JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2005; **48**: 223–229.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.910

Note

Synthesis of $^{13}C_1$-pinonaldehyde

Christopher W. Dicus, Dan Willenbring and Michael H. Nantz*
Department of Chemistry, University of California, Davis, CA 95616, USA

Summary

$^{13}C_1$-pinonaldehyde is prepared in seven steps from *cis*-pinonic acid. In the key sequence, the introduction of labeled carbon is accomplished by Lieben degradation of a methyl ketone followed by treatment of the resultant carboxylic acid with ^{13}C-methyl lithium. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: pinonaldehyde; carbon-13; Lieben degradation

Introduction

It is well known that the oxidation products of biogenic monoterpenes play a major role in tropospheric chemistry, as their atmospheric degradation by ozone and hydroxyl and nitrate radicals leads to the formation of volatile oxygenated compounds (VOCs), such as aldehydes, ketones, and carboxylic acids.[1] While this process contributes to the atmospheric accumulation of trace gases such as formaldehyde, carbon dioxide, and acetone, it has been shown that further secondary degradation of the larger oxidative products has more impact on the atmospheric budget of VOCs than the primary oxidation steps alone.[2] The understanding of this process is crucial to elucidating its role in atmospheric chemistry, however the quantification and identification of the primary and secondary terpene oxidation products continues to present a challenge.[3]

Much research efforts have focused on the ubiquitous terpene α-pinene and its major primary oxidation product, *cis*-pinonaldehyde (**1**).[4] Reported results from simulated atmospheric oxidation of these compounds illustrate the difficulty in the quantification and identification of the degradation products, with yields of pinonaldehyde from α-pinene ranging from 28 to 87%.[5] In addition, work by Nozière *et al.*[5] identifies formaldehyde as the primary oxidation product of pinonaldehyde at 150%, along with a large amount of

*Correspondence to: M. H. Nantz, Department of Chemistry, University of California, One Shields Avenue, Davis, CA 95616, USA. E-mail: mhnantz@ucdavis.edu

Received 15 October 2004
Revised 5 November 2004
Accepted 9 November 2004

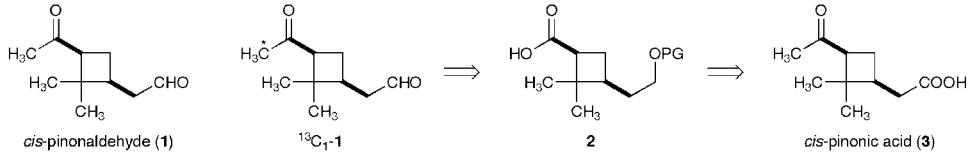


Figure 1. *cis*-Pinonaldehyde (1) and retrosynthetic analysis

unidentified carbonyls. This result was not, however, supported by theoretical calculations of this oxidative process.[6]

Because isotope dilution mass spectrometry is recognized as the most accurate method towards the quantification of low-molecular-weight VOCs,[7] we believe that ^{13}C-labeled pinonaldehyde ($^{13}C_1$-**1**) could be used as a mass spectrometry standard to improve quantification accuracy. In addition, a source of carbon-13 may also be beneficial in determining the mechanism by which formaldehyde is produced from pinonaldehyde, as well as in the structural determination of previously unidentified carbonyls arising from secondary oxidation.

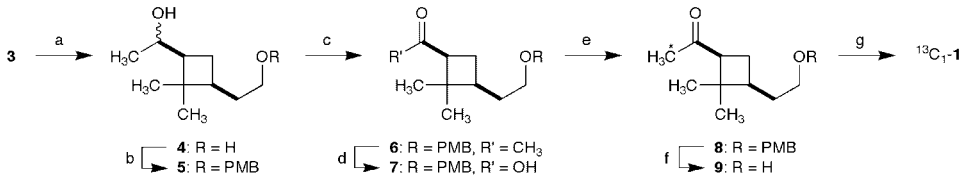
Results and discussion

Our retrosynthetic analysis (Figure 1) identifies *O*-protected carboxylic acid **2** as the proximal target. We envisioned **2** as the product of a Lieben degradation, thus suggesting commercially available *cis*-pinonic acid (**3**) as our starting material.[8] Conversion of **2** to $^{13}C_1$-**1** would proceed according to an established carboxylic acid-to-methyl ketone transformation, [for a recent example of this transformation, see ref.][9] but using ^{13}C-iodomethane as a source of labeled methyl.

The borane reduction of *cis*-pinonic acid (**3**) (Scheme 1) proceeded smoothly to give material that matched the reported NMR spectral data of diol **4**.[10,†] Selective protection of the primary hydroxyl group as a *p*-methoxybenzyl ether (PMB) was followed by PCC oxidation to provide methyl ketone **6**.[‡] Following the procedure of Moglioni *et al.* for Lieben degradation,[8] ketone **6** was degraded to carboxylic acid **7**. Subsequent transformation of **7** to methyl ketone **8** was accomplished following the method of Jorgenson.[9] The ^{13}C-MeLi required for this step was prepared *in situ* from ^{13}C-MeI.[11] The PMB group was cleaved using Yonemitsu's conditions,[12] and the title compound ($^{13}C_1$-**1**) was isolated following PCC oxidation of alcohol **9**. Spectral analysis, particularly the vicinal $^1J_{C,C}$ of the ketone carbonyl carbon and the $J_{C,H}$ of the

[†] During the course of this work, we prepared native pinonaldehyde by *bis*-oxidation of diol **4**, constituting an effective new route to this sensitive substrate. While the Swern oxidation of **4** gave a modest 46% yield, we were gratified to find that PDC oxidation provided **1** in 74% yield.

[‡] While traditional 1°-selective protecting groups (TBS, BPS) provided yields of ~95%, these compounds were not sufficiently soluble in the aqueous conditions necessary for the Lieben degradation step.



Scheme 1. Synthesis of $^{13}C_1$-1. Conditions: (a) BH_3 (2 eq), THF, 92%; (b) PMB-Cl (1 eq), NaH, DMF, 63%; (c) PCC, NaOAc, CH_2Cl_2, 90%; (d) aqueous NaOBr, 91%; (e) $^{13}CH_3$-Li (2.2 eq), Et_2O, 65%; (f) DDQ, CH_2Cl_2:H_2O, 20:1, 91%, (g) PCC, NaOAc, CH_2Cl_2, 90%

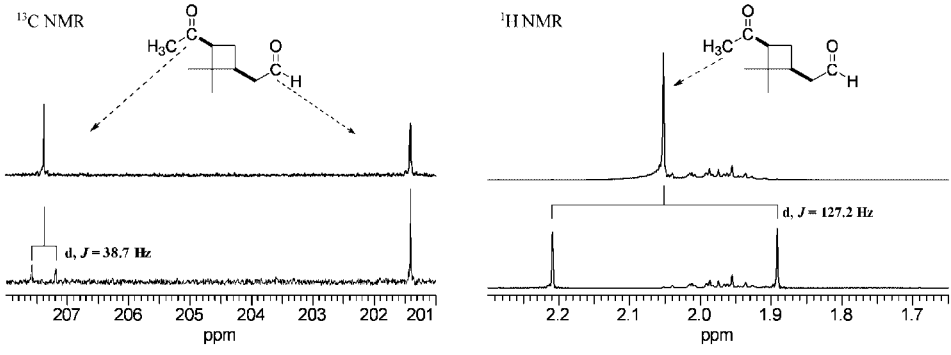


Figure 2. NMR overlays of pinonaldehyde (1) (top) and $^{13}C_1$-1 (bottom)

methyl ketone protons (Figure 2), confirm the structural integrity of the oxidation product.

Experimental

Ether and THF were distilled from sodium-benzophenone ketyl and CH_2Cl_2 was distilled from $LiAlH_4$. All chemicals were obtained from the Aldrich Chemical Company and used without further purification. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Varian Inova 400 spectrometer with ^1H and ^{13}C signals referenced to TMS and residual $CHCl_3$.

*1-[3-(2-hydroxyethyl)-2,2-dimethylcyclobutyl]ethanol (**4**)*

A solution of *cis*-pinonic acid (3.57 g, 19.4 mmol) in THF (70 ml) at 0°C was treated with $BH_3 \cdot THF$ (38.8 ml of a 1 M solution, 38.8 mmol). The reaction mixture was stirred at room temperature (rt) for 6 h whereupon methanol (20 ml) was added. After stirring an additional 12 h, the solvents were removed *in vacuo* and the residue was dissolved in methanol and concentrated ($\times 3$). Purification of the crude product by column chromatography (SiO_2; pet. ether:EtOAc, 1:1) provided diol **4** as a colorless oil (3.07 g, 92%); $R_f = 0.21$ (pet. ether:EtOAc, 1:1); IR 3347, 2953, 1460 cm^{-1}, ^1H NMR δ 1.02 (s, 3H),

1.05 (d, 2H, $J = 6.3$ Hz), 1.12 (s, 3H), 1.08–1.12 (m, 1H), 1.38–1.49 (m, 1H), 1.58–2.00 (m, 4H), 3.57 (br t, 2H, $J = 6.3$ Hz), 3.72 (br m, 1H); ^{13}C NMR δ 16.7, 21.2, 26.5, 31.3, 33.4, 38.4, 39.6, 50.4, 61.6, 69.3.

*(3-acetyl-2,2-dimethylcyclobutyl)acetaldehyde (**1**)*

To a solution of diol **4** (132 mg, 0.765 mmol) in CH_2Cl_2 (10 ml) at 0°C was added PDC (633 mg, 1.68 mmol). The reaction was warmed to rt and stirred 18 h, after which Florisil® was added to adsorb the chromium salts. The reaction mixture was stirred an additional 0.5 h and then filtered through a short pad of Celite®. The retentate was washed with CH_2Cl_2 and the filtrates were combined and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2; pet. ether:EtOAc, 8:2) to furnish *cis*-pinonaldehyde (**1**) as a colorless oil (96 mg, 74%); $R_f = 0.50$ (pet. ether:EtOAc, 1:1); IR 2950, 2908, 2818, 1720, 1703 cm^{-1}; ^{1}H NMR δ 0.85 (s, 3H), 1.34 (s, 3H), 1.90–2.05 (m, 2H), 2.05 (s, 3H), 2.36–2.53 (m, 3H), 2.93 (dd, 1H, $J = 10.0$, 7.6 Hz), 9.74 (t, 1H, $J = 1.6$ Hz); ^{13}C NMR δ 17.6, 22.7, 30.1, 30.3, 35.7, 43.2, 45.1, 54.3, 201.4, 207.4.

*1-{3-[2-(4-methoxybenzyloxy)ethyl]-2,2-dimethylcyclobutyl}ethanol (**5**)*

NaH (260 mg, 10.8 mmol) was added to a solution of diol **4** (930 mg, 5.40 mmol) in DMF (30 ml) at 0°C. The resultant suspension was stirred 20 min at rt. After cooling to 0°C, PMB-Cl (0.73 ml, 5.40 mmol) was added and the mixture was warmed to 60°C and stirred 3 h. The reaction mixture then was quenched by pouring over sat. $NaHCO_3$ and followed by extraction with ether. The combined organics were washed successively with water, brine, and dried (Na_2SO_4). The solvents were evaporated *in vacuo* and the residue was purified by column chromatography (SiO_2; pet. ether:EtOAc, 8:2) to provide **5** as a colorless oil (955 mg, 63%); $R_f = 0.45$ (pet. ether:EtOAc, 1:1); IR 3430, 2954, 2860, 1612, 1512 cm^{-1}; ^{1}H NMR δ 1.00 (s, 3H), 1.03 (d, 3H, $J = 6.4$ Hz), 1.10 (s, 3H), 1.05–1.15 (m, 1H), 1.46 (ddd, 1H, J = 13.6, 8.4, 6.8 Hz), 1.62–1.72 (m, 2H), 1.79–1.91 (m, 2H), 3.35 (t, 2H, J = 7.2 Hz), 3.70 (dq, 1H, J = 9.6, 6.4 Hz), 3.80 (s, 3H), 4.41 (s, 2H), 6.88 (m, 2H), 7.26 (m,2H); ^{13}C NMR δ 16.7, 21.2, 26.5, 30.4, 31.4, 38.8, 39.6, 50.4, 55.3, 68.7, 69.4, 72.6, 113.8, 129.2, 130.8, 159.1.

*1-{3-[2-(4-methoxybenzyloxy)ethyl]-2,2-dimethycyclobutyl}ethanone (**6**)*

To a solution of alcohol **5** (796 mg, 2.86 mmol) in CH_2Cl_2 (20 ml) at 0°C was added PCC (925 mg, 4.29 mmol) followed by NaOAc (352 mg, 4.29 mmol). The reaction mixture was warmed to rt and stirred 2.5 h whereupon Florisil® was added to adsorb the chromium salts. The reaction suspension was stirred an additional 30 min and then filtered through a short pad of Celite®. The

retentate was washed with CH_2Cl_2 and the filtrates were combined and evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2, pet. ether:EtOAc, 8:2) to give **6** as a colorless oil (710 mg, 90%); $R_f = 0.31$ (pet. ether:EtOAc, 8:2); IR 2950, 2860, 1702, 1612, 1512 cm^{-1}; ^1H NMR δ 0.84 (s, 3H), 1.27 (s, 3H), 1.42–1.55 (m, 1H), 1.59–1.70 (m, 1H), 1.76–2.10 (m, 3H), 2.03 (s, 3H), 2.81 (dd, 1H, $J = 9.9$, 7.5 Hz), 3.36 (dt, 2H, $J = 6.9$, 3.0 Hz), 3.80 (s, 3H), 4.41 (s, 2H), 6.87 (m, 2H), 7.25 (m, 2H); ^{13}C NMR δ 17.2, 23.0, 30.1, 30.4, 30.8, 38.9, 43.2, 54.3, 55.2, 68.2, 72.6, 113.7, 129.2, 130.6, 159.1, 208.0.

*3-[2-(4-methoxybenzyloxy)ethyl]-2,2-dimethylcyclobutanecarboxylic acid (**7**)*

To a solution of methyl ketone **6** (540 mg, 1.87 mmol) in dioxane (6 ml) at 0°C was added an aqueous solution of NaOBr, prepared by adding bromine (0.35 ml, 6.83 mmol) and NaOH (1.00 g, 25.0 mmol) to water (25 ml) at 0°C. After complete addition, dioxane was added until the reaction mixture was homogeneous. The reaction mixture was stirred at 0°C for 2h, at rt for 6h, and then extracted with CH_2Cl_2. The CH_2Cl_2 layer was extracted with 1N NaOH. The aqueous layers were combined and acidified to pH 3 with conc. HCl followed by addition of 40% aq. $NaHSO_3$ and extraction with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated to provide **7** (500 mg, 1.71 mmol, 91%); which was used without further purification; IR 2960, 2864, 1700, 1612, 1512 cm^{-1}; ^1H NMR δ 0.98 (s, 3H), 1.19 (s, 3H), 1.48–2.10 (m, 5H), 2.72 (dd, 1H, $J = 10.5$, 7.5 Hz), 3.36 (dt, 2H, $J = 6.9$, 1.5 Hz), 3.80 (s, 3H), 4.41 (s, 2H), 6.87 (m, 2H), 7.25 (m, 2H), 9.6 (b, 1H); ^{13}C NMR δ 17.4, 24.3, 30.1, 30.3, 39.2, 42.8, 46.0, 55.2, 68.2, 72.5, 113.7, 129.2, 130.4, 159.1, 178.5.

*$^{13}C_1$-1-{3-[2-(4-methoxybenzyloxy)ethyl]-2,2-dimethylcyclobutyl}ethanone (**8**)*

A solution of $^{13}CH_3I$ (0.25 ml, 3.9 mmol) in Et_2O (10 ml) at −78°C was treated with *t*-BuLi (4.6 ml of a 1.7 M solution, 7.8 mmol). The reaction mixture was stirred at −78°C for 30 min and then at rt for 1 h to destroy any remaining *t*-BuLi. The reaction mixture was cooled to −78°C and added dropwise via cannula into a solution of acid **7** (523 mg, 1.79 mmol) in THF (10 ml) at −78°C. On complete addition, the reaction mixture was stirred at −78°C for 30 min and then at rt for 2 h. The reaction was quenched by first cooling to 0°C followed by dropwise transfer via cannula into a rapidly stirring solution of ice cold sat. NH_4Cl. The aqueous layer was extracted with ether and the combined organics washed successively with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, pet. ether:EtOAc, 8:2) to provide ^{13}C-methyl ketone **8** as a colorless oil (340 mg, 1.17 mmol, 65%); $R_f = 0.31$ (pet. ether:EtOAc, 8:2); IR 2953, 2860,

1705, 1612, 1512 cm^{-1}; ^{1}H NMR δ 0.85 (s, 3H), 1.27 (s, 3H), 1.42–1.53 (m, 1H), 1.60–1.69 (m, 1H), 1.78–1.94 (m, 2H), 1.99–2.07 (m, 1H), 2.02 (d, 3H, $J_{C,H} = 126.8$ Hz), 2.81 (dd, 1H, $J = 10.0$, 7.2 Hz), 3.32–3.41 (m, 2H), 3.80 (s, 3H), 4.41 (s, 2H), 6.87 (m, 2H), 7.25 (m, 2H); ^{13}C NMR δ 17.2, 23.0, 30.1, 30.4, 30.8, 38.9, 43.2, 54.3 (d, $^{2}J_{C,C} = 13.6$ Hz), 55.2, 68.2, 72.5, 113.7, 129.2, 130.5, 159.1, 208.0 (d, $^{1}J_{C,C} = 38.9$ Hz); HRMS *m/z* calculated for [$^{13}C_1C_{17}H_{26}O_3$] 291.1916, found 291.1923.

*$^{13}C_1$-1-[3-(2-hydroxyethyl)-2,2-dimethylcyclobutyl]ethanone (**9**)*

To a solution of methyl ketone **8** (300 mg, 1.03 mmol) in a mixture of CH_2Cl_2:H_2O (20:1, 5 ml: 0.25 ml) was added DDQ (281 mg, 1.24 mmol). The reaction was stirred for 1 h, then filtered through Celite. The retentate was washed with CH_2Cl_2 and the filtrates were combined and washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; pet. ether:EtOAc, 8:2) provided alcohol **9** as a colorless oil (160 mg, 91%); $R_f = 0.40$ (pet. ether:EtOAc, 1:1); IR 3404, 2949, 2912, 2853, 1703 cm^{-1}; ^{1}H NMR δ 0.87 (s, 3H), 1.30 (s, 3H), 1.42–1.51 (m, 1H), 1.58–1.66 (m, 1H), 1.83–2.08 (m, 3H), 2.04 (d, 3H, $J_{C,H} = 126.8$ Hz), 2.84 (dd, 1H, $J = 10.0$, 7.2 Hz), 3.53–3.63 (m, 2H); ^{13}C NMR δ 17.2, 23.0, 30.1, 30.4, 33.0, 38.6, 43.2, 54.3 (d, $^{2}J_{C,C} = 12.9$ Hz), 61.1, 208.1 (d, $^{1}J_{C,C} = 39.5$ Hz), HRMS calculated for [$^{13}C_1C_9H_{18}O_2$] 171.1340, found 171.1341.

*$^{13}C_1$-(3-acetyl-2,2-dimethylcyclobutyl)acetaldehyde ($^{13}C_1$-**1**)*

To a solution of alcohol **9** (135 mg, 0.788 mmol) in CH_2Cl_2 (5 ml) were added PCC (255 mg, 1.18 mmol) and NaOAc (97 mg, 1.18 mmol). The reaction mixture was stirred at rt 2 h whereupon Florisil® was added to adsorb the chromium salts. The reaction suspension was filtered through a short pad of Celite®, and the retentate was washed with CH_2Cl_2. The organic filtrates were combined and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, pet ether:EtOAc, 8:2) to afford $^{13}C_1$-**1** (120 mg, 90%) as a colorless oil; $R_f = 0.50$ (pet ether:EtOAc, 1:1); IR 2956, 2905, 2847, 1720, 1703 cm^{-1}; ^{1}H NMR δ 0.85 (s, 3H), 1.34 (s, 3H), 1.90–2.05 (m, 2H), 2.05 (d, 3H, $J_{C,H} = 127.2$ Hz), 2.38–2.53 (m, 3H), 2.93 (dd, 1H, $J = 10.0$, 7.6 Hz), 9.74 (t, 1H, $J = 1.6$ Hz); ^{13}C NMR δ 17.6, 22.8, 30.1, 30.3, 35.7, 43.2, 45.1, 54.3 (d, $^{2}J_{C,C} = 12.9$ Hz), 201.4, 207.4 (d, $^{1}J_{C,C} = 38.7$ Hz); HRMS calculated for [$^{13}C_1C_9H_{16}O_2$] 169.1184, found 169.1185.

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