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ENANTIOSELECTIVE SYNTHESIS OF 11-HOMODRIM-7-EN-9α,12,13-TRIOL

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The enantioselective synthesis of 11-homodrim-7-en-9α,12,13-triol, a convenient synthon for preparing polyfunctional 11-homodrimane sesquiterpenoids, was carried out starting from norambreinolide, a cleavage product available from several bicyclic labdane diterpenoids.

Keywords: synthesis, 11-homodrimane compounds, norambreinolide.

One of the main motivators for the unwavering interest of chemists in drimane sesquiterpenoids is their broad spectrum of biological activity [1, 2]. Several syntheses of them have been developed because most of them are difficultly accessible compounds and occur in trace quantities as complicated mixtures in natural sources [2–4]. However, many of the syntheses are multi-step and inefficient. In addition, the starting compounds are not always readily available.

In contrast with drimane sesquiterpenoids, homodrimane (tetranorlabdane) compounds are more available because they can be prepared by relatively simpler methods from readily available labdane diterpenoids (sclareol, larixol, abienols, manool, manoyloxides, and zamoranic, communic, and labdanolic acids, etc.) [5].

The preparation of tetranorlabdane derivatives has been often reported. Several of these derivatives have been widely applied in the perfume, cosmetic, and tobacco industries owing to their amber aroma. Judging from the literature, most homodrimanes have not been tested for types of activity other than organoleptic. However, it was recently found that 11-homopolygodial (**1**) had antifeedant activity greater than that of natural polygodial (**2**) [6]. Therefore, it seemed interesting to synthesize polyfunctional homodrimanes.

Herein results from the synthesis of 11-homodrim-7-en-9α,12,13-triol (**3**) from commercially available norambreinolide (**4**) are reported.

Norambreinolide (**4**) was reduced by $LiAlH_4$ by the literature method [7] to sclarodiol (**5**), which was identified by comparison with an authentic sample. Diol **5** was acetylated under standard conditions by a mixture of acetic anhydride and pyridine. According to TLC, the reaction products included the desired 12-monoacetate of sclarodiol (**6**) and an impurity of a less polar compound that was separated by chromatography over a column of SiO_2 (Scheme 1). Hydroxyacetate **6** was identified by comparison with an authentic sample that was obtained by us earlier [8]. Its spectral properties agreed with those published [9–10]. Reaction of **6** with triphenylphosphine and iodine by the literature method [11] formed a mixture of unsaturated acetates **7**, in which the isomer with the tetra-substituted double bond dominated (64%) according to NMR spectroscopy. The contents of the isomers with the tri-substituted and exocyclic double bonds were 19 and 17%, respectively. Dehydration of **6** by phosphoryl chloride in pyridine afforded a product in which the isomer with the exocyclic double bond dominated [12]. The mixture of acetates **7** was oxidized by sodium chromate by the literature method [13] to 12-acetoxy-11-homodrim-8-en-7-one (**8**) (60% yield).

Ketoacetate **8** was reacted with *N*-bromosuccinimide (NBS) in order to functionalize the C-13 methyl. This produced 12-acetoxy-13-bromo-11-homodrim-8-en-7-one (**9**) in high yield (80%) (Scheme 1). Its structure was confirmed by spectral data (see Experimental). Compound **9** reacted smoothly with potassium acetate in DMF to substitute the Br by acetoxy and form ketodiacetate **10** in good yield (80%). Saponification under mild conditions by K_2CO_3 in MeOH under an inert atmosphere produced ketodiol **11**, which gave 8(9)-α-epoxy-11-homodrim-12,13-diol-7-one (**12**) upon oxidation by hydrogen peroxide in the presence of sodium hydroxide in MeOH (Scheme 1).

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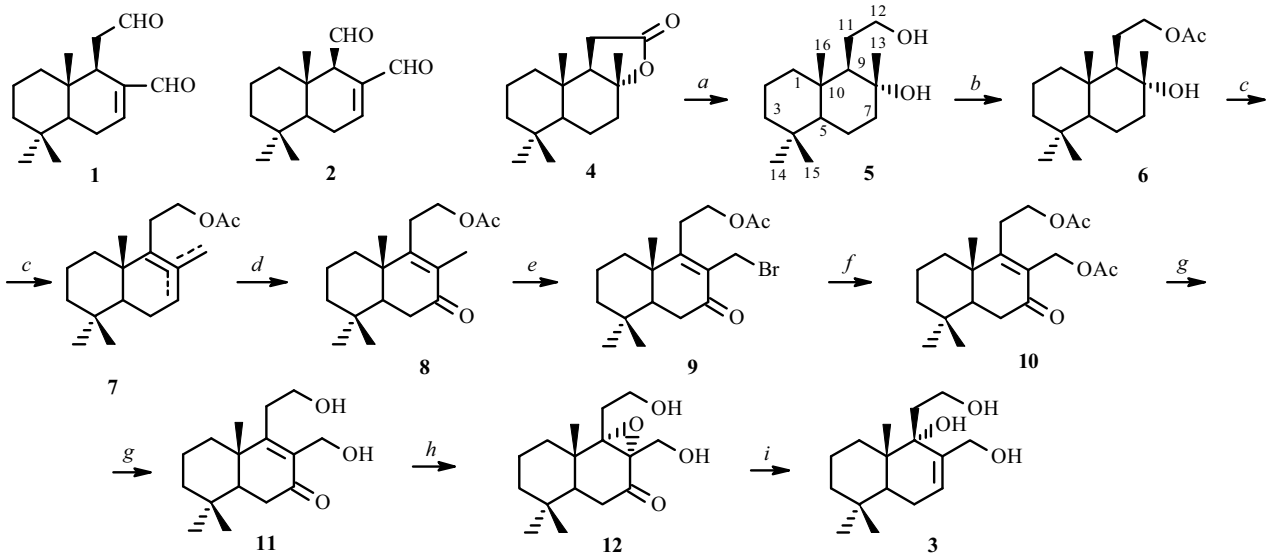
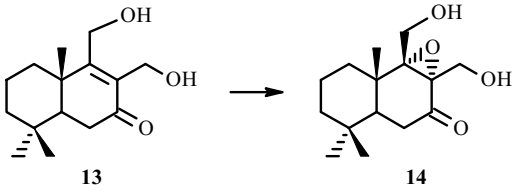


a. $LiAlH_4$, Et_2O, 2 h, 94.5%; *b*. Ac_2O, Py, 2 h, 20°C, 98%; *c.* Ph_3P, I_2, CH_2Cl_2, 2 h, 20°C, 98%; *d.* Na_2CrO_4, AcONa, Ac_2O, AcOH, C_6H_6, 60°C, 2 h, 60%; *e*. NBS, CCl_4, 2 h, Δ, 80%; *f*. AcOK, DMFA, 22°C, 2 h, 80%; *g*. 1% K_2CO_3, MeOH, 1 h, 22°C, 76%; *h*. H_2O_2, NaOH, MeOH, 22°C, 5 h, 76%; *i*. $NH_2NH_2 \cdot H_2O$, 2.5 h, 87%

Scheme 1

The oxidizing reagent should attack **11** from the α-side because its β-side is sterically strongly shielded. This followed from a literature search for compounds that were structurally similar to **11** [14, 15]. Epoxidation of unsaturated diol **13** upon oxidation by metachloroperbenzoic acid to form epoxydiol **14** (85% yield) also occurred stereospecifically [16].



NMR spectral data indicated that the epoxide group in **12** had the α-orientation. The degree of deshielding of the C-10 methyl in **12** was similar to that for epoxydiol **14**.

Reaction of **12** with hydrazine hydrate (Wharton–Bolen reaction) formed 11-homodrim-7-en-9α,12,13-triol (**3**) in high yield (87%). Its structure was confirmed by spectral data (see Experimental). Its overall yield calculated from norambreinolide (**4**) was 14.3%. The product yields were high in most steps. The used reagents were available and inexpensive.

EXPERIMENTAL

Melting points were determined on a Boetius heating stage. IR spectra were recorded on a Specord 74 spectrophotometer. PMR and ^{13}C NMR spectra were taken from $CDCl_3$ solutions (2–3%) on a Bruker Avance DRX 400 spectrometer (400.13 and 100.61 MHz) with TMS internal standard. Chemical shifts are given on the δ scale in ppm relative to $CHCl_3$ resonances as an internal standard (resonances at 7.24 and 77.00 ppm, respectively). Spin–spin coupling constants are given in Hz. Resonances in ^{13}C NMR spectra were assigned using DEPT, COSY, HMQC, and HMBC programs and by comparison with spectra of related compounds [6, 16]. High-resolution mass spectral analysis was performed on an AEI MS 902 spectrometer (EI, 70 eV). Reaction mixtures were worked up by extracting with ether, washing the extract with H_2O until neutral, drying over Na_2SO_4, filtering, and vacuum distilling solvent. The course of reactions was monitored by TLC on Sorbfil plates with detection by $Ce(SO_4)_2$ solution (1%) in aqueous H_2SO_4 (2 N) with subsequent heating at 80°C for 5 min. Column chromatography used Acros silica gel (60/200 μm). Columns were eluted by a gradient of petroleum ether:EtOAc mixtures of increasing polarity. Solvents were dried and distilled before use.

Reduction of Norambreinolide (4). A solution of **4** (10 g, 0.04 mol) in anhydrous Et_2O (400 mL) was treated in portions over 10 min with $LiAlH_4$ (4.72 g, 0.12 mol) and stirred for 2 h at 22°C (TLC monitoring). The usual work up of the solid afforded by recrystallization from ether crystalline diol **5** (10.28 g, 94.5%), mp 129.5–131°C (lit. [7] mp 131–132°C). IR spectrum (KBr, ν, cm^{-1}): 1054, 3423.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.79 (6H, s, CH_3-14, CH_3-15), 0.87 (3H, s, CH_3-16), 0.89–1.18 and 1.25–1.68 (14H, both m), 1.87–1.92 (2H, m, H-1), 3.74–3.78 (1H, m, H-9), 3.40–3.46 (1H, m, H-6), 4.20 (1H, br.s, OH).

^{13}C NMR spectrum (100.61 MHz, $CDCl_3$, δ, ppm): 15.33 (C-14), 18.41 (C-16), 20.43 (C-2), 21.48 (C-15), 24.55 (C-7), 27.83 (C-12), 33.26 (C-13), 33.42 (C-4), 38.95 (C-10), 39.34 (C-3), 41.89 (C-1), 44.10 (C-6), 56.02 (C-9), 59.32 (C-5), 63.90 (C-11), 72.86 (C-8).

Acetylation of 11-Homodriman-8α,12-diol (5). A solution of diol **5** (10.28 g, 0.04 mol) in Py (51 mL) was treated with freshly distilled Ac_2O (25.6 mL, 0.27 mol), held for 2 h at 22°C (TLC monitoring), stirred, treated with cold H_2SO_4 (10%, 50 mL), and extracted with ether (3 × 50 mL). The combined ether extract was washed with H_2SO_4 (10%, 30 mL), H_2O (30 mL), saturated $NaHCO_3$ solution (2 × 30 mL), and H_2O (2 × 30 mL); dried; and filtered. The solvent was distilled off. The liquid residue (12 g) was chromatographed over a column of SiO_2 (360 g) with elution by petroleum ether:EtOAc (8:2) to afford liquid 12-acetoxy-11-homodrim-13-ol (**6**, 11.63 g, 98%).

Spectral data of **6** were identical to those published [8–10]. Compound **6** was conclusively identified by comparison with an authentic sample that was obtained by us earlier [8]. IR spectrum (KBr, ν, cm^{-1}): 1032, 3468 (OH); 1245, 1737 (OAc).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.79 (6H, s, CH_3-14, 15), 0.87 (3H, s, CH_3-16), 0.92 (1H, dd, J = 0.5, 12, H-5), 1.07–1.81 (2H, m, H-11), 1.16 (3H, s, CH_3-13), 1.90 (1H, d, J = 4, 16, H-9), 2.05 (3H, s, $COC\underline{H}_3$), 4.13 (2H, m, H-12).

^{13}C NMR spectrum (100.61 MHz, $CDCl_3$, δ, ppm): 15.31 (C-16), 18.40 (C-2), 20.48 (C-6), 21.13 ($CO\underline{C}H_3$), 21.47 (C-15), 23.94 (C-13), 24.47 (C-11), 33.27 (C-4), 33.38 (C-14), 38.75 (C-10), 39.60 (C-1), 41.88 (C-3), 44.39 (C-7), 56.07 (C-5), 58.03 (C-9), 66.62 (C-12), 73.56 (C-8), 171.17 ($\underline{C}OCH_3$).

Dehydration of 12-Acetoxy-11-homodriman-8α-ol (6). Monoacetate **6** was dehydrated according to the literature method [11]. A solution of triphenylphosphine (12.3 g, 0.04 mol) in CH_2Cl_2 (202 mL) was stirred at room temperature, treated with iodine (5.9 g, 0.046 mol), stirred for another 10 min, treated with a solution of **6** (11.69 g, 0.039 mol) in CH_2Cl_2 (118 mL), stirred at the same temperature for another 2 h (TLC monitoring), treated with Na_2SO_3 solution (5%, 250 mL), stirred for 10 min, and extracted with CH_2Cl_2 (2 × 50 mL). The extract was washed with H_2O (2 × 100 mL) and saturated NaCl solution (2 × 100 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was vacuum distilled. The residue (20 g) was chromatographed over a column of SiO_2 (320 g) with elution by petroleum ether to afford a liquid mixture of isomeric unsaturated acetates **7** (10.68 g, 98%). IR spectrum (film, ν, cm^{-1}): 1231, 1740 (OAc).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 0.83 (3H, s, CH_3-14), 0.88 (3H, s, CH_3-15), 0.94 (3H, s, CH_3-16), 1.62 (3H, s, CH_3-13), 2.01 (3H, s, OAc), 3.97–4.03 (2H, m, H-12).

The contents of the isomers with the tri-substituted (19%) and exocyclic (17%) double bonds were determined from the ratio to the total resonance intensity of $C(12)H_2$ groups. The content of the isomer with the tetra-substituted double bond (64%) [singlet $C(13)H_3$ at 1.62 ppm] was determined by difference.

Oxidation of the Mixture of Unsaturated Acetates 7 by Sodium Chromate. The mixture of acetates **7** was oxidized by sodium chromate by the literature method [13]. A solution of the mixture of unsaturated acetates **7** (10.68 g, 0.038 mol) in anhydrous benzene (550 mL) was treated with glacial AcOH (159.5 mL, 2.81 mol) and freshly distilled Ac_2O (159.5 mL, 1.69 mol), treated with NaOAc (19.06 g, 0.288 mol) and Na_2CrO_4 (34 g, 0.158 mol), and stirred for 2 h at 60°C. A part of the benzene (185 mL) was vacuum distilled. The mixture was cooled to 22°C, treated with H_2O (300 mL), and extracted with ether (3 × 50 mL). The extract was washed with $NaHCO_3$ solution (5%, 50 mL) and H_2O (2 × 50 mL), dried over anhydrous Na_2SO_4, and filtered. The ether was vacuum distilled. The residue (10.7 g) was chromatographed over a column of SiO_2 (320 g) with elution by petroleum ether:EtOAc (96:4) to afford crystalline 12-acetoxy-11-homodrim-8(9)-en-7-one (**8**, 6.73 g, 60%), mp 59–60°C (petroleum ether). IR spectrum (KBr, ν, cm^{-1}): 1232, 1745 (OAc), 1600 (conjugated C=C), 1656 (conjugated C=O).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.89 (3H, s, CH_3-14), 0.92 (3H, s, CH_3-15), 1.09 (3H, s, CH_3-16), 1.81 (3H, s, CH_3-13), 2.07 (3H, s, OAc), 4.13 (2H, m, H-12).

^{13}C NMR spectrum (100.61 MHz, $CDCl_3$, δ, ppm): 11.78 (C-13), 18.04 (C-16), 18.57 (C-2), 20.96 (C-15), 21.30 ($CO\underline{C}H_3$), 28.71 (C-11), 32.50 (C-14), 33.13 (C-4), 35.23 (C-6), 36.01 (C-1), 40.65 (C-10), 41.21 (C-3), 50.10 (C-5), 62.37 (C-12), 132.10 (C-8), 162.45 (C-9), 170.85 ($\underline{C}OCH_3$), 200.05 (C-7).

Bromination of Ketoacetate 8 by NBS. A solution of ketoacetate **8** (6.73 g, 0.023 mol) in anhydrous CCl_4 (132.5 mL) was treated with freshly recrystallized NBS (4.15 g, 0.023 mol). The resulting mixture was refluxed for 2 h, cooled, and filtered. The solvent was vacuum distilled. The residue (8.89 g) was chromatographed over a column of SiO_2 (178 g) with elution by petroleum ether:EtOAc (99:1) to afford crystalline 12-acetoxy-13-bromo-11-homodrim-8(9)-en-7-one (**9**, 6.84 g, 80%), mp 63–64°C (petroleum ether). IR spectrum (KBr, ν, cm^{-1}): 595, 1129 (Br), 1224, 1743 (OAc), 1600 (conjugated C=C), 1671 (conjugated C=O).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, s, CH_3-15), 0.93 (3H, s, CH_3-14), 1.11 (3H, s, CH_3-16), 1.00–2.40 (11H, m), 4.22 (1H, d, J = 9.6, H-13) and 4.36 (1H, d, J = 9.6, H-13), 4.25 (2H, m, H-12).

^{13}C NMR spectrum (100.61 MHz, $CDCl_3$, δ, ppm): 17.89 (C-2), 18.43 (C-16), 20.93 (C-15), 21.37 ($CO\underline{C}H_3$), 24.36 (C-13), 28.67 (C-11), 32.43 (C-14), 33.27 (C-4), 35.20 (C-6), 35.57 (C-1), 41.04 (C-3), 41.17 (C-10), 49.52 (C-5), 62.21 (C-12), 133.66 (C-8), 167.23 (C-9), 170.84 ($\underline{C}OCH_3$), 197.17 (C-7).

Preparation of 12,13-Diacetoxy-11-homodrim-8-en-7-one (10). A solution of **9** (6.84 g, 0.018 mol) in DMF (290 mL) was treated with KOAc (4.1 g, 0.05 mol), stirred for 2 h at 22°C (TLC monitoring), treated with H_2O (300 mL), and extracted with ether (3 × 100 mL). The extract was washed with H_2O (2 × 100 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was vacuum distilled. The residue (5.56 g) was chromatographed over a column of SiO_2 (120 g) with elution by petroleum ether:EtOAc (95:5) to afford crystalline 12,13-diacetoxy-11-homodrim-8-en-7-one (**10**, 5.16 g, 80%), mp 78–79°C (petroleum ether). IR spectrum (KBr, ν, cm^{-1}): 1251, 1740 (OAc), 1600 (conjugated C=C), 1665 (conjugated C=O).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, s, CH_3-15), 0.93 (3H, s, CH_3-14), 1.13 (3H, s, CH_3-16), 2.03 (3H, s, OAc), 2.05 (3H, s, OAc), 1.0–2.20 (9H, m), 4.05–4.25 (2H, m, H-12), 4.77 (1H, d, J = 11.6) and 4.90 (1H, d, J = 11.6) (AB-system, H-13).

^{13}C NMR spectrum (100.61 MHz, $CDCl_3$, δ, ppm): 18.39 (C-16), 18.45 (C-2), 20.85 (OAc), 20.99 (OAc), 21.35 (C-15), 28.39 (C-1), 32.43 (C-14), 33.29 (C-4), 35.22 (C-6), 35.67 (C-11), 41.03 (C-3), 41.08 (C-10), 49.66 (C-5), 57.90 (C-13), 63.08 (C-12), 131.20 (C-8), 169.22 (C-9), 169.63 (OAc), 170.37 (OAc), 196.40 (C-7).

Saponification of 10. A solution of ketodiacetate **10** (5.16 g, 0.014 mol) in MeOH (90 mL) was treated with K_2CO_3 solution (1%) in MeOH (206 mL). The mixture was held at ambient temperature under an argon atmosphere for 1 h (TLC monitoring), treated with H_2O (300 mL), and extracted with ether (3 × 50 mL). The ether extract was washed with H_2SO_4 solution (10%, 100 mL) and H_2O (2 × 50 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was vacuum distilled to afford crystalline 11-homodrim-8(9)-en-12,13-diol-7-one (**11**, 2.97 g, 76%), mp 109–110°C (Et_2O). IR spectrum (KBr, ν, cm^{-1}): 1047, 3282, 3306 (OH), 1650 (conjugated C=C), 1660 (conjugated C=O).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.99 (3H, s, CH_3-15), 0.93 (3H, s, CH_3-14), 1.14 (3H, s, CH_3-16), 1.15–2.00 (3H, m), 2.30–2.80 (4H, m), 3.70–3.90 (2H, m, H-12), 4.30 (1H, d, J = 12) and 4.40 (1H, d, J = 12) (AB-system, H-13).

^{13}C NMR spectrum (100.61 MHz, $CDCl_3$, δ, ppm): 18.40 (C-16), 18.50 (C-2), 21.37 (C-15), 31.89 (C-1), 32.43 (C-14), 33.29 (C-4), 35.33 (C-6), 35.78 (C-11), 40.89 (C-10), 41.07 (C-3), 49.82 (C-5), 56.89 (C-13), 61.32 (C-12), 134.65 (C-8), 168.33 (C-9), 201.06 (C-7). Mass spectrum (EI, 70 eV, m/z, I_{rel}, %): 266.17743.

Epoxidation of 11. A solution of **11** (2.97 g, 0.01 mol) in MeOH (46.5 mL) was treated with NaOH solution (6 N) in MeOH (26.7 mL), stirred at ambient temperature for 15 min, cooled to 0°C, treated with H_2O_2 solution (26.7 mL, 35%), stirred at room temperature for 5 h (TLC monitoring), treated with H_2O (350 mL), and extracted with ether (3 × 100 mL). The extract was washed with saturated NaCl solution (100 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was vacuum distilled to afford crystalline 8,9α-epoxy-11-homodriman-12,13-diol-7-one (**12**, 2.38 g, 76%), mp 104–105°C (Et_2O). IR spectrum (KBr, ν, cm^{-1}): 1042 (epoxy group), 1053, 3342 (OH), 1702 (C=O).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85 (3H, s, CH_3-14), 0.86 (3H, s, CH_3-15), 0.96 (3H, s, CH_3-16), 1.00–1.90 (9H, m), 2.00–2.30 (3H, m), 2.48 (1H, dd, J = 7.2, 19.2, H_β-6), 3.73-3.90 (2H, m, H-12), 3.70 (1H, d, J = 12.4) and 4.18 (1H, d, J = 12.4) (AB-system, H-13).

^{13}C NMR spectrum (100.61 MHz, $CDCl_3$, δ, ppm): 16.79 (C-16), 18.42 (C-2), 20.68 (C-14), 28.46 (C-11), 32.46 (C-15), 33.33 (C-4), 34.57 (C-1), 36.06 (C-6), 38.83 (C-10), 41.08 (C-3), 41.59 (C-5), 59.69 (C-12), 60.29 (C-13), 66.47 (C-8), 74.00 (C-9), 210.87 (C-7).

Wharton–Bolen Rearrangement of 12. A mixture consisting of epoxide **12** (1 g, 3.73 mmol) and hydrazine hydrate (15 mL) was stirred at room temperature for 2.5 h under an Ar atmosphere (TLC monitoring), treated with H_2O (30 mL), and extracted with ether (3 × 20 mL). The extract was washed with saturated NaCl solution (50 mL), dried over anhydrous

Na_2SO_4, and filtered. The solvent was vacuum distilled to afford crystalline triol **3** (0.82 g, 87%), mp 106–107°C (Et_2O). IR spectrum (KBr, ν, cm^{-1}): 1037, 1153, 3310 (OH), 818, 1693 (C=C).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 0.82 (6H, s, CH_3-14, 15), 1.20 (3H, s, CH_3-16), 3.45–3.50 (6H, dd, H-11, 12, 13), 5.88–5.89 (1H, d, H-7).

^{13}C NMR spectrum (100.61 MHz, $CDCl_3$, δ, ppm): 15.66 (C-16), 18.43 (C-2), 22.18 (C-14), 29.71 (C-11), 30.72 (C-6), 32.90 (C-4), 33.38 (C-15), 33.48 (C-1), 41.70 (C-3), 41.78 (C-10), 41.94 (C-5), 60.76 (C-12), 65.93 (C-13), 77.89 (C-9), 130.92 (C-7), 139.10 (C-8).

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