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SYNTHESIS OF (+)-TRICYCLOHEXAPRENOL, A POSSIBLE PRECURSOR OF A FAMILY OF TRICYCLIC GEOTERPANES, AND SYNTHESIS OF AN ISOMER.

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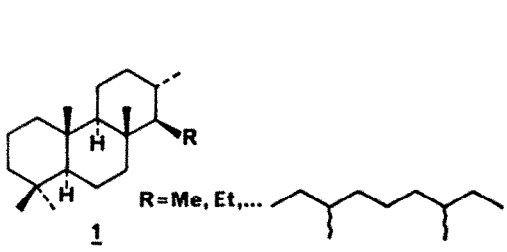
Abstract : *A synthesis of (+)-tricyclohexaprenol* 2 *starting from isocopalenol* 8 *and a synthesis of its isomer* 4 *starting from* ent-(14α H)-*isocopalenol* 26 *are described.*

The occurrence in many sediments and petroleums of a new family of tricyclic terpanes having structure 1 has been reported in recent years[1]. It has been postulated that these rather complex compounds are molecular fossils and that their precursor could be an hypothetical tricyclohexaprenol 2[§] resulting from the cyclization of hexaprenol[#]. It has also been noticed that the size, shape and polarity of compound 2 would make it a good cholesterol substitute in prokaryote membranes[2].

To allow an eventual identification of tricyclohexaprenol 2 in living organisms[+] as well as to provide a sample for the assessment of its membrane-reinforcing properties, we undertook its synthe-



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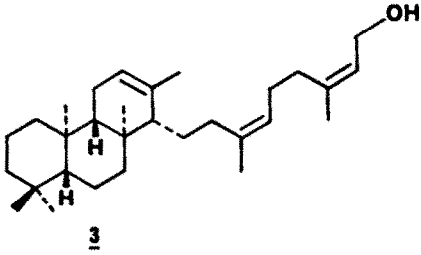

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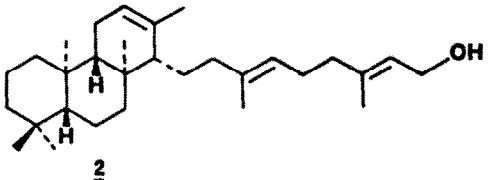

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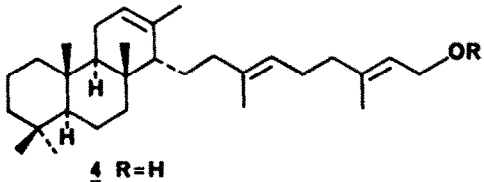


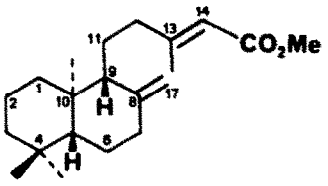
4 R=H

5 R=Me

[§] *The absolute configuration of the geoterpanes* 1 *is undetermined so far, whereas the tricyclohexaprenol which we have synthesized from (+)-isocopalenol* 8 *has the absolute configuration* 2.

[#] *Tricyclohexaprenol* 2 *which could result from an enzymatic cyclization, in an all-*pre*-chair conformation, of all-*trans*-hexaprenol is a possible precursor of the tricyclic terpanes* 1. *But we must be aware of the fact that tricyclohexaprenol* 3, *which could result from the cyclization, in a* pre*-chair-chair-boat conformation*[3], *of* ditrans, polycis*-hexaprenol (betulaprenol-6)*[20], *is another possible precursor. Tricyclohexaprenol* 3 *is readily accessible from our* Z*-dioxolane* 20.

[+] *The ring system of tricyclohexaprenol* 2 *is rather rare in nature. However,* ent*-isocopal-12-en-15-oic acid glycerides have been shown to occur among other terpenoic acid glycerides (acyclic, mono- and bicyclic) in dorid nudibranchs*[21].



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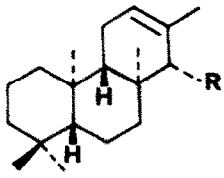
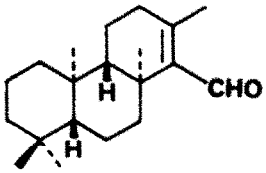


7 R=CO_2Me
8 R=CH_2OH
9 R=CHO
11 R=CH=CHCN
12 R=CH_2OMs
14 R=CH_2CN
15 R=CH_2CHO
16 R=$(CH_2)_2COCH_3$



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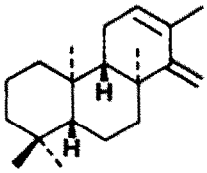

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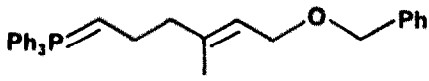

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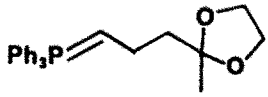

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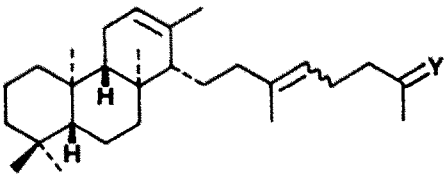
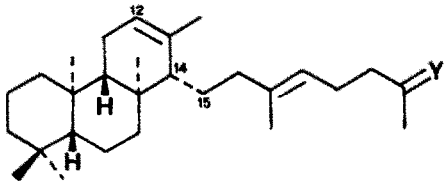


18 Y=$CHCH_2OCH_2Ph$
20 Y=OCH_2CH_2O



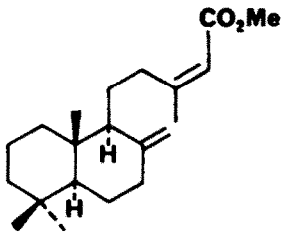
21 Y=O
22 Y=$CHCO_2Me$

Scheme 1

sis which we describe in this paper. In addition, we report a synthesis of the tricyclohexaprenol 4, bearing an axial instead of an equatorial side-chain, for comparison with a compound which has recently been obtained by enzymatic cyclization of all-trans-hexaprenyl methyl ether[3].

Easy access to the tricyclic ring system of compound 2 is provided by cyclization, in formic acid[4], of methyl ent-labda-8(17),13-E-dien-15-oate (methyl copalate) 6[5] into methyl isocopal-12-en-15-oate 7 followed by reduction into the known isocopal-12-en-15-ol 8[6].

To transform alcohol 8 into tricyclohexaprenol 2, the introduction of a geraniol unit at C-15 was needed. Inspection of a molecular model led us to the conclusion that the direct introduction of such a synthon would be disfavored by steric hindrance. Therefore, we decided to proceed stepwise. Our first target was methylketone 16. To obtain 16 we first oxidized[7] alcohol 8 into aldehyde 9 which



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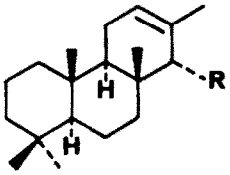
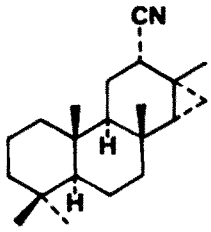


24 R=CO_2Me
26 R=CH_2OH
27 R=CH_2CN
29 R=CHO
30 R=CH=CHCN
31 R=CH_2CH_2CN
32 R=$(CH_2)_2COCH_3$



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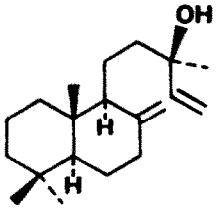

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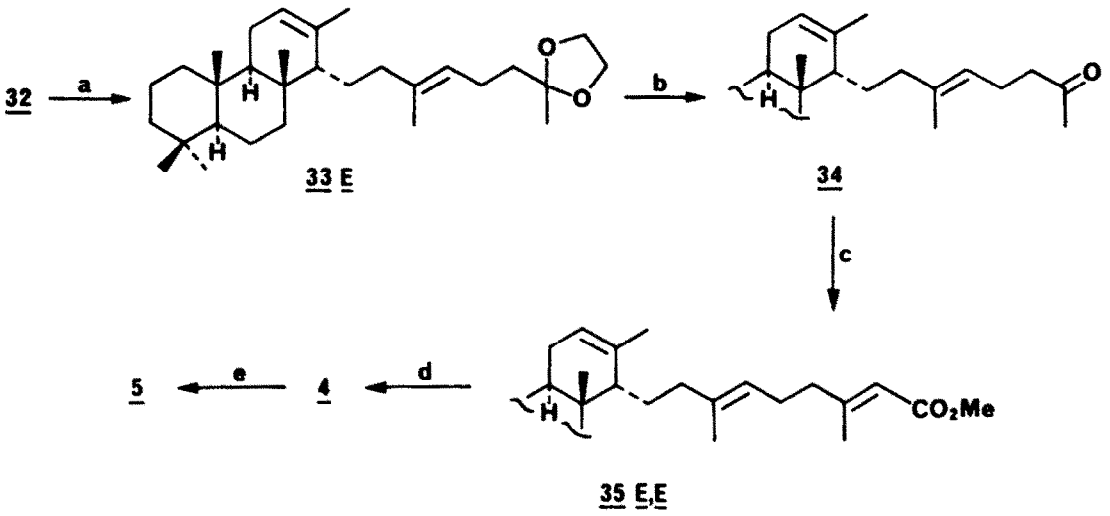
Scheme 2

we then treated with diethyl cyanomethylphosphonate-dimsylsodium[8] to obtain the α,β-unsaturated nitrile 11. But aldehyde 9 showed a marked tendency to isomerize into its conjugated counterpart 10, especially in the basic medium of the Wittig-Horner reaction, thus yielding an inseparable mixture of the α,β-unsaturated nitriles derived from aldehydes 9 and 10. While these steps were in progress, an alternative and finally better route to methylketone 16 was being explored. It consisted of treating the mesylate 12 with an unhindered nucleophile (LiC≡CH, $LiCH_2CN$, NaCN). The first results were discouraging since it turned out that 12 was either inert towards substitution or yielded mainly the elimination product isocopaladiene 13. This outcome can be explained by the possible antiperiplanar arrangement of the axial proton H-14 and of the mesyloxyl group. Nevertheless, after numerous experiments, we found that by treatment of mesylate 12 with NaCN under phase transfer catalysis, nitrile 14 could be obtained in 67% yield accompanied by only 24 % of diene 13 and 7 % of alcohol 8, resulting from the attack of the cyanide ion at sulfur.

Reduction of nitrile 14 with diisobutylaluminum hydride (DIBAH)[9] in toluene furnished a 84% yield of aldehyde 15 which, after reaction with the anion derived from (1-methoxyethyl)diphenylphosphine oxide[10] and hydrolysis of the intermediate enol ether, gave ketone 16 in 68 % yield. Reaction of ketone 16 with phosphorane 17, prepared from geraniol[11], gave a 6:4 mixture of Z,E/E,E benzyl ethers 18, which in our hands were inseparable. Since several attempts to form selectively the E,E benzyl ether 18 failed, ketone 16 was allowed to react with phosphorane 19[12]. This led to a 6:4 mixture of Z/E dioxolanes 20 which could be separated by careful flash-chromatography. After removal of the protection, the E-ketone 21 was converted into the desired tricyclohexaprenol 2 by condensation with the sodio salt of methyl diethylphosphonoacetate, chromatographic separation of the E,E and E,Z dienoates 22 and reduction with DIBAH in toluene of the E,E-isomer (overall yield from methylketone 16 : 20 %).

Comparison of the angular methyl signals in the ^{1}H-NMR spectrum of synthetic 2 with the corresponding signals of a tricyclohexaprenyl methyl ether obtained in M. Rohmer's group by enzymatic cyclization of all-trans-hexaprenyl methyl ether showed that the two compounds were different[3]. The assumption having then been made that the enzymatic cyclization product could have structure 5, we decided to undertake the synthesis of compound 5 to check this hypothesis.

Again, the ring system of tricyclohexaprenol 4 could be obtained from natural sources. It has previously been reported that by prolonged treatment with formic acid, methyl labda-8(17),13-Z-dien-15-oate 23 cyclizes into methyl ent-(14αH)-isocopal-12-en-15-oate 24[4]. To our knowledge, neither ester 23 nor the corresponding acid are naturally occurring compounds. However, it is known that when



Scheme 3 *a)* $Ph_3P{=}CHCH_2CH_2C(CH_3)OCH_2CH_2O$, *DMSO ; b) p-TsOH, acetone, water ; c)* $(EtO)_2P(O)CHNaCO_2Me$, *THF ; d) i-*Bu_2AlH, *toluene ; e) NaH, MeI, THF.*

manool 25 is allowed to react with pyridinium chlorochromate (PCC), it yields a 1:1 mixture of E and Z labda-8(17),13-dien-15-als[13]. After chromatographic separation of the Z-isomer, we oxidized it with sodium chlorite[14] into the corresponding acid which after esterification with diazomethane, gave ester 23 in 78 % yield from the aldehyde. In our case, the sodium chlorite oxidation was found more convenient and gave less Z to E isomerization than the manganese dioxide-hydrogen cyanide method[15] which has been used elsewhere for the E-isomer[16]. After reduction of ester 24 into alcohol 26[17] with lithium and aluminum hydride, we planned to transform the latter into methylketone 32 along the lines followed for methylketone 16. But when the mesylate derived from alcohol 26 was treated with sodium cyanide under phase transfer catalysis conditions, it led, in addition to several other compounds, to a mixture of two isomeric nitriles (40 % yield) which could be separated by repeated column chromatography on $AgNO_3$-silica gel. Whereas the NMR spectrum of the most abundant nitrile was in agreement with the expected compound 27, the spectrum of its companion exhibited no signals attributable to a vinyl proton or methyl. However, it displayed signals at δ 0.34 (1H), 0.68 (2H) and 2.99 (1H) which were consistent with structure 28 resulting from the nucleophilic attack of the cyanide ion at C-12 with displacement of the homoallylic mesyloxyl group.

This unexpected result made it necessary to investigate another route towards methylketone 32. Thus we decided to submit aldehyde 29 derived from alcohol 26, to a Wittig reaction. While reaction with 1-triphenylphosphoranylidene-2-propanone or the sodio derivative of dimethyl (2-oxopropyl)phosphonate gave only unchanged aldehyde 29, the reaction with diethyl cyanomethylphosphonate-dimsylsodium furnished the α,β-unsaturated nitrile 30 in 96 % yield. It must be noted that in this case, no significant isomerization of the endocyclic double bond occurred. After selective reduction of the conjugated double bond of 30 with magnesium turnings in methanol[18], treatment of the nitrile 31 with methyllithium in cold THF followed by acidic hydrolysis gave only low yields of methylketone 32. However, when methyllithium was replaced by methylmagnesium chloride, up to 66 % of methylketone 32 was obtained. Transformation of this latter compound into tricyclohexaprenol 4 was then performed as for tricyclohexaprenol 2 (Scheme 3).

Again the ^{1}H-NMR spectrum of the tricyclohexaprenyl methyl ether 5 was compared with the spectrum of the enzymatic cyclization product and again they were different. This led us to assume that the tricyclic ring-system of M. Rohmer's compound may well not have the proposed trans, anti, trans relative stereochemistry[19]. We are currently checking this assumption.

Addendum : While this paper was being prepared, Professor E.J. Corey informed us of the completion of his total synthesis of (±)-tricyclohexaprenol 2 (E.J. Corey & R.M. Burk, Tetrahedron Lett., (1987) 28, 6413).

EXPERIMENTAL

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Optical rotations were determined on chloroform solutions with a Perkin-Elmer 141 or 241 MC polarimeter. IR spectra were obtained from carbon tetrachloride solutions on a Perkin-Elmer 257, 597, or 1310 spectrophotometer and are reported in cm^{-1}. NMR spectra were recorded, unless otherwise stated, in chloroform-d solutions on a Bruker WH-90 (90 MHz), a Bruker WP-200SY (200 MHz), or a Bruker AM-400 (400 MHz) instrument; chemical shifts are reported in ppm downfield from tetramethylsilane. Mass spectra were recorded on a LKB 9000S or on a Thomson THN 208 spectrometer. Elemental analyses were performed at the Institut de Chimie, Strasbourg. Column chromatography was carried out under pressure on Merck 9385 silica gel (Kieselgel 60, 40-63 µm particle size) (flash chromatography). Thin layer chromatography was performed on Merck 5715 plates (Kieselgel 60 F254). Gas chromatographic analyses were conducted on a Carlo Erba 4130 chromatograph equipped with a FID detector and a fused silica capillary column (CP Sil 5 CB, 10 m x 0.33 mm). All reactions were run under a positive pressure of dry argon.

Isocopal-12-en-15-ol 8. This compound was prepared, as described in ref. 4 and 6, from methyl copalate 6, $[\alpha]_D$ -47° (c 1.08) (lit.[22] $[\alpha]_D$ -45°), obtained from copaiba oil according to ref. 5. Alcohol 8 : mp 126-127°C (from methanol) (lit.[6] mp 127-128°C) ; $[\alpha]_D$ +9.4° (c 0.97) (lit.[6] $[\alpha]_D$ +13.5° ; for the enantiomer[17, 21] $[\alpha]_D$ -9°) ; IR 3650, 1450, 1395, 840 ; NMR (200 MHz) 0.82 (s, 3H), 0.84 (s, 3H), 0.86 (s, 3H), 0.89 (d, J 0.6 Hz, 3H), 1.79 (s, 3H), 181-2.12 (m, 4H), 3.79 (AB of ABX J 11.2, 4.9 and 3.2 Hz, 2H), 5.51 (m, 1H).

Isocopal-12-en-15-al 9 and Isocopal-13-en-15-al 10. Alcohol 8 (100 mg, 0.34 mmole) was oxidized in dichloromethane with 6 molar equivalents of chromium trioxide-pyridine complex (Collins reagent). After 20 min, the reaction mixture was poured on top of a silica gel column and chromatographed (eluant : dichloromethane) to give aldehyde 9 (92 mg, 92 %) and a small amount of aldehyde 10 (6 mg). Aldehyde 9 : mp 67-68°C ; IR 2725, 1725; NMR (200 MHz) 0.81 (s, 3H), 0.86 (s, 3H), 0.92 (s, 3H) and 1.05 (s, 3H), 1.62 (br s, 3H), 2.00 (m, 2H), 2.60 (m, 1H), 5.65 (m, 1H), 9.70 (d, J 5.1Hz, 1H). Aldehyde 10 : IR 2725, 1675, 1610 ; NMR (200 MHz) 0.81 (s, 3H), 0.84 (s, 3H), 0.86 (s, 3H), 1.18 (s, 3H), 2.02 (s, 3H), 2.24 (m, 2H), 2.64 (dt, J 12.8 and 3.2 Hz, 1H), 10.03 (s, 1H).

Isocopal-12-en-15-ylideneacetonitrile 11. A 1.0 M solution of dimsylsodium in DMSO (2.0 ml) was added to a solution of diethyl cyanomethylphosphonate (412 µl, 2.56 mmoles) in dry DMSO (2 ml) and the mixture was stirred at room temperature for 1h. This solution (2.2 ml, 1.0 mmole) was then added under argon to a solution of aldehyde 9 (92 mg, 0.32 mmole) in dry THF (2 ml) and the mixture was allowed to react at room temperature for 1h. It was then quenched with aqueous ammonium chloride and extracted three times with ether. The combined organic phases were washed with 2N sulfuric acid, aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, evaporated and chromatographed on a silica gel column with hexane-ethyl acetate 97:3 as eluant to give an inseparable 4:1 mixture of nitrile 11 and of its isomer deriving from aldehyde 10 (84 mg, 0.27 mmole). IR 2220, 1625, 1445, 1385 ; NMR (200 MHz) 0.81, 0.84, 0.86, 0.90 (4s, 12H), 1.50 (br s, 2.4H), 2.52 (br d, J 11.0 Hz, 0.8H), 5.20 (d, J 16.7 Hz, 0.2H), 5.36 (d, J 16.3 Hz, 0.8H), 5.54 (m, 0.8H), 6.59 (dd, J 16.3 and 11.0 Hz, 0.8 H), 7.02 (br d, J 16.7 Hz, 0.2H).

Isocopal-12-ene-15-carbonitrile 14. Alcohol 8 (237 mg, 0.818 mmole) in dry dichloromethane (10 ml) was treated at 0°C, under argon, with triethylamine (170 µl, 1.23 mmole) and methanesulfonyl chloride (76 µl, 0.98 mmole). After 30 min, the reaction medium was diluted with dichloromethane (20 ml), washed with 1N hydrochloric acid and with water, and dried with magnesium sulfate. After evaporation of the solvent, chromatography on a silica gel column with hexane-ethyl acetate 9:1 as eluant, gave mesylate 12 (289 mg, 96 %), (NMR (60 MHz) 0.81 (s, 6H), 0.85 (s, 3H), 0.88 (s, 3H), 2.94 (s, 3H), 4.25 (AB of ABX, J 10, 5.5 and 3.5 Hz, 2H), 5.52 (m, 1H)). Mesylate 12 (289 mg, 0.785 mmole) was then dissolved in toluene (4 ml) and allowed to react at 100°C with a solution of sodium cyanide (192 mg, 3.92 mmoles) in water (2 ml) in the presence of Adogen 464 ® (90 mg). After 8h, the reaction medium was cooled to room temperature, the organic layer was separated and the aqueous layer was extracted three times with ether. The combined organic phases were washed twice with brine, dried over magnesium sulfate, evaporated, and chromatographed on a silica gel column with hexane-ethyl acetate 9:1 as eluant. This gave slightly impure nitrile 14 (169 mg, 0.564 mmole), 12,14-isocopaladiene 13 (51 mg, 0.19 mmole) and alcohol 8 (16 mg, 0.055 mmole). Submission of nitrile 14 to a second column chromatography with hexane-ether 97:3 as eluant, yielded pure nitrile 14 (158 mg, 64 % from alcohol 8). mp 105.5-106°C (from ethanol-water) ; $[\alpha]_D$ +14° (c 0.83) ; IR 3040, 2250, 1445, 1390 ; NMR (200 MHz) 0.82 (s, 6H), 0.86 (s, 3H), 0.89 (s, 3H), 1.79 (br s, 3H), 1.82-2.00 (m, 3H), 2.20 and 2.34 (m and AB of ABX, J 19.5, 7.0 and 6.5 Hz, 3H), 5.52 (m, 1H); MS, m/e (%) 299 (M^+, 30), 284 (7), 192 (100), 191 (37), 177 (38). Anal. Calcd for $C_{21}H_{33}N$: C, 84.21 ; H, 11.11 ; N, 4.68. Found : C, 84.6 ; H, 11.1 ; N, 4.6.

12,14-Isocopaladiene 13. mp 91.5-92°C (from methanol) (lit.[23] mp 93-94°C) ; $[\alpha]_D$ -108° (c 1.02) (lit.[23] $[\alpha]_D$ -130°) ; IR 3100, 1605, 885 ; NMR (200 MHz) 0.84 (s, 3H), 0.87 (s, 3H), 0.93 (s, 3H), 0.96 (s, 3H), 1.79 (d, J 1.5 Hz, 3H), 1.89-2.12 (m, 3H), 4.79 and 4.81 (2 br s, 2H), 5.64 (m, 1H).

Isocopal-12-ene-15-carbaldehyde 15. To a solution of nitrile 14 (158 mg, 0.527 mmole) in dry toluene (4 ml) at 0°C, was added dropwise a 0.5 M solution of diisobutylaluminum hydride in toluene (1.3 ml,

0.65 mmole). After completion of the addition, the cooling bath was removed and the reaction mixture was stirred for 1h at room temperature. Saturated aqueous ammonium chloride (1 ml) and 1N hydrochloric acid (100 µl) were then successively added and the mixture was vigorously stirred for 45 min. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic phases were washed with brine until neutral, dried over magnesium sulfate, evaporated and chromatographed on a silica gel column with hexane-ether 95:5 as eluant, to give aldehyde 15 (134 mg, 84 %). mp 84-84.5°C (from hexane) ; $[\alpha]_D$ -2.2° (c 1.15) ; IR 3030, 2710, 1730, 1390 ; NMR (200 MHz) 0.76 (s, 3H), 0.82 (s, 3H), 0.86 (s, 3H), 0.89 (s, 3H), 1.52 (br s, 3H), 1.80 (dt, J 12.2 and 3.0 Hz, 1H), 1.87-2.02 (m, 2H), 2.41 (m, 2H), 2.55 (m, 1H), 5.46 (m, 1H), 9.85 (t, J 1.7 Hz, 1H) ; MS, m/e (%) 302 (M^+, 18), 287 (3), 258 (7), 192 (100), 191 (34), 177 (64) ; Anal. Calcd for $C_{21}H_{34}O$: C, 83.38 ; H, 11.33. Found : C, 83.5 ; H, 11.5.

1-(12-Isocopalen-15-yl)-2-propanone 16. To a solution of (1-methoxyethyl)diphenylphosphine oxide (mp 77-78°C ; see ref. 10) (700 mg, 2.69 mmoles) in dry THF (7 ml) at 0°C was slowly added a 0.5 M solution of lithium diisopropylamide in THF (4.8 ml, 2.4 mmoles). After 10 min, the deep red solution was cooled to -78°C and a solution of aldehyde 15 (280 mg, 0.925 mmole) in dry THF (5 ml) was added dropwise. The reaction mixture was stirred for 30 min. Then the excess phosphine oxide anion was quenched by slow addition of 0.5 N benzoic acid in THF, until the solution faded to pale orange. N,N,N',N'-Tetramethylethylenediamine (2 ml) was added and the cooling bath was removed. The reaction mixture was stirred for 6 h at room temperature before being diluted with ether (25 ml), washed with 1N hydrochloric acid and brine, dried over magnesium sulfate, and evaporated to give a mixture of the expected enol ethers and of starting aldehyde 15. This mixture was dissolved in ether (60 ml), cooled to 0°C, stirred vigorously and treated with 70 % perchloric acid (400 µl). After 1h, the reaction mixture was washed with saturated aqueous sodium bicarbonate and with brine, dried over magnesium sulfate, evaporated and chromatographed on a silica gel column with hexane-ether 95:5 as eluant, to give starting aldehyde 15 (40 mg, 0.13 mmole) and ketone 16 (210 mg, 68 %). mp 54-54.5°C (from ethanol-water) (racemic 16 has been described as an oil[24]) ; $[\alpha]_D$ +31° (c 0.80) ; IR 3030, 1720, 1385 ; NMR (200 MHz) 0.75 (s, 3H), 0.82 (s, 3H), 0.86 (s, 3H), 0.88 (s, 3H), 1.66 (br s, 3H), 2.15 (s, 3H), 2.54 (m, 2H), 5.38 (m, 1H); MS, m/e (%) 330 (M^+, 36), 315 (3), 272 (100), 257 (17), 192 (21), 190 (59), 177 (33); Anal. Calcd for $C_{23}H_{38}O$: C, 83.57 ; H, 11.59. Found : C, 83.4 ; H, 11.8.

7-(12-Isocopalen-15-yl)-6-methyl-5-hepten-2-one ethylene acetals 20. A 1.0 M solution of dimsylsodium in DMSO (2.15 ml, 2.15 mmoles) was added to a solution of 3-(2-methyl-1,3-dioxolan-2-yl)propyl bromide (see ref. 12) (1.126 g, 2.39 mmoles) in dry DMSO-THF 5:2 (3.5 ml). The orange solution of phosphorane 19 was stirred at room temperature for 20 min. Then it was added to a solution of ketone 16 (158 mg, 0.478 mmole) in dry THF (3 ml), and the mixture was allowed to react overnight at room temperature. It was then quenched with water and extracted three times with ether. The combined organic phases were washed with 1N hydrochloric acid, saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate and evaporated. The crude product was dissolved in dichloromethane (3 ml) and chromatographed on a silica gel column with dichloromethane as eluant to give a 6:4 mixture (gas chromatography) of the Z and E acetals 20 (202 mg, 95 %). Careful chromatography of this mixture on a silica gel column with hexane-ether 97.5:2.5 as eluant, gave pure acetal 20 Z (93 mg, 0.21 mmole), pure acetal 20 E (66 mg, 0.15 mmole) and a mixture of both (30 mg). Acetal 20 Z (more mobile isomer) mp 57-58°C ; NMR (200 MHz) 0.71 (s, 3H), 0.82 (s, 3H), 0.86 (s, 3H), 0.87 (s, 3H), 1.32 (s, 3H) 1.70 (d, J 1.1 Hz, 3H), 1.74 (br s, 3H), 3.93 (m, 4H), 5.11 (t, J 6.8 Hz, 1H), 5.36 (m, 1H) ; MS, m/e (%) 442 (M^+, 0.5), 427 (3), 272 (94), 257 (19), 190 (64), 87 (100). Acetal 20 E (less mobile isomer) oil ; IR 1460, 1385, 1210, 1130, 1060; NMR (200 MHz) 0.72 (s, 3H), 0.82 (s, 3H), 0.86 (s, 3H), 0.87 (s, 3H), 1.33 (s, 3H), 1.62 (br s, 3H), 1.69 (br s, 3H), 3.94 (m, 4H), 5.12 (t, J. 6.6 Hz, 1H), 5.36 (m, 1H) ; MS, m/e (%) 442 (M^+, 0.4), 427 (3), 272 (100), 257 (26), 190 (79) 87 (68).

7-(12-Isocopalen-15-yl)-6-methyl-(E)-5-hepten-2-one 21. To a solution of acetal 20 E (57 mg, 0.13 mmole) in acetone-water 8:2 (18 ml) was added p-toluenesulfonic acid monohydrate (60 mg, 0.31 mmole). This solution was allowed to stand at room temperature for 48 h. It was then concentrated under reduced pressure, diluted with water and extracted three times with ether. The ether extracts were washed with saturated aqueous sodium bicarbonate and with brine, dried over magnesium sulfate, evaporated and chromatographed on a silica gel column with hexane-ether 95:5 as eluant, to give ketone 21 (50 mg, 97 %). Oil ; IR 1720, 1665, 1455, 1385, 1155 ; NMR (200 MHz) 0.72 (s, 3H), 0.82 (s, 3H), 0.86 (s, 3H), 0.87 (s, 3H), 1.62 (br s, 3H), 1.68 (br s, 3H), 2.14 (s, 3H), 2.26 (q, J 7 Hz, 2H), 2.47 (t, J 6.9 Hz, 2H), 5.08 (t, J 7.0 Hz, 1H), 5.35 (m, 1H) ; MS, m/e (%) 398 (M^+, 1), 383 (2), 272 (100), 257 (22), 190 (72).

Methyl 8-(12-isocopalen-15-yl)-3,7-dimethyl-2,6-octadienoates 22. Methyl diethylphosphonoacetate (368µl, 2.0 mmoles) was added to a suspension of oil-free sodium hydride (43 mg, 1.8 mmole) in dry THF (1.4ml) and allowed to react at room temperature until the hydrogen evolution ceased. The clear phosphonoacetate anion solution was then added to a solution of ketone 21 (45 mg, 0.11 mmole) in dry THF (1.5 ml) and the reaction was stirred at room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride and extracted three times with ether. The combined ether extracts were washed with 1N hydrochloric acid, with saturated aqueous sodium bicarbonate and with brine, dried over magnesium sulfate, evaporated and chromatographed on a silica gel column with hexane-ether 97.5:2.5 as eluant, to give : Dienoate 22 E,Z (more mobile isomer) (10 mg, 19 %) ; NMR (90 MHz) 0.72 (s, 3H), 0.82 (s, 3H), 0.87 (s, 6H), 1.63 (br s, 3H), 1.68 (br s, 3H), 1.89 (d, J 1.5 Hz, 3H), 3.67 (s, 3H), 5.19 (t, J 6.6 Hz, 1H), 5.37 (m, 1H), 5.68 (m, 1H) ; MS, m/e (%) 454 (M^+, 0.5), 439 (2), 272 (100), 257 (25), 203 (7),

190 (82). Dienoate 22 E,E (less mobile isomer) (37 mg, 71%) ; IR 1720, 1645, 1225, 1145 ; NMR (90 MHz) 0.72 (s, 3H), 0.82 (s, 3H), 0.86 (s, 6H), 1.61 (br s, 3H), 1.68 (br s, 3H), 2.17 (d, J 1.2 Hz, 3H), 3.68 (s, 3H), 5.12 (m, 1H), 5.38 (m, 1H), 5.69 (m, 1H) ; MS, m/e (%) 454 (M^+, 0.4), 439 (2), 423 (4), 272 (100), 257 (23), 203 (8), 190 (76).

(+)-Tricyclohexaprenol 2 [8-(12-Isocopalen-15-yl)-3,7-dimethyl-(2E,6E)-2,6-octadienol]. To a solution of dienoate 22 E,E (37 mg, 0.081 mmole) in toluene (3 ml) at -78°C was added a 0.5 M solution of diisobutylaluminum hydride in toluene (0.40 ml, 0.20 mmole). The reaction was stirred for 1 h. Water was then added and the mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with 1N hydrochloric acid, saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, evaporated and chromatographed on a silica gel column with hexane-ethyl acetate 9:1 as eluant, to give tricyclohexaprenol 2 (32 mg, 92 %). Oil ; $[\alpha]_D$ +25° (c 1.55) ; IR 3620, 3020, 1665, 1460, 1385, 1000; NMR (200 MHz) 0.72 (s, 3H), 0.82 (s, 3H), 0.86 (s, 3H), 0.87 (s, 3H), 1.61 (br s, 3H), 1.69 (br s, 6H), 4.15 (d, 6.9 Hz, 2H), 5.11 (t, J 6.8 Hz, 1H), 5.36 (m, 1H), 5.43 (t, J 6.9 Hz, 1H) ; MS, m/e (%) 426 (M^+, 4), 408 (1), 393 (1), 272 (100), 257 (14), 203 (5), 190 (52), 177 (10) ; HRMS Calcd for $C_{30}H_{50}O$: M, 426.3862. Found : M, 426.3860.

ent-(14α H)-Isocopal-12-en-15-ol 26. This compound was prepared from manool 25, via methyl labda-8(17),13-Z-dien-15-oate 23, according to ref. 13, 14, 4 and 17. mp 107-107.5°C (from methanol-water)(lit.[17] mp 107-109°C) ; $[\alpha]_D$ +56° (c 0.96) (lit.[17] $[\alpha]_D$ +52.6°) ; IR 3630, 1455, 1390, 1045 ; NMR (200 MHz) 0.83 (s, 3H), 0.87 (s, 3H), 0.89 (s, 6H), 1.72 (m, J 1.8 Hz, 3H), 3.71 (AB of ABX, J 12.0, 4.5, and 2.4 Hz, 2H), 5.54 (m, 1H) ; MS, m/e (%) 290 (M^+, 100), 275 (16), 272 (13), 259 (35), 192 (73), 191 (22), 177 (27) ; Anal. Calcd for $C_{20}H_{34}O$: C, 82.69 ; H, 11.80. Found : C, 82.8 ; H, 11.9.

ent-(14α H)-Isocopal-12-ene-15-carbonitrile 27 and ent-(14α H)-13,15-cyclo-12-isocopalanecarbonitrile 28. Alcohol 26 (72 mg, 0.25 mmole) in dry dichloromethane (3 ml) was treated at 0°C, with triethylamine (51 µl, 0.37 mmole) and methanesulfonyl chloride (23 µl, 0.30 mmole). After 30 min, the reaction mixture was diluted with dichloromethane (7 ml) and washed twice with water. After evaporation of the solvent, the rather unstable, crude mesylate was dissolved in toluene (2 ml) and allowed to react at 95°C with a solution of sodium cyanide (60 mg, 1.2 mmole) in water (1 ml) in the presence of Adogen 464® (30 mg). After 15 h, the reaction medium was cooled to room temperature, the organic layer was separated and the aqueous layer was extracted twice with ether. The combined organic phases were washed with brine, dried over magnesium sulfate, evaporated and chromatographed on a silica gel column with hexane-ether 9:1 as eluant. This led to the isolation of the nitrile spot (30 mg, 40 %) which was shown by gas chromatography-mass spectrometry to be essentially a 7:3 mixture of two isomeric compounds. Repeated column chromatography on 5 % silver nitrate-silica gel with hexane-ether 95:5 as eluant gave pure samples of the two compounds : Nitrile 27 (major, less mobile isomer). mp 94-95°C ; IR 2240, 1440, 1390 ; NMR (200 MHz) 0.83 (s, 3H), 0.89 (s, 3H), 0.90 (s, 3H), 0.93 (s, 3H), 1.73 (d, J 2.0 Hz, 3H), 2.39 (AB of ABX, J 17.6, 7.2, and 3.7 Hz, 2H, H-15), 5.44 (m, 1H, H-12) ; MS, m/e (%) 299 (M^+, 40), 284 (69), 205 (11), 202 (10), 192 (100), 191 (45), 177 (58). Nitrile 28 (minor, more mobile isomer). IR 3070 (ν_{as} CH_2 cyclopropanique), 2240, 1455, 1390 ; NMR (400 MHz) 0.34 (m, J 8.1 and 4.7 Hz, 1H, H cyclopropanique), 0.68 (m, J 6.0, 8.1, and 4.7 Hz, 2H, H cyclopropaniques), 0.80 (s, 3H), 0.81 (s, 3H), 0.86 (s, 3H), 1.10 (s, 3H), 1.17 (s, 3H), 2.99 (dd, J 7.7 and 2.0 Hz, 1H, H-12) ; NMR (400 MHz, benzene-d_6) 0.31 (AB of ABX, J 9.0, 5.9 and 5.7 Hz, 2H, H-14, H-15), 0.73 (s, 3H), 0.79 (t, J 5.8 Hz, 1H, H-15), 0.88 (s, 3H), 0.94 (s, 3H), 0.95 (s, 6H), 2.52 (dd, J 8.0 and 1.6 Hz, 1H, H-12) ; MS, m/e (%) 299 (M^+, 37), 284 (78), 257 (10), 228 (12), 214 (39), 202 (23), 191 (17), 188 (28), 137 (100), 123 (98).

ent-(14α H)-Isocopal-12-en-15-al 29. Alcohol 26 (180 mg, 0.62 mmole) was oxidized in dry dichloromethane with 6 molar equivalents of chromium trioxide-pyridine complex (Collins reagent). After 50 min, the reaction mixture was poured on top of a silica gel column and chromatographed (eluant : dichloromethane) to give aldehyde 29 (163 mg, 91 %). mp 49.5-51.5°C ; IR 2715, 1715, 1675, 1390 ; NMR (200 MHz) 0.83 (s, 3H), 0.86 (s, 3H), 0.91 (s, 6H), 1.56 (br s, 3H), 2.21 (d, J 5.3 Hz, 1H), 5.73 (m, 1H), 9.58 (d, J 5.3 Hz, 1H) ; MS, m/e (%) 288 (M^+, 100), 273 (12), 259 (25), 205 (17), 191 (34), 177 (25).

ent-(14α H)-Isocopal-12-en-15-ylideneacetonitriles 30. These compounds (E and Z isomers) were obtained in the same way than compound 11, by treatment for 4 h of aldehyde 29 (163 mg, 0.566 mmole) in dry THF (1 ml) with a 0.38 M solution of diethyl cyanomethylphosphonate anion in dry DMSO-THF 4:1 (9ml, 3.42 mmoles). A 7:3 mixture of the E and Z nitriles 30 was obtained (170 mg, 96 %). IR 2220, 1625, 1460, 1390 ; NMR (200 MHz), signals of the E-isomer, 0.82 (s), 0.87 (s, 2.1H), 0.88 (s, 2.1H), 0.92 (s, 2.1H), 1.55 (q, J 1.8 Hz, 2.1H), 2.09 (d, J 9.7 Hz, 0.7H), 5.25 (dd, J 16.2 and 0.7 Hz, 0.7H), 5.51 (m, 0.7H), 6.65 (dd, J 16.2 and 9.7 Hz, 0.7H) ; signals of the Z-isomer, 0.82 (s), 0.85 (s, 0.9H), 0.90 (s, 0.9H), 0.97 (s, 0.9H), 1.62 (q, J 1.5 Hz, 0.9H), 2.61 (d, J 11.3 Hz, 0.3H), 5.37 (d, J 10.7 Hz, 0.3H), 5.48 (m, 0.3H), 6.36 (t, J 11.0 Hz, 0.3 H) ; MS, m/e (%) E-isomer 311 (M^+, 9), 296 (8), 207 (6), 192 (100), 191 (13), 177 (33), 137 (23) ; Z-isomer 311 (M^+, 12), 296 (12), 207 (9), 192 (100), 191 (13), 177 (32), 158 (16), 137 (26).

ent-(14α H)-Isocopal-12-en-15-ylacetonitrile 31. Magnesium turnings (1.52 g, 62.5 m at-g) were added to a stirred solution of the nitriles 30 (485 mg, 1.56 mmole) in dry methanol (30 ml). After 15 min, the exothermic reaction was moderated with an ice bath. After 2 h, the supernatant was separated from

the magnesium in excess, which was washed with additionnal methanol. Cold water (20 ml) was then added to the combined methanol phases, followed by enough 1 N hydrochloric acid to obtain a clear solution. This solution was then extracted three times with ether. The ether extracts were washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, evaporated and chromatographed on a silica gel column with toluene as eluant, to give nitrile 31 (348 mg, 71 %). mp 108-108.5°C (from hexane) ; $[\alpha]_D$ + 78° (c 0.90) ; IR 3040, 2250, 1455, 1390 ; NMR (200 MHz) 0.83 (s, 3H), 0.89 (s, 9H), 1.70 (d, J 1.8 Hz, 3H), 2.38 (m, 2H), 5.31 (m, 1H) ; MS m/e (%) 313 (M^+, 24), 298 (29), 281 (7), 270 (4), 192 (100), 191 (29), 177 (48) ; Anal. Calcd for $C_{22}H_{35}N$: C, 84.28 ; H, 11.25 ; N, 4.47. Found : C, 84.4 ; H, 11.3 ; N, 4.5.

ent-1-[(14α H)-Isocopal-12-en-15yl]-2-propanone 32. To a stirred solution of nitrile 31 (49 mg, 0.16 mmole) in dry THF (5 ml), at room temperature, was added a 3.0 M solution of methylmagnesium chloride in THF (300 µl, 0.90 mmole). After 40 min, additionnal methylmagnesium chloride solution (1.30 ml, 3.90 mmoles) was added to the reaction, over a 5 h period. 1N Hydrochloric acid (5.0 ml) was then added and the mixture was vigorously stirred for 1h. The organic layer was separated and the aqueous layer was extracted three times with ether. The combined organic phases were washed with brine until neutral, dried over magnesium sulfate, evaporated and chromatographed on a silica gel column with hexane-ether 9:1 as eluant, to give starting nitrile 31 (4 mg, 0.01 mmole) and ketone 32 (34 mg, 66 %). Oil ; IR 3040, 1715, 1455, 1385 ; NMR (200 MHz) 0.82 (s, 3H), 0.867, 0.873, and 0.877 (3s, 9H), 1.66 (q, J 1.6 Hz, 3H), 2.15 (s, 3H), 2.50 (t, J 8.2 Hz, 2H), 5.26 (m, 1H) ; MS, m/e (%) 330 (M^+, 100), 315 (7), 312 (8), 272 (100), 257 (23), 192 (20), 190 (66), 177 (34).

ent-7-[(14α H)-Isocopal-12-en-15-yl]-6-methyl-5-hepten-2-one ethylene acetals 33. These compounds were obtained in the same way than the acetals 20, by treatment of ketone 32 (157 mg, 0.476 mmole) with phosphorane 19. A 6:4 mixture of the Z and E acetals 33 (200 mg, 95 %) was obtained. Careful chromatography of this mixture on a silica gel column, with hexane-ether 97:3 as eluant, gave pure acetal 33 Z (85 mg, 0.19 mmole), pure acetal 33 E (62 mg, 0.14 mmole) and a mixture of both (37 mg). Acetal 33 Z (more mobile isomer) oil ; IR 1390, 1070 ; NMR (200 MHz) 0.83 (s, 3H), 0.88 (s, 6H), 0.89 (s, 3H), 1.32 (s, 3H), 1.67 and 1.70 (2m, J 1.6 Hz and J 1.2 Hz, 6H), 3.93 (m, 4H), 5.10 (t, J 7.1 Hz, 1H), 5.21 (m, 1H) ; ^{13}C-NMR (50 MHz, chloroform-d) 23.4 (-(Me)C=, side chain), 34.2 (C-7, side chain) ; MS, m/e (%) 442 (M^+, 8), 427 (5), 272 (2), 260 (6), 245 (7), 191 (5), 182 (43), 87 (100). Acetal 33 E (less mobile isomer) oil; IR 1385, 1065 ; NMR (200 MHz) 0.83 (s, 3H), 0.86 (s, 3H), 0.88 (s, 6H), 1.33 (s, 3H), 1.63 (m, 6H), 3.94 (m, 4H), 5.13 (t, J 7.2 Hz, 1H), 5.20 (m, 1H) ; ^{13}C-NMR (50 MHz, chloroform-d) 16.1 (-(Me)C=, side chain), 41.9 (C-7, side chain) ; MS, m/e (%) 442 (M^+, 12), 427 (8), 272 (21), 260 (8), 245 (12), 190 (16), 182 (76), 87 (100).

ent-7-[(14αH)Isocopal-12-en-15-yl]-6-methyl-(E)-5-hepten-2-one 34. The procedure already described for the obtention of ketone 21 was employed to transform acetal 33 E (62 mg, 0.14 mmole) into ketone 34 (44 mg, 79 %). Oil ; IR 1715, 1455, 1385 ; NMR (200 MHz) 0.83 (s, 3H), 0.86 (s, 3H), 0.88 (s, 6H), 1.63 (br s, 6H), 2.14 (s, 3H), 2.26 (q, J 6.9 Hz, 2H), 2.47 (t, J 6.9 Hz, 2H), 5.08 (t, J 7.1 Hz, 1H), 5.21 (m, 1H) ; MS, m/e (%) 398 (M^+, 8), 383 (3), 272 (8), 260 (8), 245 (16), 191 (10), 177 (12), 138 (100).

Methyl ent-8-[(14α H)-isocopal-12-en-15-yl]-3,7-dimethyl-2,6-octadienoates 35. The procedure already described for the obtention of the esters 22 was employed to transform ketone 34 (38 mg, 0.095 mmole) into the esters 35 : Dienoate 35 E,Z (more mobile isomer) (8 mg, 18 %) oil ; IR 1720, 1650, 1440, 1380, 1160; NMR (200 MHz) 0.83 (s, 3H), 0.86 (s, 3H), 0.88 (s, 6H), 1.63 (s, 6H), 1.90 (d, J 1.3 Hz, 3H), 2.17 (q, J 7.7 Hz, 2H), 2.66 (m, 2H), 3.67 (s, 3H), 5.18 and 5.20 (t, J 7.7 Hz, and m, 2H), 5.66 (br s, 1H) ; MS, m/e (%) 454 (M^+, 34), 439 (8), 423 (5), 407 (10), 272 (29), 260 (15), 245 (21), 194 (100), 135 (87). Dienoate 35 E,E (less mobile isomer) (30 mg, 69%) oil ; IR 1720, 1650, 1435, 1385, 1225, 1145 ; NMR (200 MHz) 0.83 (s, 3H), 0.86 (s, 3H), 0.88 (s, 6H), 1.62 and 1.64 (br s and q, J 1.5 Hz, 6H), 2.17 (d, J 1.3 Hz, 3H), 3.68 (s, 3H), 5.10 (m, 1H), 5.21 (m, 1H), 5.68 (br s, 1H) ; MS, m/e (%) 454 (M^+, 18), 439 (5), 423 (9), 407 (6), 272 (21), 260 (100), 245 (64), 135 (66).

Tricyclohexaprenol 4. The procedure already described for the obtention of tricyclohexaprenol 2 was employed to reduce dienoate 35 E,E (23 mg, 0.051 mmole) into tricyclohexaprenol 4 (20 mg, 92 %). Oil; IR 3620, 1665, 1440, 1380, 1000 ; NMR (200 MHz) 0.83 (s, 3H), 0.87 (s, 3H), 0.88 (s, 6H), 1.62 (br s, 3H), 1.64 (q, J 1.6 Hz, 3H), 1.69 (br s, 3H), 4.15 (d, J 6.6 Hz, 2H), 5.12 (t, J 6.3 Hz, 1H), 5.21 (m, 1H), 5.42 (t, J 7.1 Hz, 1H) ; MS, m/e (%) (TMS ether) 498 (M^+, 10), 483 (3), 408 (13), 393 (6), 340 (4), 313 (5), 272 (14), 259 (32), 245 (20), 148 (90), 81 (97), 73 (100).

Tricyclohexaprenyl methyl ether 5. A solution of tricyclohexaprenol 4 (10 mg, 0.023 mmole) in dry THF (2 ml) and methyl iodide (100 µl, 1.60 mmole) were added to a suspension of oil free sodium hydride (10 mg, 0.42 mmole) in dry THF (2 ml). This mixture was stirred at 35°C for 1h. It was then quenched with ethanol followed by water and extracted three times with ether. The organic extracts were washed with brine, dried over magnesium sulfate, evaporated and chromatographed on a silica gel column with hexane-ethyl acetate 95:5 as eluant, to give the methyl ether 5. (9 mg, 87 %). Oil ; IR 1660, 1450, 1380, 1090 ; NMR (200 MHz) 0.83 (s, 3H), 0.86 (s, 3H), 0.88 (s, 6H), 1.61 (br s, 3H), 1.64 (q, J 1.4 Hz, 3H), 1.68 (br s, 3H), 3.32 (s, 3H), 3.93 (d, J 6.8 Hz, 2H), 5.13 (t, J 6 Hz, 1H), 5.21 (m, 1H), 5.36 (t, J 7.0 Hz, 1H) ; MS, m/e (%) 440 (M^+, 20), 425 (1), 408 (10), 393 (7), 340 (6), 313 (6), 272 (22), 260 (24), 245 (27), 190 (38), 135 (96), 81 (100) ; HRMS Calcd for $C_{31}H_{52}O$: M, 440. 4018. Found : M, 440.4009.

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