SYNTHESIS OF 3,7,11-TRIMETHYL-10-OXODODECANOIC ACID

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3,7,11-Trimethyl-10-oxododecanoic acid (*I*) was prepared from 6-bromo-2-methylhept-2-ene (*II*) in six steps.

A new sesquiterpenoid, 3,7,11-trimethyl-10-oxododecanoic acid (*I*) was isolated by Anjaneyulu et al.[1] from the marine green algal species, *Caulerpa racemosa*. Its structure was assigned on the basis of spectral data. Literature does not record any attempt towards the synthesis of the title compound. Herein, we report a short and facile synthesis; the sequence of reactions employed is outlined in Scheme 1.

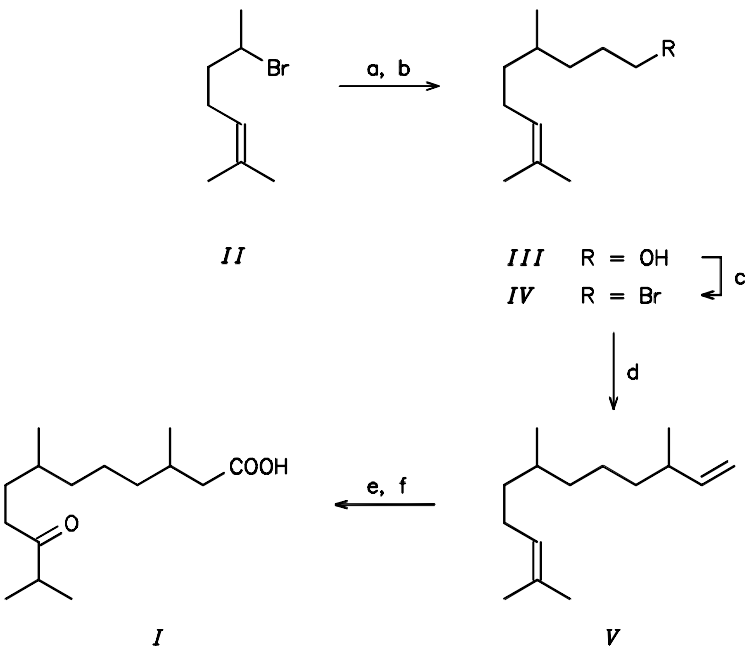
Grignard reagent prepared from 6-bromo-2-methylhept-2-ene[2] (*II*) was coupled with 3-bromopropanol[3] using copper(I) iodide as catalyst[4] in ether to afford *III*. The alcohol *III* was converted into the corresponding bromide *IV* using phosphorus tribromide in pyridine. The bromide *IV* was then coupled with the Grignard reagent prepared from 3-bromobutene (obtained by the reaction of methylmagnesium iodide with acrolein followed by bromination with phosphorus tribromide in pyridine) using dilithium tetrachlorocuprate as catalyst[5] to yield the diene *V*. This diene was subjected to hydroboration-oxidation[6,7] using sodium borohydride/acetic acid/chromic acid to get the target compound *I*.

EXPERIMENTAL

IR spectra were recorded of neat samples on Perkin–Elmer 1430 spectrometer (wavenumber in cm^{-1}). ^1H NMR spectra were recorded on a Varian EM-360 (60 MHz) and ^{13}C NMR spectra on a Bruker AC 300F (300 MHz) spectrometers using tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Mass spectra were recorded at 70 eV using VG ANALYTICAL 11-250-J70-S instrument. UV spectra were recorded on HITACHI 330 spectrometer. Purity of the samples was checked by TLC using silica gel impregnated with 13% calcium sulfate. Silica gel (Acme 100 – 200 mesh) was used for column chromatography. Unless stated otherwise, the organic extracts were dried over anhydrous sodium sulfate.

4,8-Dimethylnon-7-en-1-ol (*III*)

To a well-stirred solution of the Grignard reagent, prepared from activated magnesium turnings (0.96 g, 40 mmol), and 6-bromo-2-methylhept-2-ene[2] (*II*; 7.64 g, 40 mmol) in ether (25 ml) at −10 °C, was added dropwise under nitrogen the solution of 3-bromopropanol[3] (2.1 g, 15 mmol) in ether and the mixture was stirred at the same temperature for additional 30 min. Then the mixture was brought to room temperature and copper(I) iodide (0.02 g, 0.10 mmol) was added. After stirring for 15 min the mixture was refluxed for 4 h, decomposed with saturated aqueous ammonium chloride solution, extracted with ether and dried. Evaporation of the solvent followed by chromatographic purification yielded 1.77 g (69.4%) of *III*. IR spectrum: 3 420, 2 940, 1 450, 1 380, 1 060, 850, 700. ^{1}H NMR spectrum: 5.10 t, 1 H, J = 8 (C=CH); 3.65 t, 2 H, J = 6 (CH_2O); 2.2 bs, 1 H (OH, D_2O exchangeable); 2.03 q, 2 H, J = 8 (CH_2–CH=C); 1.67 s, 3 H (CH_3); 1.56 s, 3 H (CH_3); 1.3 m, 7 H (3 × CH_2 and CH); 0.91 d, 3 H, J = 6 (CH_3). ^{13}C NMR spectrum: 131.2, 124.7, 60.9, 39.8, 37.2, 29.2, 25.7, 25.4, 24.6, 19.5, 17.6.



a) Mg, ether; b) $BrCH_2CH_2CH_2OH$, CuI, ether; c) PBr_3, pyridine, ether;
d) $H_2C{=}CH{-}CH(CH_3)MgBr$, Li_2CuCl_4, THF; e) $NaBH_4$, AcOH, THF;
f) $H_2Cr_2O_7$, aceton, *tert*-butyl alcohol

SCHEME 1

9-Bromo-2,6-dimethylnon-2-ene (*IV*)

To an ice-cooled stirred solution of the alcohol *III* (2.55 g, 15 mmol) in ether (50 ml) containing pyridine (0.4 g, 5 mmol) was added dropwise a solution of PBr_3 (0.45 g, 5 mmol) in ether (10 ml) during 30 min. The mixture was allowed to stir for 2 h under cooling and 1 h at room temperature then decomposed with aqueous solution of sodium hydrogen carbonate and extracted with ether. The extract was washed with water and dried. Evaporation of solvent followed by chromatographic purification afforded 3.11 g (89%) of pure *IV*. IR spectrum: 3 060, 2 940, 1 460, 1 380, 890. ^{1}H NMR spectrum: 5.30 t, 1 H, J = 8 (C=CH); 3.56 t, 2 H, J = 6 (CH_2Br); 2.06 m, 2 H (C**H**$_2$–CH=C); 1.60 s, 3 H (CH_3); 1.50 s, 3 H (CH_3); 1.27 m, 7 H (3 × CH_2 and CH); 0.93 d, 3 H, J = 7 (CH_3). ^{13}C NMR spectrum: 131.2, 124.6, 53.7, 39.6, 37.4, 29.3, 25.7, 25.4, 24.7, 19.5, 17.6.

3,7,11-Trimethyldodeca-1,10-diene (*V*)

To the ice-cooled, stirred solution of the Grignard reagent prepared from magnesium turnings (0.48 g, 20 mmol) and 3-bromobutene (2.70 g, 20 mmol) in THF (40 ml) under nitrogen atmosphere was added dropwise a solution of bromide *IV* (4.43 g, 10 mmol) in THF (50 ml) during 20 min. After stirring for 45 min, 0.1 M dilithium tetrachlorocuprate in THF (2 ml) was added. The mixture was stirred at –10 °C for 3 h and then was left overnight at room temperature. The reaction mixture was decomposed with saturated aqueous solution of NH_4Cl and organic layer was separated. The aqueous phase was extracted with ether and the combined organic extracts were washed with water and dried. Evaporation of solvents and purification by column chromatography over silica gel afforded 2.85 g (72%) of *V*. IR spectrum: 2 960, 1 640, 1 420, 1 340, 905, 790. ^{1}H NMR spectrum: 5.70 m, 1 H (C**H**=CH_2); 5.40 t, 2 H, J = 10 (CH=C**H**$_2$); 4.90 t, 1 H, J = 8 (CH=C); 2.10 m, 3 H (C**H**$_2$–CH=C and C**H**(CH_3)–CH=CH_2); 1.30, 9 H (4 × CH_2 and CH); 0.96 d, 6 H, J = 6 (2 × CH_3). ^{13}C NMR spectrum: 133.2, 131.4, 129.8, 124.6, 33.9, 32.4, 30.8, 29.7, 29.2, 28.6, 26.9, 24.8, 24.4, 23.6, 22.3. Mass spectrum, *m*/*z*: 208 (M^+), 179, 164, 151, 149, 121, 101, 91, 86. UV spectrum (methanol): λ_{max} 218 nm. For $C_{15}H_{28}$ (208.4) calculated: 86.46% C, 13.54% H; found: 86.5% C, 13.6% H.

3,7,11-Trimethyl-10-oxododecanoic Acid (*I*)

To a stirred suspension of $NaBH_4$ (1.14 g, 30 mmol) in THF (100 ml), acetic acid (1.8 g, 30 mmol) was added cautiously at 0 °C under nitrogen atmosphere. The mixture were further stirred for 25 min at 0 °C and then brought to room temperature. The diene *V* (3.12 g, 15 mmol) was added dropwise and reaction mixture was stirred for 1.5 h at room temperature and then 2 h at 50 °C. The mixture was cooled to 0 °C and hydrolyzed carefully by adding water (8 ml). Then acetone (90 ml) and *tert*-butyl alcohol (15 ml) were added. Chromic acid solution, prepared from CrO_3 (9.0 g), water (15 ml) and concentrated sulfuric acid (15 ml), was added at 0 °C during 25 min. The reaction mixture was stirred further for 14 h at room temperature, the organic layer was separated and the aqueous layer was extracted with chloroform. The solvent was removed from the combined organic extract, the residue dissolved in chloroform and extracted with aqueous 2 M NaOH. The aqueous NaOH extract was acidified with concentrated hydrochloric acid and extracted with $CHCl_3$. The chloroform extract dried over anhydrous $CaCl_2$. The solvent removal followed by chromatographic purification using petroleum ether–ethyl acetate (1.5 : 8.5) afforded yield 2.42 g (63%) of pure keto acid *I*. IR spectrum: 3 405, 2 940, 1 710, 1 460, 1 340, 1 050. ^{1}H NMR spectrum: 8.7 bs, 1 H (COOH); 2.36 m, 5 H (CH_2COO and CHCOCH_2); 1.40 m, 10 H (4 × CH_2 and 2 × C**H**(CH_3)); 0.96 d, 6 H, J = 6 (2 × CH_3); 0.85 d, 6 H, J = 6 (2 × CH_3). ^{13}C NMR spectrum: 212.9, 180.2, 41.8, 33.6, 31.8, 30.6, 29.3, 29.2, 28.8, 26.7, 24.8, 24.4, 23.9, 23.3, 22.7. Mass spectrum, *m*/*z*: 256 (M^+), 213, 185, 170, 169, 129, 86,

71. UV spectrum (methanol): λ_{max} 265 nm. For $C_{15}H_{28}O_3$ (256.4) calculated: 70.27% C, 11.01% H; found: 70.2% C, 10.9% H.

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