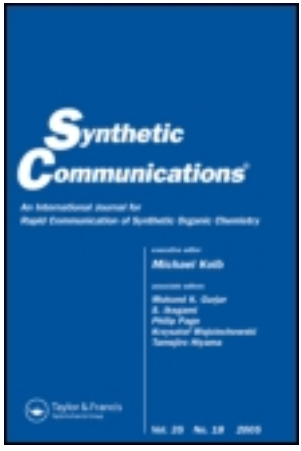

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SYNTHESIS OF 6,6-d_2-DEHYDROABIETIC ACID

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ABSTRACT: The title compound was synthesised in 23.8% yield and 98.2% isotopic purity from dehydroabietic acid using a six-step sequence.

The decarboxylation of diterpene resin acids to afford resin hydrocarbons is a well-known chemical or biological process. Resin hydrocarbons have been identified in sediments of New Zealand pulp and paper mill effluent recipients, in the extractives of pine needles, forest soils, pine tar, fossilised wood, coal and peat deposits [1-7].

Little is known, however, about the biological anaerobic fate of resin acids, and the pathways by which they degrade to resin hydrocarbons. Investigations of this type require a specifically labelled resin acid which allows it and its degradation products to be clearly distinguishable from the complex mixture of resin acids and hydrocarbons already present in the effluent or sediment under investigation. Stable isotope labelling of a resin acid and mass spectrometry detection of

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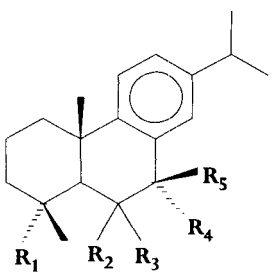
metabolic products is a method of choice for studying environmental and biological processes. Deuterium labelling of resin acids is not novel. Deuteration at C-2, C-3, C-5, C-6 and C-7 of aromatic diterpenes for mass spectrometry studies[8] was achieved by a Clemmensen reduction of the appropriate ketone treated with deuterium oxide and acetyl chloride. Methyl 2,2,3,3-d_4-dehydro-abietate, and similarly methyl 6,6,7,7-d_4-dehydroabietate, were synthesised from the 3-oxo- and 7-oxo- methyl esters respectively.

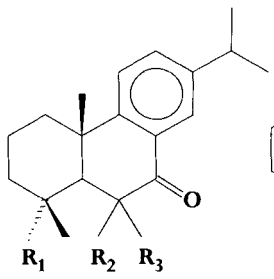
However this technique of deuteration produced a complicated isotopic composition; typically 68 %-d_4, 17 %-d_3, 3 %-d_2, 3 %-d_1, and 9 %-d_0. In a resin acid metabolic study, the tracing of a multiply-labelled resin acid would be a complicated analysis. When there is no possibility of defining which of the four possible sites was incompletely deuterated or involved in an environmental transformation, the interpretation of the deuterated molecular ion ratios would have been ambiguous.

More specific deuteration has been achieved for a mass spectrometry study of the hydroxy-dehydroabietates[9] by the enol exchange of the C-6 hydrogens of methyl 7-oxodehydroabietate **2a** using deuterium oxide and subsequent reduction using sodium borohydride or sodium borodeuteride.

The present synthesis used dehydroabietic acid **1a** (99.9% pure) as the starting material. Methyl 7-oxodehydroabietate **2a** was obtained in 60% yield by oxidation of methyl dehydroabietate **1b** with CrO_3 [10]. Deuterium exchange of the C-6 protons was performed by refluxing the C-7 ketone in benzene and D_2O with an acid catalyst with periodical azeotropic removal and replenishment with fresh



1



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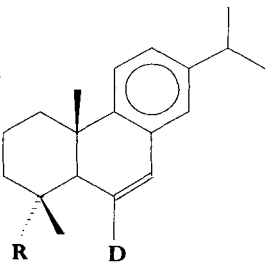

3

1	R_1	R_2	R_3	R_4	R_5
a	CO_2H	H	H	H	H
b	CO_2CH_3	H	H	H	H
c	CO_2CH_3	D	D	H	OH
d	CO_2CH_3	D	D	D	OH
e	CO_2CH_3	D	D	H	H
f	CO_2CH_3	D	H	H	H
g	CO_2CH_3	D	D	H	OTMSi
h	CH_2OH	D	D	H	H
i	CO_2H	D	D	H	H
j	CO_2CH_3	D	D	OH	H
k	CO_2CH_3	D	D	OTMSi	H

2	R_1	R_2	R_3
a	CO_2CH_3	H	H
b	CO_2CH_3	D	D
c	CO_2H	D	D
d	CO_2CH_3	D	H

3	R
a	CO_2CH_3
b	CH_2OH
c	CO_2H

D_2O until a maximal level of deuteration (98%) was achieved. Direct catalytic hydrogenation to **2b** failed to proceed at an acceptable rate, so the ketone was firstly reduced to **1c** with $NaBH_4$. Catalytic hydrogenation of **1c** over Pd/C also gave unsatisfactory results with loss of deuterium producing a 1:1:1 mixture of the desired methyl 6,6-d_2-dehydroabietate **1e**, methyl 6-d-dehydroabietate **1f** and unreacted starting material.

Transformation of the hydroxyl function of **1c** to the trimethylsilyl ether and subsequent reduction by chloroalane formed *in situ* [11] was used successfully to form the fully reduced alcohol **1h** with no significant loss of deuterium. Excess of

chloroalane was required since the methyl ester was reduced preferentially before the trimethylsilyl ether. The alcohol **1h** was subsequently oxidised with Jones' reagent in refluxing acetone to give a 74% yield of product comprising 6,6-d_2-dehydroabietic acid **1i** (90%) and keto-acid **2c** (6.2%). 6,6-d_2-Dehydroabietic acid **1i** was isolated and recrystallised 99% pure in 23.8% overall yield. The % D distribution was calculated to be 98.34% d_2, 1.45% d_1, 0.21% d_0.

EXPERIMENTAL

Dehydroabietic acid **1a** was prepared from disproportionated rosin and was 99.9% pure. ^{1}H NMR 300.33 MHz ($CDCl_3$) δ: 1.25 (3H, s, H_3-20), 1.26 (6H, d, J=6.7 Hz, H_3-16 and H_3-17), 1.32 (3H, s, H_3-19), 1.45-1.65 (2H, m, H_α-1 and $H_{\alpha/\beta}$-6), 1.70-1.95 (5H, m, H_2-2, H_2-3 and $H_{\alpha/\beta}$-6), 2.27-2.36 (2H, overlapping br dd, H-5 and H_β-1), 2.84 (1H, sept., J=7.0 Hz, H-15), 2.9-3.0 (2H, dt, H_2-7), 6.92 (1H, s, H-14), 7.03 (1H, d, J=7.2 Hz, H-12), 7.19 (1H, d, J=7.2 Hz, H-11).

^{13}C NMR and Dept-135 75.64 MHz ($CDCl_3$) δ: 16.26 (q, C-19), 18.57 (t, C-2), 21.83 (t, C-6), 24.04 (2xq, C-16, C-17), 25.18 (q, C-20), 30.05 (t, C-7), 33.52 (d, C-15), 36.81 (t, C-3), 36.91 (s, C-10), 37.98 (t, C-1), 44.64 (d, C-5), 47.51 (s, C-4), 123.95 (d, C-12), 124.17 (d, C-11), 126.97 (d, C-14), 134.74 (s, C8), 145.78 (s, C-9), 146.81 (s, C-13), 185.60 (s, C-18).

The acid (50g, 0.17 mol) was methylated with ethereal-ethanolic diazomethane to give the methyl ester in quantitative yield. MS m/z 314 ($M^{+\cdot}$, 9% rel int), 299

(M-15, 8% rel int), 239 (M-75, 100% rel int).

Methyl dehydroabietate **1b** (52.3 g, 0.17 mol) was dissolved in glacial acetic acid (700 mL) and cooled until the acetic acid had begun to solidify. Chromium trioxide (61 g, 0.61 mol) was dissolved in glacial acetic acid-water (4:1) (100 mL) and added dropwise to the stirred solution of the ester. The solution was kept at the freezing point of glacial acetic acid until the addition of the chromium trioxide was complete. The solution was then allowed to stand for three days at 4 °C. The solution was then poured into water and extracted with diethyl ether. The combined ether extract was washed with saturated sodium bicarbonate solution and then with water. The ether extract was dried over magnesium sulphate and reduced by rotary evaporation to give a yellow-green gum. Methyl 7-oxo-dehydroabietate **2a** was separated from unreacted methyl dehydroabietate **1b** and oxidation by-products by preparative silica gel column chromatography. MS m/z 328 (M^+, 6% rel int), 313 (M-15, 3% rel int), 253 (M-75, 100% rel int).

Methyl 7-oxodehydroabietate **2a** (27.35 g, 83.4 mmol) was dissolved in benzene (500 mL) and deuterium oxide (30 mL, 99.9 % D) was added. Toluene-*p*-sulphonic acid (300 mg) was added as a catalyst and the solution was refluxed under a nitrogen atmosphere for three days. The deuterium oxide was then azeotropically removed and the proportions of methyl 7-oxodehydro-abietate **2a** , methyl 6-*d*-7-oxodehydroabietate **2d** and methyl 6,6-d_2-7-oxodehydroabietate **2b** were determined by GC/MS. Fresh deuterium oxide (30 mL) was added. These steps were repeated until the desired level (>97%) of deuteration at C-6 had been

obtained. Benzene was then removed by rotary evaporation to give methyl 6,6-d_2-7-oxodehydroabietate **2b** as a green gum. MS m/z 330 ($M^{+\cdot}$, 21% rel int), 315 (M-15, 12% rel int), 254 (M-76, 100% rel int). The % D of the product was calculated to be d_2 (97.07%), d_1 (2.93%), d_0 (0%).

Methyl 6,6-d_2-7-oxodehydroabietate **2b** (27.52 g, 83.4 mmol) was dissolved in methanol/deuterium oxide (19:1) and sodium borohydride (3.16 g, 83.4 mmol) added slowly to the stirred solution kept at 0 °C. The solution was stirred overnight and then poured into water and extracted with diethyl ether. The ether extract was dried over magnesium sulphate and reduced by rotary evaporation to give a faint yellow gum, 5.09 g, 90.6 % yield. GC/MS analysis of the product using the trimethylsilyl ether derivative showed it to comprise methyl 6,6-d_2-7β–hydroxydehydroabietate **1c** (85.4 %) MS m/z 332 ($M^{+\cdot}$, 34% rel int), 313 (M-17, 3% rel int), 239 (M-17-76, 95% rel int), 238 (M-17-77, 85% rel int), 164 (100% rel int), methyl 6,6-d_2-7α-hydroxydehydroabietate **1j** (5.4 %) MS m/z 332 ($M^{+\cdot}$, 20% rel int), 313 (M-17, 25% rel int), 239 (M-17-76, 95% rel int) 238 (M-17-77, 100 rel int) 164 (35% rel int), unreacted starting material **2b** (8.3 %) and methyl 6-*d*-abieta-6,8,11,13-tetraen-18-oate **3a** (0.9 %) MS m/z 313 ($M^{+\cdot}$, 30% rel int), 298 (M-15, 5% rel int), 238 (M-75, 100% rel int).

Methyl 6,6-d_2-7-trimethylsilyloxydehydroabietate **1g** and **1k**. Methyl 6,6-d_2-7-hydroxydehydroabietate α and β epimeric mixture **1c** and **1j** (5.0 g, 15.1 mmol) was dissolved in dry pyridine (5 mL) and bis(trimethylsilyl)trifluoroacetamide (5 mL, 19 mmol) added. The solution was refluxed under a dry nitrogen atmosphere

for 16 hr. The excess of reagent and solvent was removed under dry conditions and reduced pressure to give the crude silyl ethers as a gum, used immediately for reduction.

6,6-d_2-Dehydroabietol **1h**

Lithium aluminium hydride (1.42 g, 37.5 mmol) and bis(trimethylsilyl)trifluoro-acetamide (5 mL 20 mmol) were added to dry diethyl ether (50 mL). Dry diethyl ether (5 mL) was added to the methyl 6,6-d_2-7-trimethylsilyloxydehydroabietate epimers **1g** and **1k** (6.08 g, 15.1 mmol) and the resulting mixture was added slowly to the cooled lithium aluminium hydride solution, carefully leaving the insoluble crystalline trifluoroacetamide behind. The trifluoroacetamide was washed with dry diethyl ether and these washings were added to the lithium aluminium hydride solution. Anhydrous aluminium chloride (15 g, 112.5 mmol) was dissolved in dry diethyl ether (15 mL) and added dropwise to the stirred lithium aluminium hydride solution under a dry nitrogen atmosphere. The mixture was then stirred under dry nitrogen atmosphere for 16 hr. A saturated ammonium chloride solution was added to quench unreacted reagents and the mixture was poured into water. The aqueous solution was extracted with diethyl ether and then reduced by rotary evaporation to give a pale green gum, 3.65 g, 84.7 % yield. GC/MS analysis of the crude product after having been converted to the trimethylsilylether showed it to comprise 6,6-d_2-dehydroabietol **1h** (87.1%) and 6-*d*-abieta-6,8,11,13-trien-18-ol **3b** (11.1%).

6,6-d_2-Dehydroabietic acid **1i**.

6,6-d_2-Dehydroabietol **1h** (5 g, 17.4 mmol) was dissolved in acetone (100 mL)

and Jones reagent (29 mL, 8N) was dropwise added to the solution while heated under reflux. The solution was poured into water and extracted with diethyl ether. The combined ether extract was washed, dried over magnesium sulphate and reduced by rotary evaporation to give a yellow gum, 3.67 g, 73.5 % yield. GC/MS analysis of the methylated gum showed it to be 6,6-d_2-dehydroabietic acid **1i** (89.1 %) and 6,6-d_2-7-oxodehydroabietic acid **2c** (6.2 %). The crude 6,6-d_2-dehydroabietic acid **1i** (8 g, 26.5 mmol) was dissolved in ethanol (40 mL) and heated to 70 °C. 2-Amino ethanol (1.4 g) was added and hot water (20 mL at 70-80 °C) added to the solution. The solution was allowed to cool and refrigerated at 4 °C until the salt crystallised. The salt was isolated and washed with 1:1 cold water:ethanol and dried. The acid was recovered from the salt by addition of hydrochloric acid to an ethanolic solution of the amino salt. Water was added to the solution, the acid was extracted into ether and the combined extract was dried over magnesium sulphate and reduced by rotary evaporation to give a gum. Crystallisation of the gum was achieved from hot ethanol and water solution. GC/MS analysis of the methylated final crystalline product (melting point 167-168 °C, dehydroabietic acid m.p. 168°C) showed it to be 6,6-d_2-dehydroabietic acid **1i** (99 %), 6,6-d_2-7-oxodehydroabietic acid **2c** (0.7 %), and 6-*d*-abieta-6,8,11,13-tetraen-18-oic acid **3c** (0.3 %).

Elemental Analysis: Accurate mass measurement: 302.2214 amu, $C_{20}H_{26}D_2O_2$ requires 302.2215. IR (KBr disk) 3600cm^{-1}, 1710 cm^{-1}. UV(n-octane) λ_{max}(n-octane); 276.1 nm (ε=720), 267.9 nm (ε=660) 226.6 nm (ε=2640).

^{1}H NMR 300.33 MHz ($CDCl_3$) δ: 1.23 (3H, s, H_3-20), 1.24 (6H, d, *J*=6.7 Hz, H_3-16 and H_3-17), 1.30 (3H, s, H_3-19), 1.45-1.65 (1H, m, H_α-1), 1.70-1.86 (4H, m, H_2-3 and H_2-2), 2.24 (1H, s, H-5), 2.31 (1H, br d, *J*=12.7 Hz, H_β-1), 2.84 (1H, sept., *J*=7.0 Hz, H-15), 2.90 (2H, dd, *J*=17.3 Hz, H_2-7), 6.90 (1H, s, H-14), 7.01 (1H, d, *J*=7.2 Hz, H-12), 7.18 (1H, d, *J*=7.2 Hz, H-11).

^{13}C NMR and Dept135 75.64 MHz ($CDCl_3$) δ: 16.26 (q, C-19), 18.57 (t, C-2), 24.02 (2xq, C-16 and C-17), 25.14 (q, C-20), 29.80 (t, C-7), 33.50 (d, C-15), 36.77 (t, C-3), 36.86 (s, C-10), 37.94 (t, C-1), 44.45 (d, C-5), 47.43 (s, C-4), 123.91 (d, C-12), 124.12 (d, C-11), 126.96 (d, C-14), 134.72 (s, C-8), 145.76 (s, C-9), 146.82 (s, C-13), 185.18 (s, C-18).

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