t, *J* = 6.5, 1H, OC*H*CH_2C=C) ; 2.59 (d, *J* = 4.5, 1H, OC*H*$_2$ epoxide) ; 2.27 (m, 1H, C*H*$_2$'CH=C) ; 2.17-1.94; (m, 3H, C*H*$_2$'CH=C, C*H*axCH_2CHOPMB & C*H*$_2$eqCHOPMB) ; 2.10 (d, *J* = 11.0, 1H, C*H*CHOMe) ; 1.71 (s, 3H, C*H*$_3$) ; 1.71-1.66 (m, 1H, C*H*$_2$axCHOPMB) ; 1.61 (s, 3H, C*H*$_3$) ; 1.22 (s, 3H, C*H*$_3$) ; 0.96 (dt, *J* = 14.6, 3.6, 1H, C*H*eqCH_2CHOPMB).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 159.0, 133.3, 130.9, 129.0, 119.1, 113.6, 81.4, 70.6, 70.2, 64.1, 60.1, 59.5, 56.5, 55.3, 52.0, 47.3, 29.1, 27.4, 25.8, 24.9, 17.9, 13.5.

(-)-fumagillol



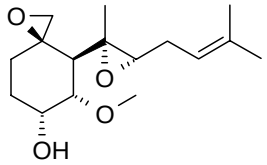
DDQ (15 mg, 68 µmol) was added to a solution of epoxide **18** (25 mg, 62 µmol) in CH_2Cl_2 (1 mL) containing water 65 µL. The mixture was stirred for 1.5 h at 20°C and the reaction was stopped by addition of saturated $NaHCO_3$ (0.5 mL). Work-up and chromatography (preparative TLC, eluent :cyclohexane/AcOEt 4/6) afforded pure fumagillol (14.6 mg, 83%)

$[\alpha]_D^{20}$ = - 66 ° (MeOH, *C* = 0.65)

^{1}H-NMR (250 MHz, $CDCl_3$) : 5.19 (tm, *J* = 7.4, 1H, C*H*=CMe_2) ; 4.35 (m, 1H, C*H*OH) ; 3.61 (dd, *J* = 2.7, 11.1, 1H, C*H*OMe) ; 3.48 (s, 3H, OCH_3) ; 2.93 (d, *J* = 4.3, 1H, OCH_2 epoxide) ; 2.57 (t, *J* = 6.5, 1H, OC*H*CH_2C=C) ; 2.52 (d, *J* = 4.3, 1H, OCH_2 epoxide) ; 2.41-2.30 (m, 2H, CH_2'CH=C & O*H*) ; 2.19 (dt, *J* = 4.5, 13.6, 1H, C*H*axCH_2CHOH) ; 2.21-2.09 (m, 1H, CH_2'CH=C) ; 1.99 (m, 1H, CH_2eqCHOH) ; 1.91 (d, *J* = 11.1, 1H, C*H*CHOMe) ; 1.75 (tdd, *J* = 13.9, 2.6, 4.5, 1H, C*H*axCHOH) ; 1.73 (s, 3H, CH_3) ; 1.64 (s, 3H, CH_3) ; 1.21 (s, 3H, CH_3) ; 0.97 (ddd, *J* = 2.5, 4.5, 13.6, 1H, C*H*eqCH_2CHOH).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 134.9, 118.5, 80.9, 64.0, 61.2, 59.8, 58.5, 56.5, 50.7, 47.0, 28.5, 27.3, 26.5, 25.7, 18.0, 13.9.

"Epi"-fumagillol



Using the same conditions as for the preparation of fumagillol, 12 mg (67 %) of "Epi"-fumagillol were obtained from 15 mg of **18'**.

^{1}H-NMR (250 MHz, $CDCl_3$) : 5.15 (tm, *J* = 7.1, 1H, C*H*=CMe_2) ; 4.31 (m, 1H, C*H*OH) ; 3.45 (dd, *J* = 2.8, 11.3, 1H, C*H*OMe) ; 3.39 (s, 3H, OCH_3) ; 3.25 (d, *J* = 4.5, 1H, OCH_2 epoxide) ; 2.63 (dd, *J* = 6.0, 7.1, 1H, OC*H*CH_2C=C) ; 2.62 (d, *J* = 4.5, 1H, OCH_2 epoxide) ; 2.34 (m, 1H, CH_2'CH=C) ; 2.24 (s, 1H, O*H*) ; 2.15 (dt, *J* = 4.4, 13.5, 1H, C*H*axCH_2CHOH) ; 2.11-1.94; (m, 2H, CH_2'CH=C & CH_2eqCHOH) ; 1.89 (d, *J* = 11.3, 1H, C*H*CHOMe) ; 1.78 (m, 1H, C*H*axCHOH) ; 1.72 (d, *J* = 1.2, 3H, CH_3) ; 1.63 (s, 3H, CH_3) ; 1.24 (s, 3H, CH_3) ; 0.97 (ddd, *J* = 2.7, 4.4, 13.5, 1H, C*H*eqCH_2CHOH).

^{13}C-NMR (62.9 MHz, $CDCl_3$) : 118.7, 81.2, 64.1, 64.0, 60.0, 59.1, 56.6, 51.8, 46.6, 28.4, 27.4, 26.7, 25.8, 17.9, 13.6.