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A Convenient Preparation of 3-[$^2H_3$]Methyl-3-buten-1-ol

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Summary

A procedure for the conversion of 3-hydroxy-3-methylglutaric anhydride to methyl 3-methyl-3-butenoate forms the basis for a convenient synthesis of 3-[$^2H_3$]methyl-3-buten-1-ol.

Keyword 3-[$^2H_3$]methyl-3-buten-1-ol

Introduction

Due in large part to expanded applications of **NMR** and **MS** methods for analysis, the use of stable isotopes in biosynthetic studies has increased dramatically in recent years. [1] This communication describes procedures for a convenient and efficient preparation of [$^2H_3$]methyl-labelled 3-methyl-3-buten-1-ol (Δ^3-isopentenyl alcohol, **IPA**), the important five-carbon unit in terpene biosynthesis; 3-methyl-4,4[$^2H_2$]-3-butene-1-ol [2] and (4**E**)- and (4**Z**)-3-methyl-4[^2H]-3-butene-1-ol [3] are the only deuterated **IPA**'s previously reported. The procedure described below is for 3- [$^2H_3$]methyl-3-buten-1-ol from which the corresponding Δ^3-isopentenyl pyrophosphate, **IPP**, can be readily prepared [4]; these are substrates designed for biosynthetic studies utilizing Selected Ion Monitoring **MS** techniques for trace analysis. However, the same protocol applies for the preparation of a variety of ^{13}C-labelled analogues more suitable for **NMR** analyses.

Results

The synthetic sequence is shown in Scheme 1. The readily available perdeuteroacetic acid was used as starting material and the source of all the label. Following Fischer esterification, a modified Barbier-Grignard [5] procedure was employed for the reaction of ethyl [$^2H_3$]acetate with two equivalents of allyl bromide. When starting with acetic acid containing 99.5 atom % ^2H, the resulting 4-[$^2H_3$]methyl-1,6-heptadiene-4-ol (**I**) consisted of 98% [$^2H_3$]-species.

Ozonolysis of **I** was performed in dichloromethane containing acetic acid and following a

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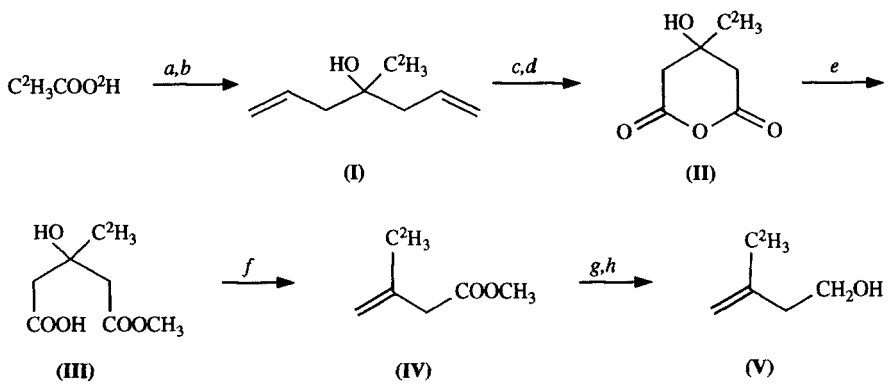
standard oxidative workup, dehydration of the resulting diacid gave 3-hydroxy-3-[$^2H_3$]methylglutaric anhydride (**II**) as previously reported. [6] Overall yields of **II** greater than 90 % were obtained consistently on preparative scales of this procedure (greater than 0.1 mole).

Decarboxylative dehydration was effected *via* the methyl 3-hydroxy-3-[$^2H_3$]methylglutarate (**III**), the product of cinchonine catalyzed methanolysis of **II**.[7] The use of N,N-dimethylformamide dineopentyl acetal was necessary since the corresponding dimethyl acetal, more commonly employed for dehydrative decarboxylations, resulted in formation of substantial amounts (30-50%) of the dimethyl ester.[8,9] Conversion of **II** to methyl 3-[$^2H_3$]methyl-3-butenoate (**IV**) was accomplished in 84% yield.

Scheme 1



a) H^+/C_2H_5OH *b)* CH_2=$CHCH_2Br/ET_2O$-THF, Mg° *c)* O_3/DCM-AcOH ; H_2O_2/AcOH *d)* Ac_2O, RT
e) Cinchonine/MeOH-Et_2O *f)* $HC(O\text{-}neoC_5H_{11})_2N(CH_3)_2/CHCl_3$ *g)* 1N *aq* NaOH *h)* LAH/Et_2O

While the LAH reduction of **IV** proceeded smoothly, separation of the desired allylic alcohol from the methanol also formed proved difficult, thus prior hydrolysis was necessary. Even then, some losses occurred during purification of **V** reducing the isolated yield to only 72%. As expected, the 3-[$^2H_3$]methyl-3-butene-1-ol obtained consisted predominantly (95%) of [$^2H_3$]-species.

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Experimental

General Methods. ^{1}**H** NMR spectra were measured at 300 *MHz* and ^{13}**C** at 75 *MHz* on a Varian XL spectrometer. An internal standard was used and chemical shifts are reported in **ppm** downfield from tetramethylsilane. Spectra of deuterated materials and unlabelled analogues were indistinguishable except for the data given in brackets. Mass spectra were measured on a Hewlett Packard Model 5988A equipped with an RTE-A data system. Samples were introduced by gas chromatography using an HP-100 fused silica capillary column (30m x 0.25 mm OD). **SIM MS** measurements were optimized over the ion region required. MS data at natural isotopic abundance is presented in brackets following that for deuterated materials.

All solvents utilized were reagent grade and purified as appropriate prior to use.

4-[$^2H_3$]Methyl-1,6-heptadiene-4-ol (I) - A modified Barbier - Grignard procedure was employed. A solution of allyl bromide (80.0 mL, 0.924 mol) and ethyl [$^2H_3$]acetate (27.3 g, 0.300 mol, prepared in 94% yield from perdeuteroacetic acid, 99.5 atom % D) in dried ether:THF (1:2, 250 mL) was added dropwise to magnesium turnings (28 g, 1.15 mol) also in dried ether:THF (1:1, 95 mL) at a rate which caused the reaction mixture to reflux gently. Additional dried ether:THF (1:2, 100 mL) was then added and the reaction mixture was heated and stirred for 2 hrs. After cooling in an ice bath, cold water (200 mL) was added followed by cold 6 **M** sulfuric acid (150 mL). After separating the organic layer, the aqueous layer was extracted with ether (4 x 100 mL) and the combined extracts were washed with brine (1 x 100 mL) and dried over anhyd. magnesium sulfate. Ether and THF were removed by distillation at atmospheric pressure and the product was distilled under reduced pressure using a dry ice/acetone-cooled receiving vessel, furnishing **I** (36.1 g, 93% yield) boiling 75-77° C / 35 mm Hg (lit. 50-51°C / 12 mm Hg).

^{1}**H NMR** (C^2HCl_3): 1.61 (br s, OH), 2.19 (m, 4H), 5.10 (m, 4H), 5.83 (m, 2H) [1.12 (s, 3H)].
^{13}**C NMR** (C^2HCl_3): 46.0, 71.4, 116.3, 133.1 [26.5].
MS, m/e (%): 111 (M-H_2O, 0.17), 88 (29.5), 69 (3.56), 46 (100) [108 (0.06), 85 (36.1), 69 (4.64), 43 (100)].
SIM MS m/e (%): 85 (0.289), 86 (0.118), 87 (2.038), 88 (100.0), 89 (5.109), 90 (0.377) [85 (100.0), 86 (5.445, 87 (0.463), 88 (6.223), 89 (0.390), 90 (0.047)] 99.3% [$^2H_3$], 0.206% [$^2H_2$], 0.181% [$^2H_1$], 0.316% [$^2H_0$].

3-Hydroxy-3-[$^2H_3$]methylglutaric anhydride (II) - Ozonolysis of **I** (18.0 g, 0.140 mol) was performed in dichloromethane:acetic acid (10:1) and as previously reported, diacid (19.6 g, 85% yield) was obtained following oxidation with hydrogen peroxide. Dehydration to give anhydride **II** was accomplished by dissolution of this crude diacid in acetic anhydride (110 mL) at room temperature (*ca* two days required for complete solution) and subsequent evaporation under reduced pressure. The **II** (17.2 g, 98% yield) obtained had m.p. 108-109 °C (lit 110-111 °C) and required no additional purification.

^{1}**H NMR** (Acetone-$^2H_6$): 2.83 (dm, J= 16.3 Hz, 2H), 2.98 (dm, J= 16.3 Hz), 3.02 (br s, OH) [1.35 (s, 3H)].
^{13}**C NMR** (Acetone-$^2H_6$): 44.0, 67.4, 167.3 [27.5].

3-Hydroxy-3-[$^2H_3$]methylglutaric acid monomethyl ester (III) - A solution of **II** (16.8 g, 0.114 mol) and methanol (92 mL) in *anhyd* ether (1 L) was treated with cinchonine (3.35 g, 11.4 mmol) and the mixture stirred for 24 hrs. Following filtration, the solvents were removed under reduced pressure furnishing **III** (22.5 g, 100% yield).

^1H NMR (C^2HCl_3): 2.64 (m, 4H), 3.68 (s, 3H) 7.3 (br s, OH) [1.35 (s, 3H),].
^{13}C NMR (C^2HCl_3): 44.63, 44.8, 51.76, 69.59, 172.22, 175.65 [27.05].
MS, m/e (%): 143 (M-H_2O-CD_3, 19.8), 120 (31.9), 106 (55.1), 88 (85.4), 46 (100) [143 (23.6), 117 (27.2), 103 (49.2), 85 (59.2), 43 (100)].

Methyl 3-[$^2H_3$]methyl-3-butenoate (IV) - A solution of **III** (20.0 g, 0.111.7 mol) dissolved in *anhyd* chloroform (1 L) was treated with dimethylformamide dineopentyl acetal (50 mL, 0.1179 mol) and the mixture was stirred overnight. After removal of volatiles at atmospheric pressure, the product was distilled under reduced pressure (*ca* 34-35° C, 30 mm Hg), while cooling the collecting flasks in a dry ice/acetone bath. Fractions containing **IV** were combined and percolated through a short silica gel column with pentane. Evaporation of the pentane furnished **IV** (11.6 g, 84% yield).

^1H NMR (C^2HCl_3): 2.99 (s, 2H), 3.75 (s, 3H), 4.81 (b s, 1H), 4.88 (b s, 1H) [1.77 (s, 3H)].
^{13}C NMR (C^2HCl_3): 43.11, 51.14, 114.37, 138.45, 171.22 [25.9].
MS, m/e (%): 117 (M, 59.6), 86 (28.56), 59 (77.6), 58 (100) [114 (M, 66.1), 83 (33.4), 59 (66.1), 55 (100)].

3-[$^2H_3$]methyl-3-buten-1-ol (V) - A solution of **IV** (11.5 g, 98.3 mmol) in 95% ethanol (50 mL) was treated with 1N sodium hydroxide (120 mL) and the mixture stirred for 2 hrs at room temperature. After the addition of water (120 mL), the resulting solution was saturated with salt and extracted with methylene chloride (4 x 50 mL). The aqueous phase was cooled in an ice bath, acidified with cold conc. hydrochloric acid (12 mL) and then extracted with ether (5 x 50 mL). The ether extracts were combined and dried over anhyd. magnesium sulfate. Evaporation of ether yielded 3-[$^2H_3$]methyl-3-butenoic acid (9.34 g, 96.8% yield).

^1H NMR (C^2HCl_3): 2.94 (b s, 2H), 4.77 (m, 1H), 4.82 (m, 1H) [1.81 (s, 3H)].
MS, m/e (%): 103 (M, 100), 75 (71.9), 61 (58.7), 58 (79.5) [100 (M, 100), 72 (65.80, 58 (36.2), 55 (61)].

A solution of this acid (6.5 g, 63 mmol) in *anhyd* ether (40 mL) was added dropwise to lithium aluminum hydride (4.5 g, 112 mmol) which had been stirred for 0.5 hr in anhyd. ether (150 mL). The reaction mixture was then heated under reflux for 2 hrs. After cooling in an ice bath, of cold water (50 mL) was added carefully followed by cold 6 N hydrochloric acid (100 mL). The ether layer was separated and the aqueous layer was saturated with sodium chloride and extracted with ether (2 x 100 mL). The combined extracts were washed successively with brine, 10% sodium carbonate, and again with brine and then dried over anhyd. sodium sulfate. Ether was evaporated at atmospheric pressure, and the residue distilled under reduced pressure (35° C, 8 mm Hg) with the collecting flasks cooled in a dry ice/acetone bath, furnishing **V** (4.10g, 74% yield).

^{1}H NMR (C^2HCl_3): 2.18 (br s, OH), 2.23 (br t, J=6.4 Hz, 2H), 3.65 (t, J=6.4 Hz, 2H), 4.72 (m, 1H), 4.79 (br s, 1H), [1.63 (s, 3H)].
^{13}C NMR (C^2HCl_3): 40.6, 60.0, 112.4, 142.1 [22.1].
MS, m/e (%): 89 (M, 26.4), 70 (58.1), 69 (52.5), 59 (100), 43 (52.9) [86 (M, 38.4), 68 (100), 56 (96), 41 (67.8)].
SIM MS, m/e (%): 86 (1.41), 87 (0.506), 88 (3.565), 89 (100), 90 (5.779), 91 (0.378) [86(100), 87 (5.523), 88 (0.34), 89 (0.02, 90 (0.005), 91 (0.017)] 94.9% [$^2H_3$], 3.35% [$^2H_2$], 0.4% [$^2H_1$], 1.34% [$^2H_0$]

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