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Synthesis of Carboxylic Acids, Esters, Alcohols and Ethers Containing a Tetrahydropyran Ring Derived from 6-Methyl-5-hepten-2-one

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Abstract: 3-hydroxy acids, 3-hydroxy-3,7-dimethyloct-6-enoic acid (1) and 3-hydroxy-2,2,3,7-tetramethyloct-6-enoic acid (2), were prepared from 6-methyl-5-hepten-2-one, and they were subsequently used to prepare (2,6,6-trimethyltetrahydropyran-2-yl)acetic acid (3) and 2-methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl)propanoic acid (4), respectively, *via* cyclization with an acidic catalyst such as boron trifluoride diethyl etherate or iodine. The reaction of carboxylic acids 3 and 4 with alcohols, including methanol, ethanol, and 1-propanol, produced the corresponding methyl, ethyl, and propyl esters, which all contained a tetrahydropyran ring. Reduction of carboxylic acids 3 and 4 afforded the corresponding alcohols. Subsequent reactions of these alcohols with several acyl chlorides produced novel esters. The alcohols also reacted with methyl iodide and sodium hydride to provide novel ethers. A one-pot cyclization–esterification of 1 to produce esters containing a tetrahydropyran ring, using iodine as a catalyst, was also investigated.

Key words: tetrahydropyran ring; cyclization, esterification

1 INTRODUCTION

Compounds containing a tetrahydropyran ring, such as rose oxide and linalool oxide, are highly valuable in the perfume industry. One method for the formation of the tetrahydropyran ring is the cyclization of 5-methyl-4-hexen-1-ol using a cationic catalyst. One common compound that contains this unit is 3,7-dimethyl-1,6-octadien-3-ol (linalool). The synthesis of 6-ethenyltetrahydro-2,2,6-trimethyl-2*H*-pyran-3-ol (linalool oxide) by the cyclization of linalool using a cationic catalyst has been reported previously[1-3]. Carboxylic acids containing a tetrahydropyran ring can be synthesized by the cyclization of the corresponding 3-hydroxy acids that contain the 5-methyl-4-hexen-1-ol unit. These carboxylic acids are valuable in the perfume industry because the side chain of the tetrahydropyran can be further modified. Robin et al. reported the cyclization of 1-ethyl 4-methyl 2-hydroxy-2-(4-methyl-3-penten-1-yl) butanedioate to produce the tetrahydropyran ring[4]. Caliezi et al.[5] and Iwamoto et al.[6] separately reported the cyclization of esters of 3-hydroxy-3,7-dimethyloct-6-enoic acid (**1**) using a cationic catalyst. However, Fkyerat et al. reported that this cyclization was accompanied by hydrolysis of the esters by the cationic catalyst, which consequently, decreased the product yield[7].

Therefore, in this report, the cyclization of 3-hydroxy-3,7-dimethyloct-6-enoic acid, rather than an ester, was attempted using a cationic catalyst to prepare the carboxylic acid containing a tetrahydropyran ring. In addition, 3-hydroxy-2,2,3,7-tetramethyloct-6-enoic acid (**2**), which has a structure similar to that of the carboxylic acid **1**, was synthesized. Ester, alcohol, and ether derivatives of carboxylic acids **1** and **2** were subsequently produced.

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2 EXPERIMENTAL

2.1 General

NMR spectra were obtained using a 400 or 300 MHz FT-NMR spectrometer (JEOL JNM-LA-400 or Bruker DPX-300) with Me_4Si as an internal standard and $CDCl_3$ as the solvent. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. Mass spectra were recorded on a JEOL JMS-HX110A, a JEOL JMS-AX500, or a Thermo Fischer Exactive type spectrometer.

2.2 Syntheses

2.2.1 Synthesis of 3-hydroxylic acids

6-Methyl-5-hepten-2-one was obtained from Tokyo Chemical Industry Co., Ltd., and used as received.

Tetrahydrofuran (150 mL), naphthalene (16.0 g, 125 mmol), lithium (1.74 g, 250 mmol), and diethylamine (18.3 g, 250 mmol) were added to a 500 mL flask equipped with a reflux condenser, a nitrogen inlet and a dropping funnel. The mixture was stirred under dry nitrogen until the lithium was fully dissolved. A solution of 2-methylpropanoic acid (8.8 g, 100 mmol) in tetrahydrofuran (60 mL) was added dropwise over 1.5 h, and the mixture was then stirred for an additional 1 h. Next, a solution of 6-methyl-5-hepten-2-one (10.1 g, 80 mmol) in tetrahydrofuran (60 mL) was added dropwise over 1 h, and the reaction mixture was stirred at room temperature for 24 h. The mixture was extracted three times with 2 M aqueous sodium hydroxide solution (30 mL). The aqueous layer was acidified with 2 M hydrochloric acid, and extracted three times with diisopropyl ether (30 mL). The organic layer was washed twice with aqueous sodium chloride solution (30 mL), dried with anhydrous sodium sulfate, and evaporated. The product was purified using column chromatography and eluted with hexane/ethyl acetate (50/1). A total mass of 11.2 g (75% yield) of **1** was obtained.

2 was prepared using a similar procedure.

3-Hydroxy-3,7-dimethyloct-6-enoic acid (1)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.31 (3H, s), 1.62 (3H, s), 1.69 (3H, s), 1.52-1.60 (2H, m), 2.06-2.12 (2H, m), 2.53, 2.59 (2H, ABq, J = 15.8Hz), 5.11 (1H, t, J = 7,1Hz)

^{13}C-NMR (δ, $CDCl_3$): 18.1, 23.0, 26.1, 27.0, 42.1, 45.2, 71.8, 124.1, 132.7, 177.7

IR (neat, cm^{-1}): 3394, 2972, 1710,1087

HRMS (ESI-MS) m/z calcd for $C_{10}H_{18}O_3$ + Na 209.1148, found 209.1146.

3-Hydroxy-2,2,3,7-tetramethyloct-6-enoic acid (2)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.23 (6H, s), 1.28 (3H, s), 1.49-1.63 (2H, m), 1.64 (3H, s), 1.70 (3H, s), 2.05-2.24 (2H, m), 5.11-5.17 (1H, m),

^{13}C-NMR (δ, $CDCl_3$): 18.1, 21.3, 21.6, 21.7, 22.6, 26.2, 36.9, 50.7, 76.5, 124.5, 133.0, 182.2

IR (neat, cm^{-1}): 3315, 2977, 2653, 1697, 1089

HRMS (ESI-MS) m/z calcd for $C_{12}H_{22}O_3$ + Na 237.1461, found 237.1459.

2.2.2 Cyclization of 3-hydroxy acids

Typical procedure:

Boron trifluoride diethyl etherate (86 mg), toluene (25 mL), and **1** (0.465 g, 2.5 mmol) were placed in a 50 mL flask equipped with a reflux condenser, and the mixture was stirred at 50℃ for 8 h. Next, water (20 mL) was added, and the mixture was extracted three times with diisopropyl ether (20 mL). The organic layer was washed twice with aqueous sodium chloride solution (20 mL), dried with anhydrous sodium sulfate, and evaporated. The product was purified using column chromatography and eluted with hexane/ethyl acetate (8/1). A total mass of 0.400 g (86% yield) of (2,6,6-trimethyltetrahydropyran-2-yl) acetic acid (**3**) was obtained.

2-methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl) propanoic acid (**4**) was synthesized using a similar procedure.

(2,6,6-Trimethyltetrahydropyran-2-yl) acetic acid (3)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.30 (3H, s), 1.33 (3H, s), 1.37 (3H, s), 1.42-1.89 (6H, m), 2.52, 2.54 (2H, ABq, J = 15.6Hz)

^{13}C-NMR (δ, $CDCl_3$): 16.3, 26.8, 28.1, 32.6, 34.5, 36.4, 49.4, 74.0, 75.0, 172.4

IR (neat, cm^{-1}): 3087, 2937, 2697, 1708

HRMS (FAB-MS) m/z calcd for $C_{10}H_{18}O_3$ + H 183.1329, found 183.1347.

2-Methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl) propanonic acid (4)

White crystals (m.p. 59.0-60.0℃).

^{1}H-NMR (δ, $CDCl_3$): 1.19 (3H, s), 1.22 (3H, s), 1.32 (3H, s), 1.35 (6H, s), 1.38-1.86 (6H, m)

^{13}C-NMR (δ, $CDCl_3$): 16.2, 20.8, 21.3, 27.6, 33.3, 36.1, 52.1, 75.3, 79.0, 178.3

IR (neat, cm^{-1}): 3060, 2971, 1697

HRMS (FAB-MS) m/z calcd for $C_{12}H_{22}O_3$ + H 215.1647, found 215.1653.

2.2.3 Esterification of **3** and **4**

Typical procedure:

Methanol (25 mL), *p*-toluenesulfonic acid (95 mg, 0.5 mmol), and **3** (0.465 g, 2.5 mmol) were placed in a 50 mL flask equipped with a reflux condenser, and the mixture was stirred with refluxing for 8 h. After cooling to room temperature, water (20 mL) was added and the mixture was extracted three times with 2 M sodium hydroxide aqueous solution (10 mL) in order to remove the acidic material. The aqueous layer was extracted three times with diisopropyl ether (10 mL). The organic layer was washed twice with aqueous sodium chloride solution (20 mL), dried with anhydrous sodium sulfate, and evaporated. The

product was purified using column chromatography and eluted with hexane/ethyl acetate (40/1). A total mass of 0.416 g (83% yield) of methyl 2-(2,6,6-trimethyltetrahydropyran-2-yl) acetate (**5a**) was obtained.

Other esters of **3** or **4** were synthesized using a similar procedure.

Methyl 2-(2,6,6-trimethyltetrahydropyran-2-yl) acetate (**5a**)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.17 (3H, s), 1.22 (3H, s), 1.31 (3H, s), 1.35-1.84 (6H, m), 2.46, 2.59 (2H, ABq, J = 13.3Hz), 3.66 (3H, s)

^{13}C-NMR (δ, $CDCl_3$): 16.7, 28.3, 29.9, 31.7, 34.3, 36.7, 48.3, 51.7, 72.2, 72.8, 172.1

IR (neat, cm^{-1}): 2973, 1726

HRMS (ESI-MS) m/z calcd for $C_{11}H_{20}O_3$ + Na 223.1305, found 223.1301.

Ethyl 2-(2,6,6-trimethyltetrahydropyran-2-yl) acetate (**5b**)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.17 (3H, s), 1.22 (3H, s), 1.26 (3H, t, J = 7.1Hz), 1.32 (3H, s), 1.35-1.85 (6H, m), 2.43, 2.57 (2H, ABq, J = 13.2Hz), 4.11 (2H, q, J = 7.1Hz)

^{13}C-NMR (δ, $CDCl_3$): 14.7, 16.8, 28.3, 29.9, 31.6, 34.3, 36.8, 48.5, 60.4, 72.2, 72.9, 171.6

IR (neat, cm^{-1}): 2975, 2935, 1734

HRMS (ESI-MS) m/z calcd for $C_{12}H_{22}O_3$ + Na 237.1461, found 237.1457.

Propyl 2-(2,6,6-trimethyltetrahydropyran-2-yl) acetate (**5c**)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 0.95 (3H, t, J = 7.4Hz), 1.17 (3H, s), 1.21 (3H, s), 1.32 (3H, s), 1.35-1.50 (2H, m), 1.59-1.83 (6H, m), 2.43, 2.58 (2H, ABq, J = 13.2Hz), 4.02 (2H, t, J = 6.5Hz)

^{13}C-NMR (δ, $CDCl_3$): 10.9, 16.8, 22.4, 28.3, 30.0, 31.6, 34.5, 36.8, 48.5, 66.2, 72.2, 72.9, 171.8

IR (neat, cm^{-1}): 2971, 1734

HRMS (ESI-MS) m/z calcd for $C_{13}H_{24}O_3$ + Na 251.1618, found 251.1612.

Methyl 2-methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl) propanoate (**6a**)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.07 (3H, s), 1.14 (3H, s), 1.17 (3H, s), 1.18 (3H, s), 1.21 (3H, s), 1.22-1.28 (2H, m), 1.44-1.95 (4H, m), 3.63 (3H, s)

^{13}C-NMR (δ, $CDCl_3$): 16.9, 21.2, 22.2, 27.7, 29.8, 33.6, 36.5, 51.7, 52.1, 71.6, 76.6, 177.7

IR (neat, cm^{-1}): 2973, 2933, 1728

HRMS (FAB-MS) m/z calcd for $C_{13}H_{24}O_3$ + H 229.1804, found 229.1818.

Ethyl 2-methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl) propanoate (**6b**)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.08 (3H, s), 1.14 (3H, s), 1.17 (6H, s), 1.22 (3H, s), 1.25 (3H, t, J = 7.1Hz), 1.08-1.50 (2H, m), 1.54-1.94 (4H, m), 4.07 (2H, t, J = 7.1Hz)

^{13}C-NMR (δ, $CDCl_3$): 14.7, 16.9, 21.3, 22.3, 27.8, 29.8, 33.6, 36.5, 51.9, 60.4, 71.5, 76.5, 177.2

IR (neat, cm^{-1}): 2974, 2931, 1720

HRMS (ESI-MS) m/z calcd for $C_{14}H_{26}O_3$ + Na 265.1774, found 265.1770.

Propyl 2-methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl) propanoate (**6c**)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 0.96 (3H, t, J = 7.4Hz), 1.09 (3H, s), 1.15 (3H, s), 1.18 (6H, s), 1.22 (3H, s), 1.21-1.29 (2H, m), 1.45-1.89 (6H, m), 3.95 (2H, t, J = 6.6Hz)

^{13}C-NMR (δ, $CDCl_3$): 11.1, 16.9, 21.2, 21.3, 22.3, 22.4, 27.8, 29.8, 33.6, 36.5, 52.1, 66.1, 71.5, 76.5, 177.3

IR (neat, cm^{-1}): 2969, 2877, 1722

HRMS (ESI-MS) m/z calcd for $C_{15}H_{28}O_3$ + Na 279.1931, found 279.1926.

2.2.4 Reduction of **3** and **4**

Typical procedure:

Lithium aluminum hydride (1.71 g, 45 mmol), and tetrahydrofuran (50 mL) were placed in a 500 mL flask equipped with a reflux condenser, a nitrogen inlet, and a dropping funnel. The flask was cooled with iced water, and a solution of **3** (2.79 g) in tetrahydrofuran (20 mL) was added dropwise over 1 h. After refluxing for 8 h, water (100 mL) was added dropwise to the reaction mixture, followed by the addition of 10% hydrochloric acid (100 mL). The mixture was extracted three times with diethyl ether (30 mL). The organic layer was washed twice with aqueous sodium chloride solution (20 mL), dried with anhydrous sodium sulfate, and evaporated. The product was purified using column chromatography and eluted with hexane/ethyl acetate (20/1). A total mass of 2.27 g (88% yield) of 2-(2,6,6-trimethyltetrahydropyran-2-yl) ethanol (**7**) was obtained.

2-(2,6,6-Trimethyltetrahydropyran-2-yl) ethanol (**7**)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.19 (3H, s), 1.24 (3H, s), 1.30 (3H, s), 1.38-1.80 (8H, m), 3.79-3.84 (2H, m), 3.93 (1H, t, J = 7.3Hz)

^{13}C-NMR (δ, $CDCl_3$): 16.6, 26.6, 27.8, 33.6, 34.9, 36.8, 46.1, 60.1, 72.7, 76.3

IR (neat, cm^{-1}): 3415, 1373, 1120

HRMS (FAB-MS) m/z calcd for $C_{10}H_{20}O_2$ + H 173.1542, found 173.1534.

2-Methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl)propanol (8)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 0.85 (3H, s), 0.94 (3H, s), 1.19 (3H, s), 1.25 (3H, s), 1.28 (3H, s), 1.27-2.05 (6H, m), 3.46-3.58 (2H, m), 4.39 (1H, t, J = 7.4Hz)

^{13}C-NMR (δ, $CDCl_3$): 16.6, 21.0, 21.2, 21.5, 27.8, 29.5, 33.6, 36.6, 42.2, 71.6, 72.7, 81.2

IR (neat, cm^{-1}): 2973, 1380, 1097

HRMS (FAB-MS) m/z calcd for $C_{12}H_{24}O_2$ + H 201.1855, found 201.1836.

2.2.5 Esterification of 7 and 8

Typical procedure:

7 (0.431 g, 2.5 mmol), triethylamine (0.379 g, 3.8 mmol), DMAP (50 mg), and tetrahydrofuran (20 mL) were placed in a 100 mL flask equipped with a funnel. A solution of acetyl chloride (0.294 g, 3.8 mmol) in tetrahydrofuran (20 mL) was added dropwise to the mixture over 30 min, then stirred overnight. Next, the reaction mixture was extracted three times with diisopropyl ether (10 mL). The organic layer was washed twice with aqueous sodium chloride solution (20 mL), dried with anhydrous sodium sulfate, and evaporated. The product was purified by column chromatography and eluted with hexane/ethyl acetate (40/1). A total mass of 0.461 g (86% yield) of 2-(2,6,6-trimethyltetrahydropyran-2-yl) methyl propanoate (9a) was obtained.

The other esters of 7 and 8 were synthesized using a similar procedure.

2-(2,6,6-Trimethyltetrahydropyran-2-yl) ethyl acetate (9a)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.17 (3H, s), 1.20 (3H, s), 1.22 (3H, s), 1.24-1.89 (8H, m), 2.04 (3H, s), 4.11-4.25 (2H, m)

^{13}C-NMR (δ, $CDCl_3$): 16.8, 21.5, 28.1, 29.6, 31.9, 35.2, 37.0, 42.2, 61.9, 71.8, 72.4, 171.7

IR (neat, cm^{-1}): 2973, 2935, 1736

HRMS (FAB-MS) m/z calcd for $C_{12}H_{22}O_3$ − H 213.1491, found 213.1491.

2-(2,6,6-Trimethyltetrahydropyran-2-yl) ethyl propanoate (9b)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.13 (3H, t, J = 7.5Hz), 1.17 (3H, s), 1.21 (3H, s), 1.22 (3H, s), 1.24-1.89 (8H, m), 2.31 (2H, q, J = 7.5Hz), 4.19-4.25 (2H, m)

^{13}C-NMR (δ, $CDCl_3$): 9.5, 16.8, 28.1, 29.7, 31.9, 35.3, 37.0, 42.3, 61.8, 71.8, 72.4, 175.0

IR (neat, cm^{-1}): 2979, 2937, 1738

HRMS (FAB-MS) m/z calcd for $C_{13}H_{24}O_3$ + H 229.1804, found 229.1815.

2-(2,6,6-Trimethyltetrahydropyran-2-yl) ethyl butanoate (9c)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 0.94 (3H, t, J = 7.4Hz), 1.17 (3H, s), 1.21 (3H, s), 1.22 (3H, s), 1.24-1.89 (10H, m), 2.27 (2H, t, J = 7.4Hz), 4.15-4.26 (2H, m)

^{13}C-NMR (δ, $CDCl_3$): 14.1, 16.8, 18.9, 28.1, 29.7, 31.9, 35.2, 26.8, 37.0, 42.3, 61.7, 71.8, 72.5, 174.3

IR (neat, cm^{-1}): 1736

HRMS (FAB-MS) m/z calcd for $C_{14}H_{26}O_3$ + H 243.1960, found 243.1956.

2-(2,6,6-Trimethyltetrahydropyran-2-yl) ethyl 2-methylpropanoate (9d)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.14 (3H, s), 1.17 (6H, d, J = 7.0Hz), 1.21 (3H, s), 1.22 (3H, s), 1.26-1.89 (8H, m), 2.54 (1H, quin, J = 7.0Hz), 4.16-4.25 (2H, m)

^{13}C-NMR (δ, $CDCl_3$): 16.8, 19.4, 28.1, 29.7, 31.9, 34.4, 35.3, 37.0, 42.3, 61.7, 71.8, 72.5, 177.7

IR (neat, cm^{-1}): 2973, 1733

HRMS (FAB-MS) m/z calcd for $C_{14}H_{26}O_3$ + H 243.1960, found 243.1949.

2-(2,6,6-Trimethyltetrahydropyran-2-yl) ethyl benzoate (9e)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.14 (3H, s), 1.23 (3H, s), 1.28 (3H, s), 1.34-2.01 (8H, m), 4.43-4.50 (2H, m), 7.43 (2H, t, J = 7.6Hz), 7.47-7.57 (1H, m), 8.02-8.05 (2H, m)

^{13}C-NMR (δ, $CDCl_3$): 16.8, 28.1, 29.7, 32.0, 35.4, 42.4, 62.4, 71.8, 72.5, 128.7, 129.9, 131.0, 133.2, 167.2

IR (neat, cm^{-1}): 2971, 2935, 1720, 712

HRMS (FAB-MS) m/z calcd for $C_{17}H_{24}O_3$ + H 277.1798, found 277.1798.

2-Methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl) propyl acetate (10a)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 0.89 (3H, s), 0.90 (3H, s), 1.10 (3H, s), 1.18 (6H, s), 1.23-1.29 (2H, m), 1.45-1.80 (4H, m), 2.06 (3H, s), 4.01, 4.12 (2H, ABq, J = 10.8Hz)

^{13}C-NMR (δ, $CDCl_3$): 16.7, 19.9, 20.1, 21.6, 21.9, 27.9, 29.5, 33.6, 36.7, 42.5, 70.4, 71.2, 76.5, 172.0

IR (neat, cm^{-1}): 2973, 1741

HRMS (FAB-MS) m/z calcd for $C_{14}H_{26}O_3$ + H 243.1955, found 243.1952.

2-Methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl) propyl propanoate (10b)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 0.89 (3H, s), 0.90 (3H, s), 1.09 (3H, s), 1.15 (3H, t, J = 7.6Hz), 1.18 (6H, s), 1.23-1.80 (6H, m), 2.34 (2H, q, J = 7.6Hz), 4.02, 4.13 (2H, ABq, J = 10.8Hz)

^{13}C-NMR (δ, $CDCl_3$): 9.7, 16.7, 19.9, 20.1, 21.9, 27.9, 28.3, 29.5, 33.6, 36.7, 42.6, 70.2, 71.2, 76.5, 175.3

IR (neat, cm^{-1}): 2974, 1738

HRMS (FAB-MS) m/z calcd for $C_{15}H_{28}O_3$ + H 257.2117, found 257.2112.

2-Methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl)propyl butanoate (10c)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 0.89 (3H, s), 0.90 (3H, s), 0.96 (3H, t, J = 7.4Hz), 1.10 (3H, s), 1.18 (6H, s), 1.21-1.31 (2H, m), 1.44-1.83 (6H, m), 2.30 (2H, t, J = 7.4Hz), 4.02,4.13 (2H, ABq, J = 10.8Hz)

^{13}C-NMR (δ, $CDCl_3$): 14.1, 16.7, 19.0, 20.1, 21.9, 27.9, 29.5, 33.6, 36.7, 42.6, 70.1, 71.2, 76.5, 77.0, 174.5

IR (neat, cm^{-1}): 2970, 2877, 1734

HRMS (FAB-MS) m/z calcd for $C_{16}H_{30}O_3$ + H 271.2273, found 271.2269.

2-Methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl)propyl 2-methylpropanoate (10d)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 0.90 (6H, s), 1.10 (3H, s), 1.17 (6H, d, J = 7.0Hz),1 .18 (6H, s), 1.24-1.84 (6H, m), 2.56 (1H, quin, J = 7.0Hz), 4.02-4.11 (2H, ABq, J = 10.8Hz)

^{13}C-NMR (δ, $CDCl_3$): 16.8, 19.5, 19.9, 20.1, 21.9, 27.9, 29.5, 33.6, 34.8, 36.7, 70.1, 71.2, 77.0, 177.9

IR (neat, cm^{-1}): 2973, 2877, 1734

HRMS (FAB-MS) m/z calcd for $C_{16}H_{30}O_3$ + H 271.2273, found 271.2276.

2-Methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl)propyl benzoate (10e)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.02 (6H, s), 1.13 (3H, s), 1.21 (3H, s), 1.25 (3H, s), 1.04-1.82 (6H, m), 4.29, 4.83 (2H, ABq, J = 10.8Hz), 7.42-7.45 (2H, m), 7.45-7.59 (1H, m), 8.08-8.08 (2H, m)

^{13}C-NMR (δ, $CDCl_3$): 16.8, 20.2, 20.4, 22.0, 27.9, 33.6, 36.7, 43.0, 70.9, 71.3, 76.6, 128.7, 129.9, 131.3, 133.1, 167.4

IR (neat, cm^{-1}): 2972, 1720, 712

HRMS (FAB-MS) m/z calcd for $C_{19}H_{28}O_3$ + H 305.2117, found 305.2108.

2.2.6 Etherification of alcohol **3** or **4**

Typical procedure:

Tetrahydrofuran (30 mL) and 60% sodium hydride in paraffin solution (0.120 g, 3.0 mmol) were placed in a 100 mL flask equipped with a funnel. A solution of **7** (0.431 g, 2.5 mmol) in tetrahydrofuran (5 mL) was added dropwise over 30 min. The mixture was stirred for 2 h, and then a solution of methyl iodide (0.532 g, 3.75 mmol) in tetrahydrofuran (5 mL) was added dropwise over 3 h. The reaction mixture was stirred overnight, and then water (20 mL) was added dropwise with cooling. Next, the reaction mixture was extracted three times with diisopropyl ether (10 mL). The organic layer was washed twice with aqueous sodium chloride solution (20 mL), dried with anhydrous sodium sulfate, and evaporated. The product was purified using column chromatography and eluted with hexane/ethyl acetate (40/1). A total mass of 0.340 g (73% yield) of 2-(2-methoxyethyl)-2,6,6-trimethyltetrahydropyran (**11a**) was obtained.

11b was synthesized using a similar procedure.

2-(2-Methoxyethyl)-2,6,6-trimethyltetrahydropyran (11a)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 1.20 (3H, s), 1.21 (3H, s), 1.22 (3H, s), 1.26-1.89 (8H, m), 3.34 (3H, s), 3.45-3.57 (2H, m)

^{13}C-NMR (δ, $CDCl_3$): 16.9, 28.4, 30.2, 31.6, 35.5, 37.2, 42.9, 59.0, 69.7, 71.7, 72.7

IR (neat, cm^{-1}): 2971, 2933, 2870, 1118

HRMS (ESI-MS) m/z calcd for $C_{11}H_{22}O_2$ + Na 209.1512, found 209.1510.

2-(2-Methoxy-1,1-dimethylethyl)-2,6,6-trimethyltetrahydropyran (11b)

Colorless oil.

^{1}H-NMR (δ, $CDCl_3$): 0.88 (3H, s), 0.89 (3H, s), 1.10 (3H, s), 1.15 (3H, s), 1.18 (3H, s), 0.92-1.79 (6H, m), 3.24, 3.33 (2H, ABq, J = 9.5Hz), 3.32 (3H, s)

^{13}C-NMR (δ, $CDCl_3$): 16.8, 20.0, 20.3, 22.0, 28.0, 29.5, 33.7, 36.9, 43.2, 59.7, 71.0, 76.5, 77.0, 79.2S

IR (neat, cm^{-1}): 2927, 1101

HRMS (ESI-MS) m/z calcd for $C_{13}H_{26}O_2$ + Na 237.1825, found 237.1824.

2.2.7 One-pot syntheses of esters **5a-c** from **1**

Typical procedure:

Iodine (0.132 g, 0.5 mmol), toluene (25 mL), and **1** (0.466 g, 2.5 mmol) were placed in a 100 mL flask, and the mixture was stirred at 50℃ for 8 h. After cooling to room temperature, ethanol (25 mL) was added. A reflux condenser was attached to the flask, and the mixture was stirred for 8 h with refluxing. After the reaction mixture was chilled to room temperature, water (20 mL) was added. Next, sodium thiosulfate (2.0 g) was added with stirring, and the reaction mixture was extracted three times with diisopropyl ether (10 mL). The organic layer was washed twice with aqueous sodium chloride solution (20 mL), dried with anhydrous sodium sulfate, and evaporated. The product was purified by column chromatography and eluted with hexane/ethyl acetate (20/1). A total mass of 0.379 g (71% yield) of ethyl 2-(2,6,6-trimethyltetrahydropyran-2-yl)acetate (**5b**) was obtained.

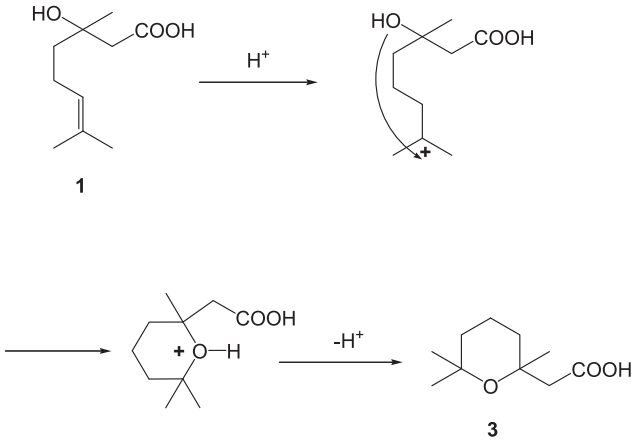
The other esters of **5a** and **5c** were synthesized using a similar procedure.

3 Results and discussion

1 has been reported to be obtained by the hydrolysis of the corresponding nitrile[8]. However, in this study, carboxylic acids **1** and **2** were synthesized by the reaction of 6-methyl-5-hepten-2-one with acetic acid or 2-methylpropanoic acid, respectively, using lithium naphthalenide and diethylamine, because the reactions could be carried out under milder conditions. The method using lithium naphthalenide has been previously reported[9]. The 3-hydroxy acids **1** and **2** were obtained in moderate yields (**1**, 75%; **2**, 51%).

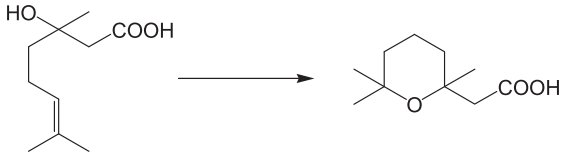
Cyclization of the 3-hydroxy acid **1** was performed using boron trifluoride diethyl etherate or iodine as a catalyst and the results are summarized in Table 1. Cyclization reactions were carried out at a 5:1 molar ratio of material to catalyst. In the case of iodine, with acetonitrile as the solvent, and reaction temperature at room temperature, the desired product was successfully obtained. Spectroscopic data acquired for the product indicated the shown structure of the carboxylic acid, which contains a tetrahydropyran ring (**3**). The achieved yield was 62% (entry 1), but this decreased to 53% when the temperature was raised to 80℃ (entry 2). When the solvent was changed to hexane or diethyl ether, cyclization did not occur (entries 3 and 4). We previously reported that acetonitrile was a suitable solvent for the solution reaction using iodine as a catalyst[10] and similar results were observed in this work. Boron trifluoride diethyl etherate was used as an acidic catalyst. When the reaction was carried out under the same conditions as entry 2 (solvent: acetonitrile, temperature: 80℃), **3** was obtained in 73% yield (entry 5). When the solvent was changed to toluene (entry 6), the yield increased to 86%. Thus, from **1**, a carboxylic acid containing a tetrahydropyran ring was obtained in high yield. A possible reaction mechanism is illustrated in Scheme 1. Addition of hydrogen to the double bond forms a tertiary carbocation, which an electron pair from the hydroxyl group then attacks the tertiary carbocation producing a tetrahydropyran ring. In the case of iodine, hydrogen iodide, which is initially formed by the interaction of iodine with the hydroxyl group, acts as an acidic catalyst[10].

Cyclization of 3-hydroxy acid **2** was carried out using acidic catalysts such as iodine, boron trifluoride diethyl etherate, and *p*-toluenesulfonic acid and the results are il-



Scheme 1

Table 1 Intramolecular etherification of **1**.



1 **3**

Entry	Catalyst	Solvent	Time (h)	Temp. (℃)	Yield (%)
1	I_2[a]	acetonitrile	3	r.t.[c]	62
2	I_2[a]	acetonitrile	3	80	53
3	I_2[a]	hexane	3	r.t.[c]	–[d]
4	I_2[a]	diethyl ether	3	r.t.[c]	–[d]
5	$BF_3 \cdot OEt_2$[b]	acetonitrile	8	80	73
6	$BF_3 \cdot OEt_2$[b]	toluene	8	80	86
7	$BF_3 \cdot OEt_2$[b]	toluene	8	110	40

Reaction conditions: 3-hydroxy acids 2.5 mmol, catalyst 0.5 mmol, solvent 25 mL.

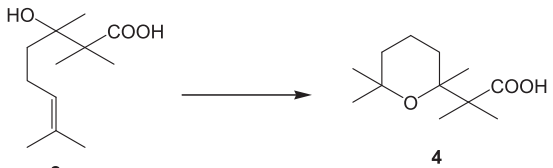
[a] Iodine.

[b] Boron trifluoride diethyl etherate.

[c] Room temperature.

[d] **3** was not obtained.

Table 2 Intramolecular etherification of 2.



2 4

Entry	Catalyst	Solvent	Temp.(℃)	Yield(%)
1	I_2[a]	toluene	50	73
2	I_2[a]	toluene	110	57
3	I_2[a]	acetonitrile	50	52
4	I_2[a]	acetonitrile	80	42
5	$BF_3 \cdot OEt_2$[b]	toluene	50	83
6	$BF_3 \cdot OEt_2$[b]	toluene	110	50
7	$BF_3 \cdot OEt_2$[b]	acetonitrile	50	63
8	$BF_3 \cdot OEt_2$[b]	acetonitrile	80	48
9	*p*-TsOH[c]	toluene	50	76
10	*p*-TsOH[c]	toluene	110	60
11	*p*-TsOH[c]	acetonitrile	50	79
12	*p*-TsOH[c]	acetonitrile	80	69

Reaction conditions: 3-hydroxy acids 2.5 mmol, catalyst 0.5 mmol, solvent 25 mL, time 24 h.
[a] Iodine.
[b] Boron trifluoride diethyl etherate.
[c] *p*-Toluenesulfonic acid.

Table 3 Esterification of 3.

3 5a-c

Entry	R^2	Product	Catalyst	Yield(%)
1	methyl	5a	I_2[a]	88
2	methyl	5a	*p*-TsOH[b]	83
3	ethyl	5b	I_2[a]	74
4	ethyl	5b	*p*-TsOH[b]	78
5	propyl	5c	I_2[a]	86
6	propyl	5c	*p*-TsOH[b]	95

Reaction conditions: **3** 5.0 mmol, catalyst 1.0 mmol, alcohols 50 mL, refluxing for 8 h.
[a] Iodine.
[b] *p*-Toluenesulfonic acid.

lustrated in Table 2. In the case of iodine(entries 1-4), the cyclization proceeded to produce the carboxylic acid **4**, but the yields were modest, ranging from 42 to 73%. In the case of *p*-toluenesulfonic acid(entries 9-12), the yields increased somewhat, ranging from 60 to 79%. Using boron trifluoride diethyl etherate, the yield increased even further. When toluene was used as a solvent and the reaction temperature was 50℃(entry 5), the yield was the highest out of all the reactions(83%).

Esterification of the carboxylic acid **3** with alcohols was performed using iodine or *p*-toluenesulfonic acid as a catalyst and the results are summarized in Table 3. Iodine has

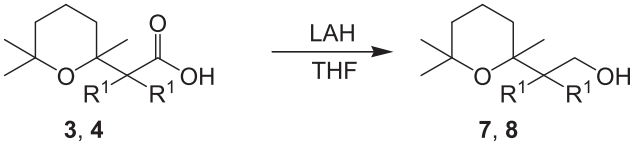
Table 4 Esterification of **4**.

Entry	R^2	Product	Catalyst	Yield (%)
1	methyl	6a	*p*-TsOH[a]	–[b]
2	methyl	6a	sulfuric acid	44
3	ethyl	6b	sulfuric acid	37
4	propyl	6c	sulfuric acid	44

Reaction conditions: carboxylic acid **4** 5.0 mmol, catalyst 1.0 mmol, alcohols 50 mL, refluxing for 8 h.
[a] *p*-Toluenesulfonic acid.
[b] **6a** was not obtained.

previously been reported to be an effective catalyst for the esterification reaction[11, 12]. In the production of the methyl ester **5a** (entries 1, 2), ethyl ester **5b** (entries 3,4), and propyl ester **5c** (entries 5,6), both iodine and *p*-toluenesulfonic acid were effective as catalysts. The yield of each was above 74%. Esterification of **4** with several different alcohols was also attempted (Table 4). When *p*-toluenesulfonic acid was used as a catalyst in the production of the methyl ester, esterification did not proceed (entry 1). Accordingly, the catalyst was changed to sulfuric acid, and the methyl ester **6a** was obtained in 44% yield (entry 2). Similarly, the production of the ethyl ester **6b** (entry 3) or propyl ester **6c** (entry 4) was attempted. Each ester was obtained in moderate yield. These relatively low yields were attributed to the steric hindrance of carboxylic acid **4**.

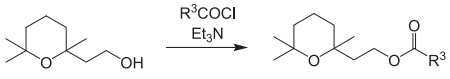
Reduction of carboxylic acid **3** or **4** to produce the novel corresponding alcohol containing a tetrahydropyran ring was carried out using lithium aluminum hydride in tetrahydrofuran, as shown in Scheme 2. The alcohol **7** was obtained in 88% yield, and **8** was produced in 93% yield. Using these alcohols with several acyl chlorides and triethylamine, novel esters were produced. The results using **7** are summarized in Table 5. In the case of each aliphatic acyl chloride used, the esters **9a-d** were obtained in excellent yields (entries 1-4). However, when benzyl chloride was used, the yield decreased considerably (entry 5). This was attributed to the reactivity of benzyl chloride being



7: R^1 = H, 88%
8: R^1 = CH_3, 93%

Scheme 2

Table 5 Esterification of alcohol **7**.



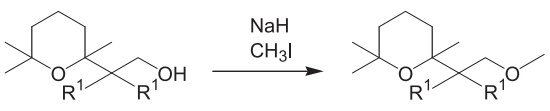
Entry		R^3 group	Yield (%) of **9**
1	a	methyl	86
2	b	ethyl	93
3	c	propyl	92
4	d	isopropyl	90
5	e	phenyl	77

Reaction conditions: alcohol 2.5 mmol, triethylamine 3.8 mmol, acyl chloride 3.8 mmol, DMAP 0.41 mmol, solvent (tetrahydrofuran) 10 mL, time 12 h.

lower than that of the aliphatic acyl chlorides. The results using **8** are shown in Table 6. Similar to the esterification of **7**, esters **10** were produced in excellent yields using aliphatic acyl chlorides, but the yield decreased slightly in the esterification with benzyl chloride (entry 5).

Etherification of the alcohol **3** or **4** with methyl iodide using sodium hydride was carried out as shown in Scheme 3. The yield of the ether **11a** was 73%, and that of **11b** was 43%. The lower yield of **11b** was attributed to the steric hindrance of the two methyl groups.

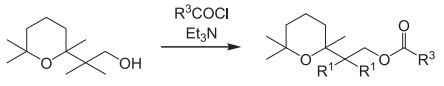
As mentioned above, iodine was an effective catalyst in the esterification of **3** as well as in the cyclization of **1**. Ac-



11a: R^1=H, 73%
11b: R^1=CH_3, 43%

Scheme 3

Table 6 Esterification of alcohol **8**.



8 10a-e

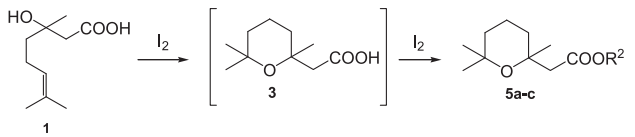
Entry		R^3 group	Yield (%) of **10**
1	a	methyl	90
2	b	ethyl	90
3	c	propyl	91
4	d	isopropyl	99
5	e	phenyl	84

Reaction conditions: alcohol 2.5 mmol, triethylamine 3.8 mmol, acyl chloride 3.8 mmol, DMAP 0.41 mmol, solvent (tetrahydrofuran) 10 mL, time 12 h.

cordingly, a one-pot method of cyclization-esterification of **1** was attempted. First, **1** (2.5 mmol) and iodine (0.5 mmol) and toluene were added to a flask, and the mixture was stirred at 50℃ for 8 h. Second, after cooling to room temperature, ethanol (25 mL) was added to the flask, and the mixture was stirred with refluxing for 8 h. In the cases where ethanol was added, iodine was not added. The yield of **5b** from **1** was 71% (entry 2), which was higher than that in the cases of the cyclization, and the esterification was carried out separately. The results of this one-pot method are illustrated in Table 7. When methanol was used, the yield of **5a** from **1** was 66% (entry 1). In the case of 1-propanol, the yield of **5c** was 63% (entry 3). Thus, using iodine as a catalyst, the one-pot method of cyclization-esterification of **1** proceeded smoothly.

In conclusion, the reaction of 6-methyl-5-hepten-2-one with acetic acid or 2-methylpropanoic acid affords the corresponding 3-hydroxy acids, which subsequently react using boron trifluoride diethyl etherate or iodine as an acidic catalyst to give carboxylic acids containing a tetrahydropyran ring. The reactions of these carboxylic acids with alcohols produce esters. Reduction of these carboxylic acids using lithium aluminum hydride produces alcohols. These alcohols that contain the tetrahydropyran ring could be derivatized to esters or ethers. Additionally, a one-pot method of cyclization–esterification of **1** gives esters **5** without the requirement for isolation of the carboxylic acids.

Table 7 One-pot syntheses of esters **5a-c** from **1**.



1 3 5a-c

Entry	R^2	Product	Yield (%)
1	methyl	5a	66
2	ethyl	5b	71
3	propyl	5c	63

Reaction conditions: **1** 2.5 mmol, catalyst (iodine) 0.5 mmol, solvent (toluene) 25 mL, alcohols 25 mL, first step 50℃ for 8 h, second step refluxing for 8 h.

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