A Convenient One-Pot Synthesis of Quaternary α-Methoxy- and α-Hydroxycarboxylic Acids

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Several α-methoxy- and α-hydroxycarboxylic acids have been synthesized by a new one-pot synthesis using ketones, tribromomethane, and potassium hydroxide in methanol and water, respectively, in good yields.

Key words hydroxy acid; α-methoxycarboxylic acid; ketone; chiral anisotropic reagent

We have synthesized 1- and 2-naphthylmethoxyacetic acid [1NMA (**1**) and 2NMA (**2**)], the chiral anisotropic reagents for the absolute configuration of secondary alcohols,[1] by a reaction of 1- and 2-naphthaldehyde, respectively, with tribromomethane and potassium hydroxide in methanol according to reference.[2] The reaction seems to proceed through the dibromoepoxide (**3**) formed by the action of a tribromomethyl anion or dibromocarbene, followed by an attack of the methoxide and hydrolysis of the resulting acyl bromide.

It was considered that if ketones instead of aldehydes were employed as starting materials, quaternary α-methoxycarboxylic acids (**4**) would be produced.

Furthermore, when water is used as the solvent of the reaction, ketones will be converted to quaternary α-hydroxy carboxylic acids (**5**). Actually, various quaternary methoxy and hydroxy acids were produced in good yields as summarized in Table 1 by the following procedures.

A One-Pot Reaction Giving a Quaternary Methoxycarboxylic Acid To an ice-cooled mixture of 2-butanone (2 ml, 22 mmol) and tribromomethane (10 ml, 229 mmol) was added a solution of KOH (10 g, 179 mmol) in methanol (30 ml) for 1 h. The temperature was maintained at 0—5 °C during the addition. The mixture was stirred vigorously for 1 h at room temperature. After the work-up (extraction with ether), 2-methoxy-2-methylbutanoic acid (**6**) was obtained in 85% yield.

A One-Pot Reaction Giving a Quaternary Hydroxycarboxylic Acid A solution of KOH (10 g) in water (10 ml) was used in place of KOH/MeOH. 2-Hydroxy-2-methylbutanoic acid (**18**) was obtained in 80% yield.

The use of chloroform instead of tribromomethane greatly reduces the yield (*ca*. 20%). These reactions work for sterically unhindered ketones: Relatively simple ketones such as cyclohexanone and 2-octanone gave excellent to good yields of the methoxy (**6**—**12**) and hydroxy (**19**—**24**) carboxylic acids. On the contrary, yields of methoxy (**13**—**17**) and hydroxy (**25**, **26**) carboxylic acids are greatly reduced in the case of hindered ketones. 2-Methylcyclohexanone, 2-methyl-2-butanone, and 2,2-dimethyl-2-butanone gave no hydroxy carboxylic acids.

The present method is superior to the conventional two-step synthesis *via* hydrocyanation and subsequent hydrolysis[3] or the formation of a haloform adduct followed by hydrolysis[4] with respect to yield, ease of the operation, and, above all, the low cost of the reagents.

Experimental

^{1}H-NMR spectra were taken on Bruker ARX-400. Mass Spectra were recorded on JEOL JMX-SX102A and JEOL JMS-AM150.

2-Methoxy-2-methylbutanoic Acid (6) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, J=7.0 Hz, 4-CH_3), 1.25—1.66 (m, 2H, 3-CH_2), 1.42 (s, 3H, 1′-CH_3), 3.30 (s, 3H, OCH_3), 11.62 (s, 1H, CO_2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.0 (q, C-4), 16.6 (q, C-1′), 34.6 (t), 56.4 (q, OCH_3), 75.1 (s, C-2), 181.2 (s, C-1). HRMS (EI) *m/z*: 132.0780 (Calcd for $C_6H_{12}O_3$: 132.0786). MS *m/z* (rel. int. %): 132 (M^+, 24), 115 (81), 104 (100). *Anal*. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.55; H, 9.21.

2-Methoxy-2-methylpentanoic Acid (7) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 3H, J=7.0 Hz, 5-CH_3), 1.23—1.83 (m, 4H, 3—4-CH_2), 1.39 (s, 3H, 1′-CH_3), 3.26 (s, 3H, OCH_3), 11.60 (s, 1H, CO_2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.0 (q, C-5), 16.6 (q, C-1′), 26.6 (t), 42.6 (t), 56.6 (q, OCH_3), 75.1 (s, C-2), 181.2 (s, C-1). HRMS (EI) *m/z*: 146.0945 (Calcd for $C_7H_{14}O_3$ 146.0943). MS *m/z* (rel. int. %): 146 (M^+, 17), 104 (100). *Anal*. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.75; H, 9.50.

2-Methoxy-2-methylhexanoic Acid (8) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, J=7.0 Hz, 6-CH_3), 1.21—1.75 (m, 6H, 3—5-CH_2), 1.37 (s, 3H, 1′-CH_3), 3.28 (s, 3H, –OCH_3), 11.23 (s, 1H, CO_2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.8 (q, C-6), 22.7 (q, C-1′), 25.5 (t), 26.6 (t), 40.2 (t), 56.2 (q, OCH_3), 75.8 (s, C-2), 181.3 (s, C-1). HRMS (EI) *m/z*: 160.1098 (Calcd for $C_8H_{16}O_3$: 160.1099). MS *m/z* (rel. int. %): 160 (M^+, 17), 104 (100). *Anal*. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.11; H, 10.03.

2-Ethyl-2-methoxylpentanoic Acid (9) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.84 (s, 3H, J=7.0 Hz, 6-CH_3), 0.87 (t, 3H, J=7.0 Hz, 1-CH_3), 1.25—1.69 (m, 8H, 2-, 4—5-CH_2), 3.31 (s, 3H, –OCH_3), 11.12 (s, 1H, CO_2H). HRMS (EI) *m/z*: 160.1091 (Calcd for $C_8H_{16}O_3$: 160.1099). MS *m/z* (rel. int. %): 160 (M^+, 14), 118 (100). *Anal*. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C,

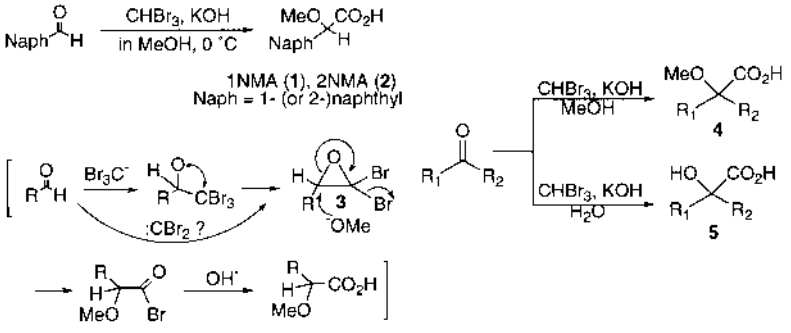

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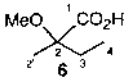
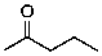
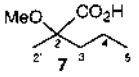
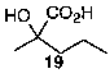
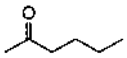
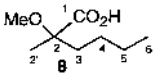
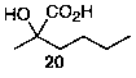
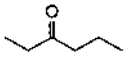
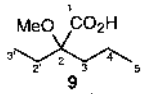
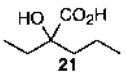
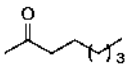
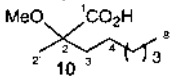
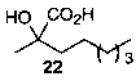
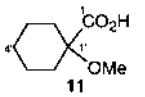
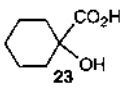
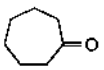
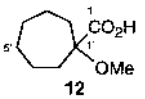
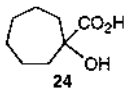
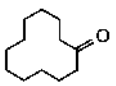
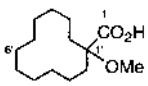
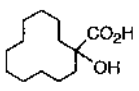
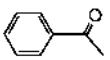
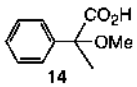
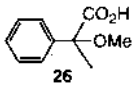
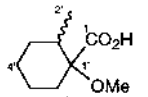
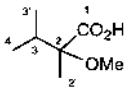
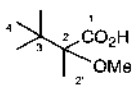
Table 1. Reaction of Ketones with Potassium Hydroxide and Tribromomethane in Methanol and Water

Ketone	Conditions $CHBr_3$, KOH	Product	Yield (%)	Conditions $CHBr_3$, KOH	Product	Yield (%)
	MeOH	 **6**	85	H_2O	 **18**	80
	—	 **7**	80	—	 **19**	75
	—	 **8**	90	—	 **20**	70
	—	 **9**	70	—	 **21**	60
	—	 **10**	90	—	 **22**	70
	—	 **11**	93	—	 **23**	95
	—	 **12**	78	—	 **24**	98
	—	 **13**	7	—	 **25**	6
	—	 **14**	30	—	 **26**	12
	—	 **15**	16	—	—	0
	—	 **16**	16	—	—	0
	—	 **17**	7	—	—	0

60.13; H, 10.33.

2-Methoxy-2-methyloctanoic Acid (10) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, 3H, J=7.0 Hz, 8-C$\underline{H}_3$), 1.25—1.97 (m, 10H, 3—7-C$\underline{H}_2$), 1.45 (s, 3H, 1′-C$\underline{H}_3$), 3.33 (s, 3H, OC$\underline{H}_3$), 11.36 (s, 1H, $CO_2\underline{H}$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9 (q, C-8), 22.3 (t), 23.3 (t), 26.6 (q, C-1′), 29.2 (t), 31.5 (t), 40.5 (t), 56.3 (q, OMe), 75.9 (s, C-2), 181.2 (s, C-1). HRMS (EI) *m/z*: 188.1411 (Calcd for $C_{10}H_{20}O_3$: 188.1412). MS *m/z* (rel. int. %): 188 (M^+, 16), 104 (100). *Anal*. Calcd for $C_{10}H_{20}O_3$: C, 65.31; H, 10.96. Found: C, 65.16; H, 11.12.

1-Methoxycyclohexanecarboxylic Acid (11) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.31—2.01 (m, 10H, 2′—4′-C$\underline{H}_2$), 3.34 (s, 3H, –C$\underline{H}_3$), 11.61 (s, 1H, $CO_2\underline{H}$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 22.1 (t), 25.6 (t), 34.2 (t), 56.3 (q), 75.4 (s), 181.0 (s). HRMS (EI) *m/z*: 158.1411 (Calcd for $C_8H_{14}O_3$: 158.0911). MS *m/z* (rel. int. %): 158 (M^+, 18), 141 (45).

1-Methoxycycloheptanecarboxylic Acid (12) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45—1.99 (m, 12H, 2′—4′-C$\underline{H}_2$), 3.28 (s, 3H, OC$\underline{H}_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.9 (t), 29.2 (t), 35.1 (t), 51.9 (q), 82.8 (s), 180.3 (s). HRMS (EI) *m/z*: 172.1098 (Calcd for $C_9H_{16}O_3$: 172.1099).

1-Methoxycyclododecanecarboxylic Acid (13) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21—1.98 (m, 22H, 2′—7′-C$\underline{H}_2$), 3.31 (s, 3H, OC$\underline{H}_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 18.1 (t), 21.3 (t), 23.1 (t), 24.2 (t), 25.8 (t), 31.1 (t), 60.4 (q), 79.1 (s), 179.9 (s). HRMS (EI) *m/z*: 242.1880 (Calcd for $C_{14}H_{26}O_3$: 242.1882).

2-Methoxy-2-phenylpropanoic Acid (14) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.46 (s, 3H, C$\underline{H}_3$), 3.28 (s, 3H, OC$\underline{H}_3$), 7.27—7.72 (m, 5H, $C_6\underline{H}_5$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.6 (q), 55.4 (q), 82.1 (s), 128.0 (d), 128.3 (d), 130.1 (d), 133.7 (s), 180.3 (s). HRMS (EI) *m/z*: 180.0785 (Calcd for $C_{10}H_{12}O_3$: 180.0786).

1-Methoxy-2-methylcyclohexanecarboxylic Acid (15) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21—1.67 (m, 12H), 3.29 (s, 3H, C$\underline{H}_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.0 (q), 20.1 (t), 20.9 (t), 21.5 (t), 21.6 (t), 25.4 (t), 60.3 (s), 78.8 (s), 180.2 (s). HRMS (EI) *m/z*: 172.1126 (Calcd for $C_9H_{16}O_3$: 172.1123).

2-Methoxy-2,3-dimethylbutanoic Acid (16) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (d, 3H, J=7.0 Hz, C$\underline{H}_3$), 0.91 (d, 3H, J=7.0 Hz, C$\underline{H}_3$), 1.49 (s, 3H, C$\underline{H}_3$), 1.71 (m, 1H, C$\underline{H}$), 3.31 (s, 3H, C$\underline{H}_3$). ^{13}C-NMR (100 MHz,

$CDCl_3$) δ: 20.1 (q), 22.5 (q), 25.4 (d), 31,2 (q), 56.8 (q), 79.5 (s), 180.2 (s). HRMS (EI) *m/z*: 146.0945 (Calcd for $C_7H_{14}O_3$: 146.0943).

2-Methoxy-2,3,3-trimethylbutanoic Acid (17) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 9H, C$\underline{H}_3$), 3.28 (s, 3H, C$\underline{H}_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 22.8 (q), 56.7 (q), 80.1 (s), 180.1 (s). HRMS (EI) *m/z*: 160.1094 (Calcd for $C_8H_{16}O_3$: 160.1099).

2-Hydroxy-2-methylbutanoic Acid (18) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, 3H, *J*=7.0 Hz, 4-C$\underline{H}_3$), 1.30—1.74 (m, 2H, 3-C$\underline{H}_2$), 1.44 (s, 3H, 1′-C$\underline{H}_3$), 11.60 (s, 1H, $CO_2\underline{H}$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.0 (q, C-4), 16.6 (q, C-1′), 34.6 (t, C-3), 75.1 (s, C-2), 181.2 (s, C-1). HRMS (EI) *m/z*: 118.0649 (Calcd for $C_5H_{10}O_3$: 118.0630). MS *m/z* (rel. int. %): 118 (M^+, 15), 90 (100). *Anal*. Calcd for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 50.66; H, 8.75.

2-Hydroxy-2-methylpentanoic Acid (19) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.94 (t, 3H, *J*=7.0 Hz, 5-C$\underline{H}_3$), 1.31—1.63 (m, 4H, 3—4-C$\underline{H}_2$), 1.47 (s, 3H, 1′-C$\underline{H}_3$), 11.47 (s, 1H, $CO_2\underline{H}$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.0 (q, C-5), 16.6 (q, C-1′), 26.6 (t), 42.6 (t), 75.1 (s, C-2), 181.2 (s, C-1). HRMS (EI) *m/z*: 132.0779 (Calcd for $C_6H_{12}O_3$: 132.0786). MS *m/z* (rel. int. %): 132 (M^+, 21), 90 (100). *Anal*. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.63; H, 9.35.

2-Hydroxy-2-methylhexanoic Acid (20) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 3H, *J*=7.0 Hz, 6-C$\underline{H}_3$), 1.21—1.53 (m, 10H, 3—5-C$\underline{H}_2$), 1.45 (s, 3H, 1′-C$\underline{H}_3$), 11.63 (s, 1H, $CO_2\underline{H}$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.8 (q, C-6), 22.7 (q, C-1′), 25.5 (t), 26.6 (t), 40.2 (t), 75.8 (s, C-2), 181.3 (s, C-1). HRMS (EI) *m/z*: 146.0941 (Calcd for $C_7H_{14}O_3$: 146.0943). MS *m/z* (rel. int. %): 146 (M^+, 15), 104 (100). *Anal*. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.72; H, 9.66.

2-Ethyl-2-hydroxypentanoic Acid (21) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.81 (s, 3H, *J*=7.0 Hz, 5-C$\underline{H}_3$), 0.87 (t, 3H, *J*=7.0 Hz, 2′-C$\underline{H}_3$), 1.25—1.96 (m, 8H, 1′-, 3—4-C$\underline{H}_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.0 (q, C-5), 20.1 (q, C-2′), 23.3 (t), 24.3 (t), 42.2 (t), 75.5 (s, C-2), 181.3 (s, C-1). HRMS (EI) *m/z*: 146.0951 (Calcd for $C_7H_{14}O_3$: 146.0943). MS *m/z* (rel. int. %): 146 (M^+). *Anal*. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.75; H, 9.69.

2-Hydroxy-2-methyloctanoic Acid (22) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.86 (t, 3H, *J*=7.0 Hz, 8-C$\underline{H}_3$), 1.21—1.93 (m, 10H, 3—7-C$\underline{H}_2$), 1.45 (s, 3H, 1′-C$\underline{H}_3$), 11.60 (s, 1H, $CO_2\underline{H}$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9 (q, C-8), 22.3 (t), 23.3 (t), 26.6 (q, C-1′), 29.2 (t), 31.5 (t), 40.5 (t), 75.9 (s, C-2), 181.2 (s, C-1). HRMS (EI) *m/z*: 174.1255 (Calcd for $C_9H_{18}O_3$: 174.1256). MS *m/z* (rel. int. %): 174 (M^+, 16), 90 (100). *Anal*. Calcd for $C_9H_{18}O_3$: C, 63.80; H, 10.71. Found: C, 63.69; H, 10.77.

1-Hydroxycyclohexanecarboxylic Acid (23) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45—1.98 (m, 10H, 2′—4′-C$\underline{H}_2$), 11.61 (s, 1H, $CO_2\underline{H}$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 22.0 (t), 2.5.2 (t), 32.8 (t), 75.0 (s), 181.3 (s). HRMS (EI) *m/z*: 144.1752 (Calcd for $C_7H_{12}O_3$: 144.1754). MS *m/z* (rel. int. %): 144 (M^+, 17), 127 (100).

1-Hydroxycycloheptanecarboxylic Acid (24) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.42—1.93 (m, 12H, 2′—5′-C$\underline{H}_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.2 (t), 25.6 (t), 32.3 (t), 81.4 (s), 180.1 (s). HRMS (EI) *m/z*: 158.0940 (Calcd for $C_8H_{14}O_3$: 158.0943).

1-Hydroxycyclododecanecarboxylic Acid (25) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.24—1.95 (m, 22H, 2′—7′-C$\underline{H}_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 17.4 (t), 23.3 (t), 23.5 (t), 24.1 (t), 25.9 (t), 30.7 (t), 80.5 (s), 181.2 (s). HRMS (EI) *m/z*: 228.1724 (Calcd for $C_{13}H_4O_3$: 228.1725).

2-Hydroxy-2-phenylpropanoic Acid (26) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 3H, C$\underline{H}_3$), 7.22—7.69 (m, 5H, $C_6\underline{H}_5$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.1 (q), 80.1 (s), 125.0 (d), 128.2 (d), 130.2 (d), 134.1 (s), 180.1 (s). HRMS (EI) *m/z*: 166.0633 (Calcd for $C_9H_{10}O_3$: 166.0630).

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