Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 8, pp. 1599-1603, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00226-6

A Facile Synthesis of Homochiral 1-Norbornanecarboxylic Acids and 1-Norbornanecarbonitriles

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Abstract: A general method for the preparation of the title compounds from naturally occurring homochiral 2-norbornanones is presented. The key step is the Tf_2O induced Wagner-Meerwein rearrangement of the corresponding cyanohydrins.

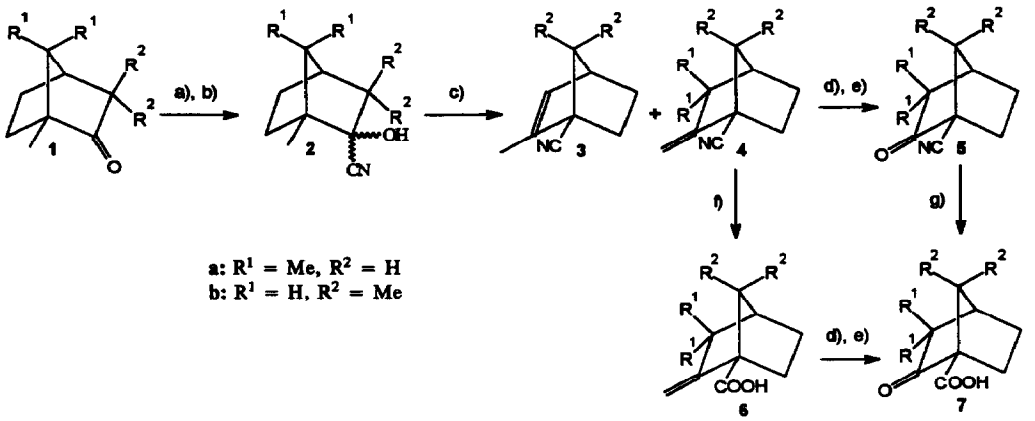
A convenient entry into bridgehead-substituted norbornanes is *via* the corresponding carboxylic acids and nitriles.[1] Moreover, camphor derived homochiral carboxylic acids, such as (+)-ketopinic acid (ent-**6b**)[2] or camphanic acid,[3] have proved to be highly versatile in a great number of asymmetric reactions. Due to these reasons, there is a great demand for homochiral substituted 1-norbornanecarboxylic acids (**6** and **7**), and 1-norbornanecarbonitriles (**4** and **5**).

We report here on the synthesis of **4-7** from naturally occurring 2-norbornanones **1**, (+)-camphor (**1a**) or (-)-fenchone (**1b**) (Scheme 1). The ketones **1** were converted to the corresponding cyanohydrins **2** by a standard procedure.[4] The Wagner-Meerwein rearrangement of the triflates of **2**, prepared by reaction with Tf_2O/pyridine, happens so rapidly that they could not be isolated. Although α-cyano-substituted carbocations (as tight ions pairs) are probably formed as intermediates,[5] only the bridgehead nitrile **4a**, or a mixture of **3b** and **4b** (major isomer) were formed as products (Scheme 1).

The synthesis of the 2-oxo-1-norbornanecarbonitriles **5** and the 2-oxo-1-norbornanecarboxylic acid (**7a**), was carried out by ozonolysis of the corresponding methylene derivatives **4** and **6a**. The ozonolysis of **6b**, as well as the oxidation with $NaIO_4/KMnO_4$, yields a complex mixture of compounds in which the desired acid **7b** appears as a minor component. The basic hydrolysis of the 2-methylene-1-norbornanecarbonitriles **4** affords

the acids **6**. In the end, the 2-oxo-1-norbornanecarboxylic acids **7** were obtained straightforward by hydrolysis of the corresponding 2-oxo-1-norbornancarbonitriles **5** in acidic media. The $[\alpha]_D$ values for **5b**,[6] **6a**,[7] **7a**[7a] and **7b**[6,8] agree with the data reported in the literature, this fact vouches for the enantiospecificity of our method.

In conclusion, we have presented new facile practical routes to both 1-norbornanecarboxylic acids and 1-norbornanecarbonitriles from readily available 2-norbornanones.



a: R^1 = Me, R^2 = H
b: R^1 = H, R^2 = Me

a) TMSCN/ZnI_2/pentane, 2h., r.t.; b) 10% HCl, 12h., 100°C; c) Tf_2O/pyridine/CH_2Cl_2, 24h., r.t.; d) O_3/MeOH, -40°C; e) Me_2S; f) NaOH/diglyme/diethylene glycol, 12h., 162°C; g) 35% HCl, 2h. (12h for **5b**), 100°C.

Scheme 1

EXPERIMENTAL

^1H NMR and ^{13}C NMR were recorded on Varian-XL 300 MHz spectrometer in deuterochloroform, and chemical shifts are expresed in ppm. IR spectra were recorded on Perkin-Elmer 781 spectrometer. Mass spectra were recorded on Shimadzu QP-5000 instrument. Optical rotations were measured on Perkin-Elmer 241 Polarimeter. Melting points were determined on Gallenkamp apparatus and are uncorrected. Capillary GC data were recorded on Perkin-Elmer Sigma 300 apparatus (column type: OV-101, 25 m).

General procedure for the synthesis of 2-methylene-1-norbornancarbonitriles 4.

To a cooled (0°C) suspension of the corresponding 2-norbornanone (**1**) (30.0 mmol) and ZnI_2 (as catalyst) in pentane (25 mL), was slowly added trimethylsilylcyanide (35.0 mmol) and stirred for 2 h (the reaction was monitored by GC). The solvent was eliminated by distillation under reduced pressure and the residue was treated with 10% HCl (50 mL) an stirred 12 h at 100°C (the hydrolysis was controled by GC). The reaction mixture was extracted with CH_2Cl_2 (5x20 mL) and dried over $MgSO_4$. The corresponding cyanohydrin was obtained by evaporation of the solvent under reduced pressure, and used without purification in the next step.

To a cooled (0°C) solution of the corresponding cyanohydrin (30.0 mmol) and pyridine (75.0 mmol) in CH_2Cl_2 (25 mL), was slowly added a solution of triflic anhydride (33.0 mmol) in CH_2Cl_2 (15 mL) and

stirred 24 h at room temperature (the reaction was monitored by GC). The reaction mixture was treated with a saturated solution of $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (5x20 mL). The organic layer was washed with 10% HCl (2x25 mL), saturated solution of $NaHCO_3$ (25 mL), brine (2x25 mL) and dried over $MgSO_4$. The extract was concentrated under reduced pressure and the corresponding 2-methylene-1-norbornanecarbonitrile purified by column chromatography (silica gel, pentane/CH_2Cl_2 20:1).

(+)-(1*R*)-3,3-Dimethyl-2-methylene-1-norbornanecarbonitrile (4a)

^1H NMR δ: 4.92 (1H, s), 4.58 (1H, s), 1.90-1.75 (3H, m), 1.65-1.30 (4H, m), 0.87 (3H, s), 0.86 (3H, s); ^{13}C NMR δ: 159.4 (C2), 120.4 (CN), 102.0 (=CH_2), 47.1 (C4), 44.8 (C1), 41.8 (C7), 41.3 (C3), 33.6 (C6), 28.9 (Me), 25.0 (Me), 23.4 (C5); IR (CCl_4) ν: 3080 (=CH_2), 2980, 2900, 2250 (CN), 1670 (C=C), 1470, 1370, 1120, 910 cm^{-1}; MS m/e (%B): 161 ($M^{+\cdot}$, 39), 146 (84), 132 (43), 119 (58), 118 (90), 105 (34), 104 (39), 95 (100), 91 (39), 76 (25), 68 (39), 67 (30), 65 (27), 41 (78); mp: 34.2-35.7°C; bp: 124.0-128.0 (16-18 torr); $[\alpha]_D^{20}$ +34.8 (c=3.92, MeOH); yield: 82 %.

(+)-(1*S*)-7,7-Dimethyl-2-methylene-1-norbornanecarbonitrile (4b)

^1H NMR δ: 5.15 (1H, t, J=2.4 Hz), 4.82 (1H, t, J=2.0 Hz), 2.44 (1H, dm, J=16.5 Hz), 2.15 (1H, td, J=12.0 Hz, J=4.8 Hz), 1.96-1.82 (3H, m), 1.70 (1H, m), 1.32 (1H, m), 1.06 (3H, s), 0.98 (3H, s); ^{13}C NMR δ: 150.4 (C2), 120.1 (CN), 106.2 (=CH_2), 52.3 (C1), 51.2 (C7), 44.4 (C4), 36.2 (C3), 33.7 (C6), 28.1 (C5), 20.0 (Me), 19.4 (Me); IR (CCl_4) ν: 3080 (=CH_2), 2960, 2880, 2240 (CN), 1665 (C=C), 1475, 1450, 1395, 1375, 1130, 895 cm^{-1}; MS m/e (%B): 161 ($M^{+\cdot}$, 17), 146 (32), 132 (20), 120 (17), 119 (100), 118 (66), 117 (37), 106 (40), 105 (73), 104 (52), 92 (25), 91 (36), 78 (19), 77 (27), 69 (30), 65 (23), 43 (62), 41 (72); bp: 118.0-120.0°C (18-20 torr); $[\alpha]_D^{20}$ +4.2 (c=0.85, MeOH); yield: 79%.

General procedure for the synthesis of the 2-methylene-1-norbornancarboxylic acids 6.

To a mixture of NaOH (16.0 g) and diethylene glycol (60 mL), was added a solution of the corresponding 2-methylene-1-norbornanecarbonitrile (**4**) (20 mmol), in diglyme (10 mL). The reaction mixture was stirred 12 h at diglyme reflux temperature (the reaction was monitored by GC). The mixture was diluted with water (200 mL) and extracted with hexane (3x25 ml), the aqueous layer was acidified with 10 % HCl and extracted with hexane (5x25 mL). The organic layer was washed with brine (2x 25 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, pure 2-methylene-1-norbornanecarboxylic acid was obtained without further purification.

(+)-(1*R*)-3,3-Dimethyl-2-methylene-1-norbornanecarboxylic acid (6a)

^1H NMR, IR, mp: see lit[7b]; ^{13}C NMR δ: 180.7 (COOH), 162.5 (C2), 101.2 (=CH_2), 59.5 (C1), 47.4 (C4), 43.0 (C3), 40.8 (C7), 31.9 (C6), 29.7 (Me), 26.1 (Me), 24.6 (C5); MS m/e (%B): 180 ($M^{+\cdot}$, 24), 165 (74), 152 (27), 137 (70), 123 (21), 119 (41), 107 (34), 105 (23), 95 (85), 93 (100), 91 (72), 79 (43), 77 (47), 67 (42), 43 (40), 41 (93); $[\alpha]_D^{20}$ +93.2 (c=0.50 MeOH); yield: 91 %.

(+)-(1*S*)-7,7-Dimethyl-2-methylene-1-norbornanecarboxylic acid (6b)[10]

^1H NMR δ: 11.55 (1H, bs), 5.02 (1H, t, J=2.1 Hz), 4.85 (1H, t, J=1.9 Hz), 2.75 (1H, bd, J=14.3 Hz), 2.33 (1H, td, J=12.2 Hz, J=4.2 Hz), 2.00 (1H, bd, J=16.1 Hz), 1.94-1.64 (3H, m), 1.29 (1H, m), 1.10 (3H, s),

1.08 (3H, s); ^{13}C NMR δ: 179.9 (COOH), 153.2 (C2), 105.1 (=CH_2), 62.5 (C1), 50.3 (C7), 46.4 (C4), 37.4 (C3), 32.2 (C6), 27.4 (C5), 21.0 (Me), 19.6 (Me); IR (CCl_4) ν: 3400-2500 (COOH), 2960, 1700 (C00H), 1660 (C=C), 1320, 1295, 1255, 1220, 890 cm^{-1}; MS m/e (%B): 180 ($M^{+\cdot}$, 10), 165 (13), 137 (100), 124 (26), 93 (55), 91 (47), 79 (47), 77 (33), 43 (35), 41 (93); mp: 170.0-172.2°C; $[\alpha]_D^{20}$ +15.0 (c=0.52, MeOH); yield: 90 %.

General procedure for the synthesis of the 2-oxo-1-norbornanecarbonitriles 5 and the 2-oxo-1-norbornanecarboxylic acid 7a.

Ozone was passed through a cooled (-40°C) solution of the corresponding 2-methylene-1-norbornyl derivative (20.0 mmol) in methanol (50 mL). After 2 h (the reaction was monitored by GC), the cold solution was purged with nitrogen to remove the excess of ozone, and treated with dimethyl sulfide (2 mL). The reaction mixture was stirred for 10 minutes and allowed to warm up to room temperature. The resulting solution was diluted with water (100 mL) and extracted with CH_2Cl_2 (2x25 mL). The organic layer was washed with brine (2x25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The nitriles **5** were purified by column chromatography (silica gel pentane/CH_2Cl_2 4:1) and the acid **7a** by recrystallization from hexane.

(+)-(1*S*)-3,3-Dimethyl-2-oxo-1-norbornanecarbonitrile (5a)

^{1}H NMR δ: 2.42-2.32 (2H, m), 2.23 (1H, m), 2.03 (1H, dd, J=9.4 Hz, J=1.9 Hz), 1.95-1.80 (3H, m), 1.16 (3H, s), 1.11 (3H, s); ^{13}C NMR δ: 210.8 (C2), 117.7 (CN), 49.2 (C3), 46.9 (C1), 45.3 (C4), 39.6 (C7), 29.7 (C6), 23.4 (C5), 23.3 (Me), 21.2 (Me); IR (CCl_4) ν: 2970, 2920, 2220 (CN), 1750 (CO), 1460, 1390, 1365, 1285, 1125, 1105, 1020, 965, 930 cm^{-1}; MS m/e (%B): 163 ($M^{+\cdot}$, 5), 135 (5), 134 (4), 120 (10), 107 (6), 93 (53), 69 (100), 66 (14), 53 (11), 43 (33), 41 (85); mp: 89.7-90.5°C; $[\alpha]_D^{20}$ +58.4 (c=0.96, MeOH); yield: 89%.

(-)-(1*S*)-7,7-Dimethyl-2-oxo-1-norbornanecarbonitrile (5b)

^{1}H NMR δ: 2.55 (1H, ddd, J=18.8 Hz, J=4.6 Hz, J=3.4 Hz), 2.36-2.06 (3H, m), 2.00 (1H, d, J=15.7 Hz), 1.92 (1H, m), 1.52 (1H, ddd, J=12.6 Hz, J=9.2 Hz, J=3.8 Hz), 1.80 (3H, s), 1.20 (3H, s); ^{13}C NMR δ: 206.3 (C2), 116.6 (CN), 57.5 (C1), 52.3 (C7), 42.7 (C3), 42.5 (C4), 27.9 and 27.0 (C5 and C6), 19.9 (Me), 19.4 (Me); IR (CCl_4) ν: 2970, 2890, 2240 (CN), 1770 (CO), 1450, 1400, 1380, 1300, 1040, 1030 cm^{-1}; MS m/e (%B): 163 ($M^{+\cdot}$, 42), 148 (3), 134 (7), 120 (100), 119 (55), 106 (66), 94 (63), 93 (71), 81 (32), 79 (41), 77 (30), 69 (38), 67 (43), 55 (23), 53 (33), 41 (74); mp: 186.5-189.7°C; $[\alpha]_D^{20}$ -29.4 (c=0.67, MeOH); yield: 90 %.

(+)-(1*R*)-3,3-Dimethyl-2-oxo-1-norbornanecarboxylic acid (7a)

^{1}H NMR, IR, and mp: see lit[9a]; ^{13}C NMR: see lit[9b]; MS m/e (%B): 182 ($M^{+\cdot}$, 7), 154 (17), 112 (63), 109 (18), 94 (10), 69 (100), 67 (30); MS m/e (%B): 182 ($M^{+\cdot}$, 7), 154 (17), 112 (63), 109 (18), 94 (10), 69 (100), 67 (29), 43 (26), 41 (77); $[\alpha]_D^{20}$: see lit[7a]; yield: 89%

General procedure for the synthesis of the 2-oxo-1-norbornanecarboxylic acids 7.

A suspension of the corresponding 2-oxo-1-norbornanecarbonitrile (**5**) (20.0 mmol) in 35 % HCl (50 mL), was stirred for 1h (12 h in the case of **5b**) at 100°C (the reaction was monitored by GC). The resulting

mixture was treated with 10 % NaOH to basic pH and extracted with diethyl ether (2x25 mL). The aqueous layer was acidified with 10 % HCl, extracted with diethyl ether (5x25 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the corresponding acid **7** purified by recrystallization from hexane.

(+)-(1*R*)-3,3-Dimethyl-2-oxo-1-norbornanecarboxylic acid (7a)

Described above; yield 90%.

(-)-(1*R*)-7,7-Dimethyl-2-oxo-1-norbornanecarboxylic acid, (-)-ketopinic acid, (7b)

^{1}H NMR δ: 11.26 (1H, sa), 2.60 (1H, dt, J=18.8 Hz, J=3.4 Hz), 2.43 (1H, m), 2.17-2.10 (2H, m), 2.03 (1H, d, J=18.8 Hz), 1.81 (1H, ddd, J=13.9 Hz, J=9.5 Hz, J=4.7 Hz), 1.46 (1H, m), 1.21 (3H, s), 1.12 (3H, s); ^{13}C NMR δ: 174.0 (COOH), 67.0 (C1), 49.9 (C7), 44.1 (C4), 43.7 (C3), 27.2 and 26.9 (C5 and C6), 20.9 (Me), 20.0 (Me); IR (CCl_4) *ν*: 3500-2500 (COOH), 2960, 1750 (COOH), 1700 (CO), 1460, 1420, 1380, 1290, 1160, 1120, 1010, 930, 910 cm^{-1}; MS m/e (%B): 182 ($M^{+\cdot}$, 7), 164 (9), 154 (11), 139 (31), 138 (45), 121 (24), 112 (61), 109 (39), 99 (26), 95 (86), 93 (30), 81 (22), 79 (34), 77 (23), 69 (55), 67 (76), 55 (60), 53 (39), 43 (35), 41 (60); mp: see lit[11]; $[\alpha]_D^{20}$: see lit[8]; yield: 91 %.

ACKNOWLEDGEMENT

We thank the DGICYT (Spain) for financial support of this work (Grants PB 91-0354 and PB 90-0070). S. de la M. C. thanks the Ministerio de Educacion y Ciencia for a fellowship.

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(*Received in UK* 2 *June* 1994)