Stereo- and Regioselectivity in Dynamic Gas Phase Thermo-Isomerization (DGPTI): Novel Route to β -Campholanic Acid and Derivatives

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Supporting Information

Experimental

General. TLC: glass plates covered with silica gel 60 F_{254} (Merck) or Polygram Alox N/UV₂₅₄ (Macherey-Nagel); visualization by UV light or by spraying with ‘mostain’ solution ((NH₄)₆Mo₇O₂₄·4H₂O (40 g), Ce(SO₄)₂ (0.8 g), 10% H₂SO₄ soln. (800 ml)) and heating (blue spots). Column chromatography (CC) and flash chromatography (FC): silica gel 60 (Merk), grain size 0.040–0.063 mm, or aluminium oxide, Fluka, type 5016 A basic, Brockmann grade IV, or Alox ICN Alumina N neutral, Brockmann grade III. M.p. (not corrected): Mettler FP 5/52. UV/VIS Spectra: were recorded on a Perkin-Elmer Lambda 19 spectrometer; λ (nm), in parentheses log ϵ . IR Spectra: Perkin-Elmer 1600 Series FT-IR spectrometer; wave numbers in cm⁻¹; characterization of the band intensities (transmission): 0–20% vs, 20–40% s, 40–60% m, 60–80% w, 80–100% vw. NMR Spectra: Bruker ARX-300 (300/75 MHz), Avance DRX 500 (500/125 MHz), and Avance DRX 600 (600/150 MHz); chemical shifts (δ , ppm) relative to CD(H)Cl₃ (7.27/77.00 ppm), coupling constants J in Hz; for complete assignments of ¹H NMR signals COSY, TOCSY, NOESY, ROESY 2D- or 1D NMR methods were applied; for complete assignments of ¹³C NMR signals HMBC and HSQC 2D NMR methods were employed. If not stated otherwise, the spectra were recorded at 300 and 75 MHz, resp., in CDCl₃. MS: Varian SSQ 700; Ionization by EI (70 eV) or CI (NH₃): m/z , rel. intensities (%). GC/MS: Hewlett Packard HP-5971 Series (mass-selective detector; EI, 70 eV) and HP-5890 Series II (GC); carrier gas He; WCOT capillary column HP-5; 25 m $\times$ 0.3 mm, 0.2 μ m. GC conditions: injector temp. 280°, starting temp. 60° over 2 min, rate 20°/min, term. temp. 250° over 5 min.

General Procedure for DGPTI of 2-arylisoborneols **3a-d** and 2-phenylfenchol **10**.

The thermo-isomerization device consists of an electrically heatable tube furnace (one meter-long), a condenser unit with a cooling trap at the outlet side and a kugelrohr oven as the evaporation unit at the inlet side. A quartz tube (110 cm long, 2.5 cm i. d.), which fitted into the furnace, was connected to a trap (cooled with liquid N₂) on one side and to a bulb placed in the kugelrohr oven on the other. The starting material (typically 1-3 g) was placed in the bulb equipped with a capillary inlet device for the inert flow gas (N₂) and a magnetic stirrer. After evacuation of the apparatus with a high-vacuum oil pump the starting material was distilled directly through the preheated reactor tube (1–3 g/h). After all of the starting material had been distilled, the apparatus was vented and the frozen products were transferred to a bulb using Et₂O as solvent. The resulting solution was dried over anhydrous MgSO₄ and evaporated under reduced pressure.

The following parameters are typical for the DGPTI process: (i) the kugelrohr oven was heated up to 140–160 °C; (ii) a flow of N₂ was adjusted from 0.8–1.4 L/h; (iii) the reactor tube was heated up to 610–630 °C; (iv) the high-vacuum was adjusted from 2–4 × 10⁻² mbar.

(1R,3S)-2-(2,2,3-Trimethyl-cyclopentyl)-1-phenyl-ethanone (**4a**)

Isoborneol **3a** was thermo-isomerized at 630 °C. The dark yellow crude product was chromatographed on silica gel (hexane/ethyl acetate (20:1) as eluent), giving **4a** (73%) as a slightly yellow oil. An analytical sample was further purified by bulb-to-bulb distillation (kugelrohr).

[α]_D²³ = +54.7 (*c* 0.6, MeOH). IR (film) 3060, 3027, 2958, 2871, 1687, 1598, 1580, 1448, 1366, 1285, 1215, 1180, 1016, 1002, 752, 690 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 7.95 (dd, *J* = 8.3, 1.4, 2H), 7.54 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.45 (t, *J* = 7.9, 2H), 3.03 (dd, *J* = 16.2, 4.0, 1H), 2.73 (dd, *J* = 16.0, 10.4, 1H), 2.20 (m, 1H), 1.93 (m, 1H), 1.85 (m, 1H), 1.66 (sext., *J* = 7.1, 1H), 1.25–1.20 (m, 2H), 0.89 (s, 3H), 0.88 (s, 3H), 0.86 (d, *J* = 7.1, 3H). ¹³C NMR (150 MHz, CDCl₃): δ 201.1, 137.6 (2 s), 133.0, 128.7, 128.3, 44.3, 43.7 (5 d), 42.4 (s), 40.7, 31.6, 29.7 (3 t), 24.4, 23.8, 16.5 (3 q). MS (70 eV) (*m/z*): 230 (12, *M*⁺), 221 (2), 187 (1), 173 (45), 145 (7), 120 (82, [*M* –

COPh]⁺), 105 (100, [*M* – PhAc]⁺), 95 (23), 77 (30), 69 (11). Anal. calc. for C₁₆H₂₂O (230.35): C 83.43, H 9.63; found: C 83.31, H 9.62.

(1*R*,3*S*)-2-(2,2,3-Trimethyl-cyclopentyl)-1-(4-methylphenyl)-ethanone (4b)

Isoborneol **3b** was thermo-isomerized at 620 °C. The orange crude product was purified by column chromatography (silica gel, hexane/ethyl acetate (30:1) as eluent), giving **4b** (45%) as a colorless oil.

[α]_D²³ = +53.2 (*c* 1.0, hexane). IR (film) 3031, 2958, 2872, 1682, 1608, 1451, 1366, 1289, 1224, 1181, 1016, 806 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.85 (A of AA'BB' 2H), 7.25 (B of AA'BB' 2H), 3.00 (dd, *J* = 15.4, 4.0, 1H), 2.70 (dd, *J* = 15.4, 10.4, 1H), 2.41 (s, 3H), 2.18 (m, 1H), 1.95–1.80 (m, 2H), 1.65 (sext., *J* = 7.1, 1H), 1.28–1.14 (m, 2H), 0.89 (s, 3H), 0.87 (s, 3H), 0.86 (d, *J* = 7.0, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 199.4, 163.2, 130.5 (3 s), 130.2, 113.5 (2 d), 55.3 (q), 44.3, 43.4 (2 d), 42.1 (s), 40.0, 31.3, 29.4 (3 t), 24.1, 23.5, 16.2 (3 q). MS (70 eV) (*m/z*): 260 (5, *M*⁺), 203 (10), 189 (7), 163 (1), 150 (100), 135 (90), 110 (7, [*M* – ArAc – H]⁺), 92 (9), 77 (12), 69 (3), 55 (4).

(1*R*,3*S*)-2-(2,2,3-Trimethyl-cyclopentyl)-1-(4-methoxyphenyl)-ethanone (4c)

Isoborneol **3c** was thermo-isomerized at 610 °C. The dark yellow crude product was purified by column chromatography (silica gel, hexane/ethyl acetate (30:1) as eluent), giving **4c** (62%) as a yellow oil.

[α]_D²³ = +50.0 (*c* 1.0, hexane). IR (film) 2966, 2872, 1677, 1601, 1510, 1418, 1365, 1259, 1170, 1032, 829 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.94 (A of AA'BB' 2H), 6.93 (B of AA'BB' 2H), 3.86 (s, 3H), 2.97 (dd, *J* = 15.3, 4.0, 1H), 2.67 (dd, *J* = 15.3, 10.4, 1H), 2.18 (m, 1H), 1.95–1.80 (m, 2H), 1.65 (sext., *J* = 7.1, 1H), 1.28–1.14 (m, 2H), 0.89 (s, 3H), 0.87 (s, 3H), 0.86 (d, *J* = 7.0, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 199.4, 163.2, 130.5 (3 s), 130.2, 113.5 (2 d), 55.3 (q), 44.3, 43.4 (2 d), 42.1 (s), 40.0, 31.3, 29.4 (3 t), 24.1, 23.5, 16.2 (3 q). MS (70 eV) (*m/z*): 260 (5, *M*⁺), 203 (10), 189 (7), 163 (1), 150 (100), 135 (90), 110 (7, [*M* – ArAc – H]⁺), 92 (9), 77 (12), 69 (3), 55 (4).

(1*R*,3*S*)-2-(2,2,3-Trimethyl-cyclopentyl)-1-(4-trifluoromethylphenyl)-ethanone (4d)

Isoborneol **3d** was thermo-isomerized at 610 °C. The dark yellow crude product was purified by column chromatography (silica gel, hexane/ethyl acetate (25:1) as eluent), giving **4d** (71%) as a colorless oil.

$[\alpha]_D^{23} = +40.2$ (*c* 1.0, hexane). IR (film) 2961, 2874, 1694, 1512, 1470, 1410, 1367, 1325, 1289, 1214, 1170, 1133, 1110, 1067, 1016, 994, 857, 825 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 8.05 (d, *J* = 8.2, 2H), 7.72 (d, *J* = 8.2, 2H), 3.06 (dd, *J* = 15.9, 4.1, 1H), 2.75 (dd, *J* = 15.9, 10.2, 1H), 2.18 (m, 1H), 1.98–1.82 (m, 2H), 1.67 (sext., *J* = 7.2 Hz, 1H), 1.27–1.14 (m, 2H), 0.89 (s, 3H), 0.88 (s, 3H), 0.87 (d, *J* = 7.2, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 199.7, 140.0 (2 s), 134.0 (q, *J* = 32.6), 128.6 (d), 125.4 (q, *J* = 3.5), 123.5 (q, *J* = 271.2), 44.0, 43.4 (2 d), 42.1 (s), 40.7, 31.2, 29.4 (3 t), 24.1, 23.4, 16.1 (3 q). MS (70 eV) (*m/z*): 298 (4, M^+), 279 (5), 241 (88), 213 (8), 188 (81), 173 (100), 145 (95), 125 (16(22, M^+), 155 (8), 138 (24), 127 (19), 111 (25, [$M - \text{COAr} + \text{H}]^+$), 110 (76, [$M - \text{ArAc}]^+$), 95 (98), 84 (37), 69 (79), 55 (68).

(1R,3S)-1-Methyl-3-(1-methyl-ethyl)-phenyl-methanone (11)

Fenchol **10** was thermo-isomerized at 630 °C. The yellow crude product was chromatographed on silica gel (hexane/ethyl acetate (30:1) as eluent), giving **11** (48%) as a pale yellow oil. An analytical sample was purified by bulb-to-bulb distillation (kugelrohr).

$[\alpha]_D^{23} = -6.7$ (*c* 1.0, hexane). IR (film) 3060, 2957, 2871, 1674, 1598, 1579, 1447, 1384, 1367, 1284, 1236, 1184, 1159, 1077, 1003, 975, 942, 797, 714, 656 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 7.86 (dd, *J* = 7.2, 1.4, 2H), 7.47 (tt, *J* = 7.4, 1.2, 1H), 7.41 (t, *J* = 7.5, 2H), 2.45 (ddd, *J* = 13.2, 9.4, 3.7, 1H), 1.89 (d, *J* = 8.9, 2H), 1.88 (m, 1H), 1.75 (sext., *J* = 7.9, 1H), 1.66 (ddd, *J* = 16.9, 8.7, 3.7, 1H), 1.42 (s, 3H), 1.38 (sext $\square$ d, *J* = 6.7, 1.7 Hz, 1H), 1.30–1.23 (m, 1H), 0.90 (d, *J* = 6.6, 3H), 0.89 (d, *J* = 6.6, 3H). ^{13}C NMR (150 MHz, CDCl_3): δ 206.7, 136.9 (2 s), 131.8, 129.2, 128.3 (3 d), 54.7 (s), 46.9 (d), 43.2, 37.6 (2 t), 33.6 (d), 30.6 (t), 28.0, 21.8, 21.7 (3 q). MS (70 eV) (*m/z*): 230 (4, M^+), 212 (1, [$M - \text{H}_2\text{O}]^+$), 187 (10), 124 (25, [$M - \text{COPh}]^+$), 105 (100, COPh^+), 81 (63), 69 (80), 55 (28). Anal. calc. for $\text{C}_{16}\text{H}_{22}\text{O}$ (230.35): C 83.43, H 9.63; found: C 83.39, H 9.66.

General procedure for Baeyer-Villiger oxidation. The ketone (5 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) and *m*-CPBA (technical grade: 80–85%, 2.24 g, 13 mmol) was added. The suspension was cooled to 0 °C and TFA (0.57 g, 5 mmol) was added dropwise over 15 min.

(1*R*,3*S*)-(2,2,3-Trimethyl-cyclopentyl)-acidic acid 4-methoxyphenyl ester (6)

The reaction flask protected from light was stirred over night at room temperature, whereupon the ketone was completely consumed (GC analysis). The mixture was diluted with CH_2Cl_2 (50 mL) washed once each with 10% aqueous Na_2SO_3 solution, saturated aqueous K_2CO_3 solution, and H_2O . The organic phase was dried over MgSO_4 and evaporated. The residue was taken up in hexane and filtered over a short pad of silica gel to give **6** (99%) as a colorless oil.

$[\alpha]_{\text{D}}^{23} = +27.5$ (*c* 1.0, MeOH). IR (CHCl_3) 2962, 2874, 1747, 1506, 1467, 1368, 1290, 1249, 1195, 1145, 1103, 1036 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 6.98 (A of AA'BB' 2H), 6.88 (B of AA'BB' 2H), 3.79 (s, 3H), 2.59 (dd, *J* = 14.5, 4.6, 1H), 2.30 (dd, *J* = 14.5, 10.3, 1H), 2.15 (m, 1H), 2.00 (m, 1H), 1.88 (m, 1H), 1.66 (sext., *J* = 7.2, 1H), 1.43–1.19 (m, 2H), 0.89 (s, 3H), 0.88 (d, *J* = 7.2, 3H), 0.86 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 172.8, 157.1, 144.2 (3 s), 122.2, 114.3 (2 d), 55.5 (q), 44.8, 43.4 (2 d), 42.1 (s), 36.5, 31.2, 29.1 (3 t), 23.8, 23.4, 15.9 (3 q). MS (70 eV) (*m/z*): 276 (3, M^+), 219 (1), 153 (1), 135 (1), 124 (100), 109 (14, [$M - \text{ArAc}$] $^+$), 81 (3), 69 (10), 55 (7).

(1*R*,3*S*)-(4-Trifluormethyl-benzoyloxy)-(2,2,3-trimethyl-cyclopentyl)-methane (7)

The reaction flask protected from light was stirred over 10 d at room temperature. Workup in the same fashion as described above provided **7** (89%) as a colorless oil.

$[\alpha]_{\text{D}}^{23} = +27.7$ (*c* 1.0, hexane). IR (film) 2961, 2874, 1725, 1469, 1412, 1326, 1276, 1170, 1067, 1018, 863, 776, 705 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 8.14 (d, *J* = 8.1, 1H), 7.70 (d, *J* = 8.1, 1H), 4.39 (dd, *J* = 10.9, 6.1 Hz, 1H), 4.23 (dd, *J* = 10.9, 7.5 Hz, 1H), 2.08 (m, 1H), 1.99–1.83 (m, 2H), 1.68 (sext., *J* = 7.1, 1H), 1.35–1.19 (m, 2H), 0.96 (s, 3H), 0.92 (s, 3H), 0.89 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 165.4, 134.4 (2 s), 133.7 (q, *J* = 31.8), 129.8 (d), 125.3 (q, *J* = 3.5), 123.7 (q, *J* = 270.3), 67.5 (t), 47.3, 44.1 (2 d), 41.7 (s), 31.4, 26.8 (2 t), 24.3, 23.6, 15.2 (3 q). MS

(70 eV) (m/z): 314 (1, M^{+}), 295 (6), 258 (3), 231 (3), 211 (1), 173 (100, [COAr + H]⁺), 145 (43), 124 (40), 109 (56), 95 (18), 82 (42), 69 (43), 55 (16).

(+)-*trans*- α -Campholanic acid (1), (1*R*,3*S*)-2-(2,2,3-trimethyl-cyclopentyl)-acidic acid

To a stirred solution of **6** (1.27 g, 4.59 mmol) in MeOH (10 mL) at 0 °C was added a saturated aqueous LiOH solution (10 mL). The mixture became immediately dark and cloudy. After stirring for 15 min at room temperature H₂O was added and the solution was treated with 10% aqueous HCl solution (pH < 3). The resulting mixture was extracted three times with saturated aqueous NaHCO₃ solution. The aqueous layer was acidified again and extracted three times with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄ and evaporated to yield 0.76 g (97%) of **1** as a colorless oil. An analytical sample was purified by bulb-to-bulb distillation (kugelrohr).

$[\alpha]_D^{23} = +40.6$ (c 1.0, hexane). IR (CHCl₃) 3517, 2961, 2874, 2680, 1704, 1470, 1452, 1412, 1389, 1368, 1296, 1230, 1178, 1136 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 2.43 (dd, $J = 15.1, 3.5$, 1H), 2.12 (dd, $J = 15.6, 10.4$, 1H), 2.06–1.91 (m, 2H), 1.85 (m, 1H), 1.62 (sext., $J = 7.1$, 1H), 1.31–1.17 (m, 2H), 0.86 (d, $J = 6.9$, 3H), 0.84 (s, 3H), 0.81 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 180.6 (s), 44.5, 43.3 (2 d), 42.0 (q), 36.2, 31.1, 29.1 (3 t); 23.7, 23.3, 16.0 (3 q). MS (70 eV) (m/z): 170 (10, M^{+}), 127 (11), 114 (37), 110 (26, [M – AcOH – H]⁺), 95 (42), 84 (67), 69 (100), 55 (23).

(1*S*,3*S*)-(2,2,3-Trimethyl-cyclopentyl)-methanol (8)

To a stirred solution of **7** (1.40 g, 4.45 mmol) in MeOH (10 mL) at 0 °C was added a saturated aqueous LiOH solution (10 mL). The mixture became immediately dark and cloudy. After stirring for 30 min at room temperature 2 N NaOH solution (10 mL) was added and the mixture was extracted three times with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄ and evaporated to afford 0.62 g (98%) of **8** as a colorless oil.

$[\alpha]_D^{23} = +49.9$ (c 1.0, hexane). IR (CHCl₃) 3623, 3469, 2961, 2874, 1681, 1598, 1581, 1469, 1450, 1388, 1367, 1285, 1217, 1181, 1022 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ

3.71 (dd, $J = 10.4, 5.7$, 1H), 3.44 (dd, $J = 10.4, 8.2$, 1H), 1.91–1.73 (m, 3H), 1.65 (sext., $J = 7.0$, 1H), 1.53 (br. s, 1H), 1.46–1.16 (m, 2H), 0.87 (s, 3H), 0.85 (d, $J = 7.0$, 3H), 0.85 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 65.0 (t), 50.9, 44.0 (2 d), 41.5 (s), 31.5, 26.7 (2 t), 24.2, 23.4, 15.1 (3 q). MS (70 eV) (m/z): 142 (2, M^+), 124 (6, $[M - \text{H}_2\text{O}]^+$), 109 (78), 99 (14), 95 (10), 84 (33), 69 (100), 55 (30).

(1S,3S)-2,2,3-Trimethyl-cyclopentanecarboxylic acid (9)

Jones Reagent prepared by dissolving CrO_3 (1.13 g, 11.30 mmol) in H_2O (3.5 mL) and H_2SO_4 (1 mL) was added dropwise to a solution of **8** (0.5 g, 3.52 mmol) in acetone (25 mL) at 0 °C. After stirring for 30 min at room temperature H_2O (20 mL) and Et_2O (30 mL) were added. The mixture was extracted with 2 N NaOH solution (3 $\times$ 20 mL) and the aqueous layer acidified with 10% aqueous HCl solution to pH 3. The aqueous phase was extracted with Et_2O (2 $\times$ 30 mL) and the combined organic extracts were dried and evaporated, and the residual oil was filtered through a sort pad of silica gel to provide 0.55 g (100%) of **9** as a colorless oil.

$[\alpha]_D^{23} = +51.2$ (c 1.0, hexane). IR (film) 2963, 2875, 2748, 2668, 1700, 1471, 1420, 1369, 1291, 1239, 1190, 941, 713 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 2.53 (dd, $J = 8.4, 6.0$, 1H), 1.97–1.89 (m, 2H), 1.88–1.79 (m, 2H), 1.35–1.21 (m, 1H), 0.98 (s, 3H), 0.94 (s, 3H), 0.86 (d, $J = 7.0$, 3H). ^{13}C NMR (150 MHz, CDCl_3): δ 182.6 (s), 54.9 (d), 44.7 (s), 43.5 (d), 32.1, 25.8 (2 t), 24.5, 24.1, 14.9 (3 q). MS (70 eV) (m/z): 156 (6, M^+), 138 (4), 123 (4, $[M - \text{CO}_2 + \text{H}]^+$), 113 (6), 101 (10), 96 (12), 84 (100), 69 (70), 55 (19).