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A TOTAL SYNTHESIS OF (±)-HOP ETHER

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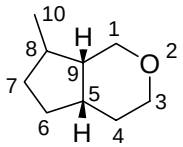
Abstract – A total synthesis of the iridoid monoterpene (±)-hop ether (**2**) is described. The Norrish I type fragmentation of bicyclo[2.2.1]heptanone (**5**) is the key step.

INTRODUCTION

The iridoid monoterpenes represent a large family of cyclopentanopyran natural products.[1] Among the various iridoids, the cyclopenta[*c*]pyran bearing the 2-oxo-*cis*-bicyclo[4.3.0]nonane (**1**) moiety as a fundamental ring system is the most widely distributed.[2] Hop ether (**2**),[3] isolated from Japanese hops[4] and regarded as a hop constituent which markedly affects the aroma and taste of beer,[5] is one of the most simple iridoids. It occupies a unique position in the iridoid monoterpenes because, biogenetically, it is the most straightforward one from the geraniol (**3**) precursor,[6] and it has no functional group on both of the isopropyl methyl groups of the iridane skeleton. Herein, we describe a total synthesis of racemic hop ether.



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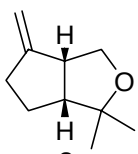

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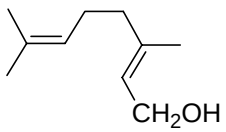

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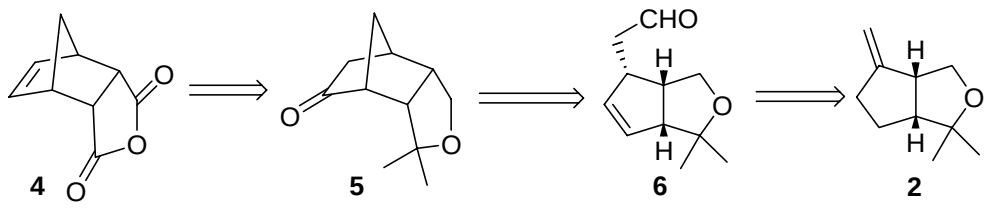
RESULTS AND DISCUSSION

Our approach to hop ether (**2**) is shown in Scheme 1. The crucial steps include (1) converting

Scheme 1.

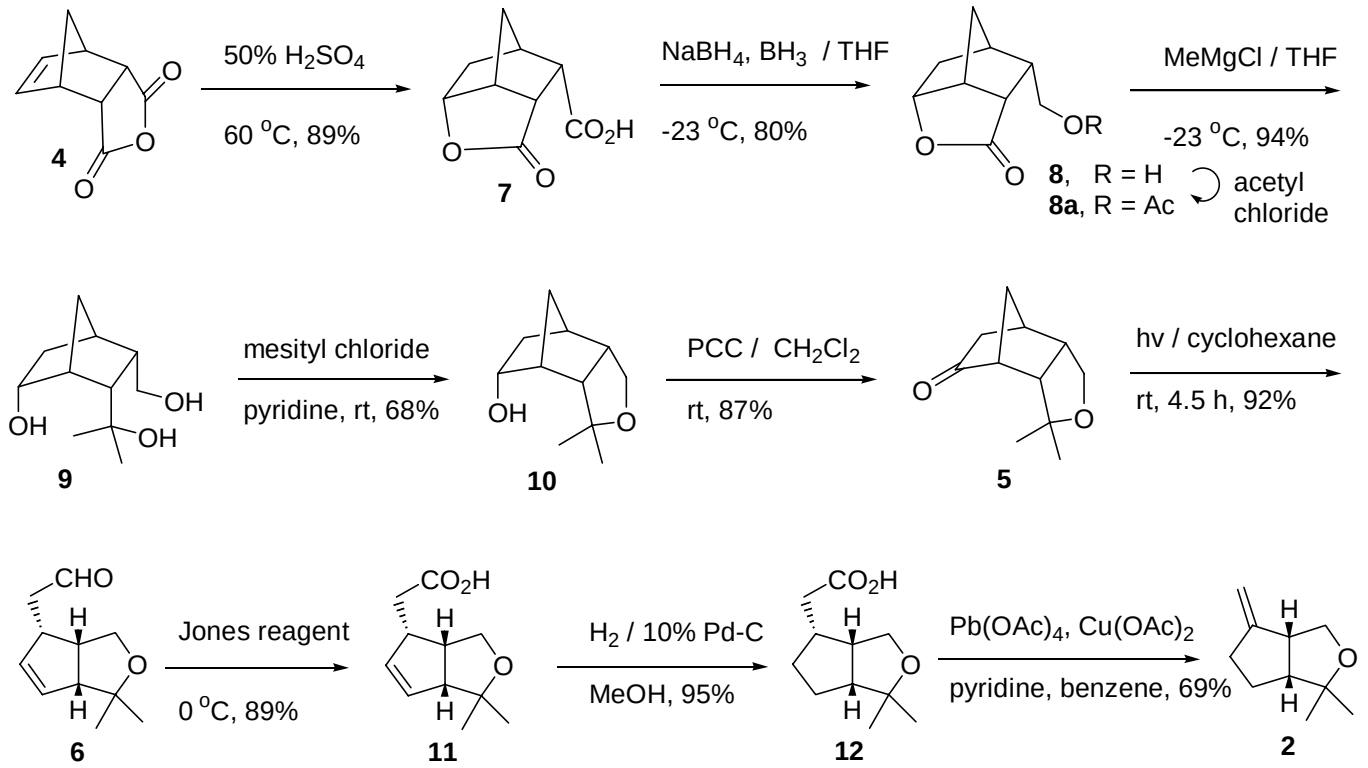


4 **5** **6** **2**

anhydride (**4**) into ketone (**5**), and (2) performing a Norrish type I reaction on ketone (**5**) to produce aldehyde (**6**). The compound (**6**) is a reasonable precursor for the synthesis of hop ether (**2**).

Lactone (**7**), easily prepared from the known Diels-Alder adduct (**4**) by hydration with 50% aqueous sulfuric acid,[7] was chosen as the starting material (as shown in Scheme 2). The lactone (**7**) was treated with diborane, which was generated using sodium borohydride and boron trifluoride etherate *in situ*,[8] in tetrahydrofuran to produce the corresponding hydroxy ester (**8**) (80%).[9] Acylating **8** with acetyl chloride yielded quantitative **8a**.[10] The spectral data of compound (**8a**) were high and agreed with those reported in the literature.[10] Treating compound (**8**) (or **8a**) with excess methyl magnesium chloride at –23 °C yielded triol **9** (94%). Regioselective monosulfonation of the primary hydroxyl group in triol (**9**), and then cyclizing the resulting sulfonate to compound (**10**), was examined in solvents, phenylsulfonyl chlorides, and reaction temperatures. Using mesitylenesulfonyl chloride in pyridine at room temperature yielded the largest amount of compound (**10**). To our surprise, even the amount of mesitylenesulfonyl chloride more than doubled, and the ratio of compound (**10**) (61%) and starting material (**9**) (25%) was closely maintained. Oxidating alcohol (**10**) using pyridinium chlorochromate yielded bicyclo[2.2.1]heptanone (**5**) (87%).

Scheme 2.



Photolysis of **5** in a freely oxygenated solution produced the Norrish type I cleavage product (**6**) (92%).[11] Converting the requisite **6** to the target molecule was quite straightforward. We then examined the oxidation of the formyl group in **6** using Jones reagent, which produced acid **(12)** (89%). Catalytically

hydrogenating **12** yielded **13** (95%). Finally, removing one carbon atom from **13** by treating it with lead tetraacetate in the presence of copper (II) acetate yielded 69% hop ether (**2**).[12]

In conclusion, we have developed a facile route to synthesis of (±)-hop ether (**2**) in 9 steps.

EXPERIMENTAL

General. THF were distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen (except those concerned with aqueous solutions) in spherical flasks with magnetic stirring. Extract was dried using anhydrous magnesium sulfate before it was concentrated *in vacuo*. Crude products were purified using preparative TLC or column chromatography on silica gel. All reported temperatures were uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-2000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX 200 spectrometer, with TMS (or solvent peak) as the internal standard. MS spectra were measured on a VGQUATTRO 5022 mass spectrometer. HRMS spectra were determined on a JEOL JMSHY 110 mass spectrometer. Elemental analyses were performed on a Heraeus CHN-O analyzer.

5-Oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carboxylic acid (7) A suspension of **4** (4.00 g, 24.4 mmol) in 50% (w/w) aqueous sulfuric acid (20 mL) was stirred at 60 ^{o}C for 2 h. The mixture was poured onto crashed ice (50 g). The precipitate was filtered and washed with ice water. After drying, the solid was recrystallized on methanol to afford lactone acid (**7**) (3.72 g, 84%) as white solid: mp 199-200 ^{o}C; IR (KBr, cm^{-1}) ν 3600–2400, 1771, 1694; MS (EI, 30 eV) 182 (M^{+}, 0.2), 79 (100); HRMS (ESI, M^{+}+H) calcd for $C_9H_{11}O_4$ 183.0657, found 183.0656; ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.41 (br s, 1H), 4.76 (dd, *J* = 5.1, 7.9 Hz, 1H), 3.22 (t, *J* = 3.9, 4.8 Hz, 1H), 2.97 (dt, *J* = 7.9, 2.1 Hz, 1H), 2.65 (dd, *J* = 4.8, 10.8 Hz, 1H), 2.52-2.45 (m, 1H), 1.95 (dd, *J* = 2.7, 14.1 Hz, 1H), 1.70-1.50 (m, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 178.3 (s), 172.9 (s), 80.1 (d), 48.1 (d), 48.0 (d), 41.4 (d), 39.4 (t), 37.3 (t), 32.6 (t); Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53; Found C, 59.02; H, 5.68.

9-Hydroxymethyl-4-oxatricyclo[4.2.1.0^{3,7}]nonan-5-one (8) A suspension of acid (**7**) (2.05 g, 11.3 mmol) in THF (30 mL) at -23 ^{o}C was added dropwise of boron trifluoride (1.0 mL, 7.9 mmol). After 30 min, the mixture was stirred at rt for 2 h and then quenched with saturated aqueous sodium bicarbonate (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2x30 mL). The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was chromatographied (hexane / ethyl acetate = 3:1) to furnish alcohol (**8**) (1.51 g, 80%) as colorless oil: IR (CH_2Cl_2, cm^{-1}) ν 3483, 1772; MS (EI, 30 eV) 168 (M^{+}, 0.2), 77 (100); HRMS (ESI, M^{+}+H) calcd for $C_9H_{13}O_3$ 169.0865, found 169.0864; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.86-4.78 (m, 1H), 3.81 (dd, *J* = 7.9, 11.6 Hz, 1H), 3.66 (dd, *J* = 7.17.1, 11.6 Hz, 1H), 3.27 (t, *J* = 4.8 Hz, 1H), 2.71 (dd, *J* = 4.8, 10.6 Hz, 1H),

2.69 (br s, 1H), 2.50-2.35 (m, 2H), 1.79-1.60 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.3 (s), 81.3 (d), 60.9 (t), 47.4 (d), 45.9 (d), 41.7 (d), 38.0 (d), 37.8 (t), 32.4 (t).

9-Ethanoyloxymethyl-4-oxatricyclo[4.2.1.0^{3,7}]nonan-5-one (8a) A solution of acid (**8**) (1.50 g, 8.9 mmol) in dichloromethane (20 mL) at 0 ^{o}C was added dropwise of acetyl chloride (1.2 mL, 16.8 mmol). After 30 min, the reaction was quenched with saturated aqueous sodium bicarbonate (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3x30 mL). The combined organic layers were washed with brine, dried, filtered, and concentrated. The crude product (**8a**) was pure enough without further purification. mp: 79-81 ^{o}C; IR (KBr, cm^{-1}) ν 1764, 1730; MS (EI, 30 eV) 210 (M^+, 0.1), 91 (100); HRMS (ESI, M^++H) calcd for $C_{11}H_{15}O_4$ 211.0970, found 211.0972; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.85-4.75 (m, 1H), 4.31 (dd, *J* = 6.0, 11.6, 1H), 4.14 (dd, *J* = 8.5, 11.6 Hz, 1H), 3.27 (t, *J* = 4.5 Hz, 1H), 2.67 (dd, *J* = 4.5, 10.8 Hz, 1H), 2.53-2.35 (m, 2H), 2.08 (s, 3H), 1.88-1.62 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.4 (s), 170.5 (s), 80.6 (d), 62.1 (t), 47.5 (d), 42.1 (d), 41.2 (d), 38.3 (d), 37.5 (t), 32.4 (t), 20.7 (q). The NMR spectra data were in accordance with the reported in the literature.[10]

5-Hydroxymethyl-6-(1-hydroxy-1-methyethyl)bicyclo[2.2.1]heptan-2-ol (9) To a solution of compound (**8**) (1.30 g, 7.74 mmol) in THF (30 mL) at -23 ^{o}C was added dropwise a solution of methylmagnesium chloride (10.0 mL, 3 M, 30 mmol). After being stirred at -23 ^{o}C for 3 h, the reaction was quenched with saturated ammonium chloride (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3x30 mL). The combined organic layers were washed witn brine, dried, filtered and evaporated. Purification (hexane/ethyl acetate = 1/2) yielded triol (**9**) (1.45 g, 94%) as white solid: mp: 169-170 ^{o}C; IR (KBr, cm^{-1}) ν 3254, 3180; MS (FAB) 201 (M^++1, 32), 154 (100); HRMS (ESI, M^++H) calcd for $C_{11}H_{21}O_3$ 201.1491, found 201.1490; ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.01 (d, *J* = 5.8 Hz, 1H), 5.47 (s, 1H), 4.12-4.00 (m, 2H), 3.95-3.75 (m, 2H), 2.33-2.13 (m, 3H), 1.98 (dd, *J* = 3.1, 11.8 Hz, 1H), 1.75-1.57 (m, 1H), 1.40-1.20 (m, 2H), 1.18 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 71.6 (d), 69.8 (s), 59.1 (t), 51.8 (d), 45.7 (d), 42.6 (d), 39.5 (d), 37.9 (t), 31.6 (t), 31.5 (q), 30.3 (q); Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07; Found C, 65.81; H, 9.95.

5,5-Dimethyl-4-oxatricyclo[5.2.1.0^{2,6}]decan-8-ol (10) To a solution of **9** (1.00 g, 5.0 mmol) in pyridine (15 mL) at 0 ^{o}C was added mesitylenesulfonyl chloride (1.20 g, 5.5 mmol). The mixture was stirred at rt for 6 h. Water was added and the resulting mixture was extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. The residue was chromatographied (hexane/ethyl acetate = 2/1) to afford starting material (**9**) (250 mg, 25%) and the desired product (**10**) (555 mg, 61%) as a colorless oil: IR (CH_2Cl_2, cm^{-1}) ν 3410; MS (EI, 30 eV) 182 (M^+, 0.8), 107 (100); HRMS (ESI, M^++H) calcd for $C_{11}H_{19}O_2$ 183.1385, found 183.1385; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.15-3.95 (m, 2H), 3.96 (dd, *J* = 2.9, 10.4 Hz, 1H), 3.81 (dd, *J* = 8.0, 10.4 Hz, 1H), 2.95-2.75 (m, 1H), 2.45-2.31 (m, 2H), 2.30-2.15 (m, 1H), 2.10-1.95 (m, 1H), 1.58 (s, 3H), 1.53-1.23 (m, 3H), 1.18

(s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 80.4 (s), 72.2 (d), 65.4 (t), 57.3 (d), 44.7 (d), 43.6 (d), 42.0 (t), 39.5 (d), 35.1 (t), 26.4 (q), 22.9 (q); Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95; Found C, 72.08; H, 9.67.

5,5-Dimethyl-4-oxatricyclo[5.2.1.0^{2,6}]decan-8-one (5) A suspension of alcohol (**10**) (1.12 g, 6.15 mmol), PCC (1.32 g, 6.12 mmol) and celite (5.0 g) in dichloromethane (50 mL) was stirred at rt for 3 h. The mixture was poured into a short silica gel column and eluted with dichloromethane. After evaporating of solvent, the residue was chromatographied (hexane/ethyl acetate = 4/1) to yield product (**5**) (960 mg, 87%) as white solids: mp: 44-45 ^{o}C; IR (KBr, cm^{-1}) 1731; MS (EI, 30 eV) 180 (M^+, 4), 79 (100); HRMS (ESI, M^++H) calcd for $C_{11}H_{17}O_2$ 181.1228, found 181.1229; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.80-3.70 (m, 2H), 2.95-2.85 (m, 1H), 2.70-2.60 (m, 2H), 2.54 (dd, *J* = 4.7, 9.6 Hz, 1H), 2.40-2.25 (m, 1H), 2.00-1.85 (m, 1H), 1.80-1.70 (m, 2H), 1.34 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 216.7 (s), 80.3 (s), 65.4 (t), 57.4 (d), 54.2 (d), 43.5, (d), 40.6 (t), 39.4 (t), 37.6 (d), 26.5 (q), 22.1 (q); Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95; Found C, 73.54; H, 9.12.

2-(1,1-Dimethyl-3,3a,4,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-4-yl)acetaldehyde (6) A solution of **5** (1.20 g, 6.59 mmol) in oxygen free cyclohexane (250 mL) was irradiated under a nitrogen atmosphere with a UV lamp (λ > 310 nm) using a pyrex glass filter at rt for 4.5 h. The solvent was evaporated and the crude product was purified by column chromatography (hexane/ethyl acetate = 4/1) to afford aldehyde (**11**) (1.10 g, 92%) as a colorless oil: IR (CH_2Cl_2, cm^{-1}) ν 3055, 2872, 1723; MS (EI, 30 eV) 181 (M^++1, 11), 91 (100); HRMS (ESI, M^++H) calcd for $C_{11}H_{17}O_2$ 181.1228, found 181.1229; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.2 Hz, 1H), 5.65-5.50 (m, 2H), 3.70 (dd, *J* = 7.1, 9.5 Hz, 1H), 3.49 (dd, *J* = 4.8, 9.5 Hz, 1H), 3.37-2.95 (m, 3H), 2.56 (dd, *J* = 1.2, 7.4 Hz, 2H), 1.18 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.2 (d), 133.7 (d), 130.6 (d), 82.0 (s), 66.3 (t), 60.7 (d), 45.0 (t), 44.6 (d), 40.9 (d), 27.8 (q), 24.2 (q).

2-(1,1-Dimethyl-3,3a,4,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-4-yl)acetic acid (11) To a solution of **11** (400 mg, 2.22 mmol) in acetone (15 mL) at 0 ^{o}C was treated with excess Jones reagent. The mixture was stirred for 15 min, then quenched with 2-propanol. Water (20 mL) was added and the mixture was extracted with ethyl acetate (4x40 mL). The combined organic layers were washed with brine (2x10 mL), dried, filtered and concentrated. The residue was chromatographied (hexane/ethyl acetate = 1/1) to yield acid (**11**) (388 mg, 89%) as white solids: mp: 71-72 ^{o}C; IR (KBr, cm^{-1}) ν 3500–2400, 3047, 1701, ; MS (EI, 30 eV) 197 (M^++1, 7), 91 (100); HRMS (ESI, M^++H) calcd for $C_{11}H_{17}O_3$ 197.1178, found 197.1178; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.65-5.63 (m, 2H), 3.82 (dd, *J* = 7.2, 9.6 Hz, 1H), 3.66 (dd, *J* = 5.1, 9.6 Hz, 1H), 3.22-3.07 (m, 3H), 2.53-2.45 (m, 2H), 1.24 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (50 MHz, CDCl3) δ 178.4 (s), 134.0 (d), 130.7 (d), 82.4 (s), 66.2 (t), 60.9 (d), 44.8 (t), 43.7, (d), 35.0 (d), 28.0 (q), 24.3 (q); Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22; Found C, 67.15; H, 8.35.

2-(1,1-Dimethyl-hexahydro-1*H*-cyclopenta[*c*]furan-4-yl)acetaldehyde (12) A suspension of **11** (450 mg, 2.30 mmol) and 10% palladium on charcoal (20 mg) in methanol (20 mL) under hydrogen at atmosphere pressure was stirred for 2 h. The mixture was filtered by a short celite column and the filtrate was evaporated under reduced pressure to leave **12** (432 mg, 95%), which was pure enough for further work, as white solids: mp: 65-66 ^{o}C; IR (KBr, cm^{-1}) ν 3300–2400, 1705; MS (EI, 30 eV) 199 (M^{+}+1, 0.3), 79 (100); HRMS (ESI, M^{+}+H) calcd for $C_{11}H_{19}O_3$ 199.1334, found 199.1333; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.77 (d, *J* = 9.6 Hz, 1H), 3.61 (dd, *J* = 5.4, 9.6 Hz, 1H), 3.00-2.90 (m, 1H), 2.55-2.35 (m, 4H), 1.80-1.70 (m, 2H), 1.59-1.30 (m, 1H), 1.22 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.5 (s), 83.2 (s), 65.3 (t), 52.3 (d), 47.2 (d), 39.2 (d), 35.6 (t), 31.2 (t), 28.2 (q), 26.6 (t), 23.4 (q); Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; Found C, 66.57; H, 9.12.

Hop ether (2) To a stirred solution of **13** (300 mg, 2.30 mmol), copper(II) acetate (10 mg) and pyridine (1 mL) in oxygen free benzene (15 mL) was added lead tetraacetate (2.55 g, 5.47 mmol). The mixture was refluxed for 4 h, then cooled to rt. Water (15 mL) was added. The layers were separated and the aqueous layer was extracted with hexane (2x20 mL). The combined organic layers were washed with brine, dried, filtered and concentrated. The residue was chromatographied (hexane / ethyl acetate = 10:1) to afford the pure desired **2** (160 mg, 69%) as a colorless oil: IR (CH_2Cl_2, cm^{-1}) ν 3055, 1605; MS (EI, 30 eV) 152 (M^{+}, 13), 107 (100); HRMS (ESI, M^{+}+H) calcd for $C_{10}H_{17}O$ 153.1279, found 153.1278;^{1}H NMR ($CDCl_3$, 200 MHz) 4.87 (br s, 1H), 4.75 (br s, 1H), 4.05 (t, *J* = 8.8 Hz, 1H), 3.63 (dd, *J* = 4.8, 8.8 Hz, 1H), 3.35-3.25 (m, 1H), 2.45-2.15 (m, 3H), 1.75-1.50 (m, 2 H), 1.23 (s, 3H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 M Hz) 156.3 (s), 105.7 (t), 82.5 (s), 72.2 (t), 54.0 (d), 49.4 (d), 34.9 (t), 27.5 (q), 27.4 (t), 23.3 (q). In the literature report, the signal of 27.5 (t) in ^{13}C NMR spectrum was missing.[3b]

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