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"Preorganization of Achiral Molecules for Asymmetric Synthesis through Crystallization-Induced Immobilization in Homochiral Conformations

Brian Patrick, John R. Scheffer* and Carl Scott

7-(*p*-Fluorobenzoyl)-7-methylbicyclo[2.2.1]heptane (i): 7-Methyl-7-carboxy-norbornane[1] (0.65 g, 4.2 mmol) was converted to its corresponding acid chloride by treatment with oxalyl chloride (3.0 mL, 35 mmol) and DMF (2 μL) in methylene chloride (50 mL). After stirring for 3 h at room temperature the solvent and residual oxalyl chloride were removed *in vacuo* and replaced with fresh methylene chloride (25 mL). The fresh solvent was removed *in vacuo*, then replaced and removed one final time to ensure complete removal of any residual oxalyl chloride. The yellow oil was then taken up in THF (50 mL), placed under a nitrogen atmosphere and cooled to 0 ºC in an ice bath. *p*-Fluorophenylmagnesium bromide (5 mL, 1 M, 5 mmol) was added dropwise and the resulting solution stirred for 3 h, at which time the reaction was allowed to warm to room temperature and stir overnight. After quenching with saturated aqueous ammonium chloride (20 mL) the mixture was extracted with ether (2 x 25 mL). The combined organic fractions were washed with 10% sodium hydroxide (2 x 25 mL) and water (3 x 25 mL) before being dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow oil, which was purified by column chromatography (2% ether/pet. ether) to give 7-(*p*-fluorobenzoyl)-7-methylbicyclo[2.2.1]heptane (**i**) as a colorless solid (0.42 g, 43%).

mp: 80 - 81 ºC (hexanes)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (m, 2H), 1.29 (m, 2H), 1.38 (s, 3H), 1.49 (m, 2H), 1.86 (m, 2H), 2.41 (m, 2H), 7.06 (m, 2H), 7.69 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.50 (-), 27.93 (+), 28.72 (+), 42.90 (-), 62.65 (+), 115.05 and 115.33 (-, $^{2}J_{C-F}$ = 21.5 Hz), 131.12 and 131.00 (-, $^{3}J_{C-F}$ = 8.9 Hz), 133.27 and 133.23 (+, $^{4}J_{C-F}$ = 2.7 Hz), 166.59 and 163.23 (+, $^{1}J_{C-F}$ = 251.9 Hz), 203.54 (+).

IR (KBr): ν = 2952, 2868, 1666, 1599, 1503, 1278, 1227, 1158, 972, 844, 767, 615 cm^{-1}.

UV/VIS (methanol, 1.55 x 10^{-4} M): 212 (8239), 246 (12,583), 322 (114) nm ($M^{-1}cm^{-1}$).

LRMS (EI): 232 (16, M^{+}), 178 (34), 177 (13), 163 (13), 151 (30), 123 (100), 109 (73), 95 (53), 94 (11), 81 (25), 79 (14), 75 (14), 67 (59), 55 (17).

HRMS (EI): calcd for [$C_{15}H_{17}OF$]: 232.1263; found: 232.1263.

Anal: calcd for [$C_{15}H_{17}OF$]: C, 77.56; H, 7.38. Found: C, 77.95; H, 7.43.

7-(*p*-Cyanobenzoyl)-7-methylbicyclo[2.2.1]heptane (ii) Ketone **i** (0.42 g, 1.8 mmol) was dissolved in DMSO (50 mL) with potassium cyanide (0.24 g, 4 mmol) and placed under a nitrogen atmosphere. The solution was then heated for 16 h at 85 ºC. After cooling the solution to room temperature, water (10 mL) was slowly added and the mixture was extracted with ether (3 x 20 mL). The combined ethereal fractions were washed with water (3 x 25 mL) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded an off-white solid, which was purified by column chromatography (10% ether/pet. ether) to give ketone **ii** as a colorless solid (0.40 g, 93%).

mp: 125 - 126 ºC (hexanes)

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.17 (m, 2H), 1.29 (m, 2H), 1.37 (s, 3H), 1.42 (m, 2H), 1.85 (m, 2H), 2.37 (m, 2H), 7.69 (dt, *J* = 8.7, 1.9 Hz, 2H), 7.97 (dt, *J* = 8.7, 1.9 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.30 (-), 27.83 (+), 28.59 (+), 42.70 (-), 62.82 (+), 115.26 (+), 117.96 (+), 128.72 (-), 132.04 (-), 146.49 (+), 203.98 (+).

IR (KBr): ν = 2961, 2876, 2229, 1672, 1462, 1273, 1164, 971, 849, 768 cm^{-1}.

UV/VIS (methanol, 1.67 x 10^{-4} M): 214 (8322), 244 (14362), 288 (2350), 332 (114) nm ($M^{-1}cm^{-1}$).

LRMS (EI): 239 (13, M^+), 197 (12), 196 (10), 185 (38), 184 (10), 170 (16), 130 (32), 109 (100), 102 (44), 94 (11), 81 (48), 80 (11), 79 (17), 67 (72), 55 (20), 53 (12).

HRMS (EI): calcd for [$C_{16}H_{17}ON$]: 239.1310; found: 239.1312.

Anal: calcd for [$C_{16}H_{17}ON$]: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.20; H, 7.25; N, 5.86.

7-(*p*-Carboxybenzoyl)-7-methylbicyclo[2.2.1]heptane (1a). Ketone **ii** (0.40 g, 1.7 mmol) was suspended in a water (75 mL) – ethanol (15 mL) solution containing 13.5 g (241 mmol) of potassium hydroxide. The solution was heated to reflux for 18 h and then cooled to room temperature and acidified with conc HCl. The white precipitate formed upon acidification was removed by extraction with ether (3 x 25 mL). The combined organic fractions were washed with water (3 x 25 mL) and dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a yellow solid, which was purified by recrystallization from methanol to give keto-acid **1a** as a colorless solid (0.42g, 98%).

mp: 215 - 217 ºC (methanol)

^{1}H NMR (400 MHz, DMSO): δ = 1.14 (m, 2H), 1.24 (m, 2H), 1.34 (m, 2H), 1.36 (s, 3H), 1.85 (m, 2H), 2.36 (br s, 2H), 7.99 (m, 2H), 8.02 (m, 2H).

^{13}C NMR (75 MHz, DMSO): δ = 16.94 (-), 27.45 (+), 28.20 (+), 42.06 (-), 62.47 (+), 128.20 (-), 139.34 (-), 133.69 (+), 139.93 (+), 166.59 (+), 204.49 (+).

IR (KBr): ν = 3200-2500 (br), 2957, 2872, 2554, 1676, 1430, 1319, 1295, 1272, 1250, 969, 930, 864, 736 cm^{-1}.

UV/VIS (methanol, 1.24 x 10^{-4} M): 210 (7662), 252 (15,984), 290 (sh) (1677), 332 (sh) (159) nm ($M^{-1}cm^{-1}$).

LRMS (EI): 259 (3, M+!), 258 (13, M^+), 213 (23), 204 (28), 177 (10), 159 (16), 150 (21), 149 (32), 109 (100), 94 (11), 81 (26), 67 (46), 65 (23), 53 (15).

HRMS (EI): calcd for [$C_{16}H_{18}O_3$]: 258.1256; found: 258.1255.

Anal: calcd for [$C_{16}H_{18}O_3$]: C, 74.40; H, 7.02. Found: C, 74.40; H, 7.03.

(*S*)-(-)-1-Phenylethylamine salt of keto-acid 1a: (*S*)-(-)-1-phenylethylamine (37.7 μL, 0.29 mmol) was added to a solution of acid **1a** (73 mg, 0.28 mmol) in methanol (5 mL). Upon standing a precipitate formed, which was isolated by suction filtration to give the 1:1 salt (84 mg, 79%) as colorless prisms.

mp: 197 - 199 ºC (solvent?)

^{1}H NMR (DMSO, 400 MHz): δ = 1.14 (m, 2H), 1.25 (m, 2H), 1.37 (m, 2H), 1.37 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 3H), 1.87 (m, 2H), 2.38 (m, 2H), 4.32 (q, *J* = 6.5 Hz, 1H), 7.30 (m, 1H), 7.37 (m, 2H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.88 (d, *J* = 8 Hz, 2H), 7.94 (d, *J* = 8 Hz), 8.0 - 8.8 (br).

^{13}C NMR (DMSO, 75 MHz): δ = 17.53, 22.69, 27.94, 28.72, 42.59, 50.39, 62.84, 126.94, 128.00, 128.68, 128.89, 129.31, 137.88, 141.73, 142.57, 168.72, 205.00.

IR (KBr): ν = 3200-2600 (br), 2963, 1667, 1618, 1573, 1521, 1396, 1973, 1256, 969, 818, 762, 745, 695 cm^{-1}.

HRMS (ESI, +, 0.1% HCOOH in MeOH): calcd for [$C_{34}H_{30}O_3N$] (M+1): 380.2226; found: 380.2220.

Anal: calcd for [$C_{24}H_{29}O_3N$]: C, 75.96; H, 7.70; N, 3.69. Found: C, 76.23; H, 7.57; N, 3.67. The structure was confirmed by X-ray crytallographic analysis.

Preparative scale irradiation of (*S*)-(-)-1-phenylethylamine salt 1c: The salt (25 mg) was crushed between two Pyrex microscope slides and sealed in a polyethylene bag under a positive pressure of nitrogen. The sample was irradiated to complete conversion (60 min) by using a 450 W medium pressure mercury lamp. The product of this reaction, (*S*)-(-)-1-phenylethylamine salt **2c**, exhibited the following physical and spectroscopic properties.

mp: 162-163 °C.

^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 0.84 (dd, *J* = 10.7, 1.8 Hz, 1H), 0.99 (dd, *J* = 10.5, 6.7 Hz, 1H), 1.23 (s, 3H), 1.36 (d, *J* = 6.7 Hz, 3H), 1.41 (m, 1H), 1.53 (m, 2H), 1.79 (m, 2H), 2.51 (m, 1H), 2.63 (m, 1H), 4.16 (m, 1H), 5.28 (br s, 1H), 7.21 (m, 2H), 7.24 (m, 1H), 7.33 (m, 1H), 7.42 (m, 1H), 7.83 (m, 2H).

^{13}C NMR (DMSO, 75 MHz): δ = 10.87, 21.23, 24.01, 28.01, 33.12, 41.36, 46.46, 47.92, 50.19, 57.29, 83.14, 125.76, 126.09, 126.88, 128.19, 128.92, 132.51, 145.20, 147.80, 168.12.

IR (KBr): ν = 3607, 3250-2500 (br), 2940, 2865, 2543, 1612, 1523, 1455, 1397, 1296, 1035, 864, 841, 792, 696 cm^{-1}.

HRMS (ESI, 0.1% HCOOH in MeOH): calcd for [$C_{24}H_{30}O_3N$] (M+1): 380.2226; found: 380.2222.

Recrystallization of this salt from methanol afforded colorless prisms.

mp: 160-162 °C (methanol).

IR (KBr): ν = 3348 (br), 3200-2500 (br), 2951, 2864, 1619, 1509, 1396, 854, 795, 697 cm^{-1}.

The structure of the recrystallized salt was confirmed by X-ray diffraction analysis.

Keto-ester 2b: Following irradiation, the salt crystals were suspended in an excess of ethereal diazomethane solution and allowed to stand until dissolution was complete. Ether and excess diazomethane were removed *in vacuo* and the residue taken up in methylene chloride and passed through a short plug of silica gel to remove the chiral auxiliary. This afforded cyclobutanol **2b** as a colorless solid. GC analysis (HP 35 column) showed a single peak and no remaining starting material. Chiral HPLC analysis (Chiralcel OC column) indicated an enantiomeric excess of 97% (dextrorotatory at 589 nm by polarimetry).

mp: 125.5-127 °C (solvent?).

^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 0.95 (dd, J = 11.3, 2.2 Hz, 1H), 1.10 (dd, J = 11.2, 6.3 Hz, 1H), 1.30 (s, 3H), 1.50 (m, 1H), 1.61 (m, 2H), 1.88 (m, 1H), 1.89 (m, 1H), 2.11 (br s, 1H), 2.62 (m, 1H), 2.71 (m, 1H), 3.87 (s, 3H), 7.35 (m, 2H), 7.96 (m, 2H).

^{13}C NMR (CD_2Cl_2, 75 MHz): δ = 10.96 (-), 21.89 (+), 28.55 (+), 33.72 (+), 42.48 (-), 47.61 (-), 49.04 (-), 52.29 (-), 58.04 (+), 85.11 (+), 126.70 (-), 129.43 (+), 130.03 (-), 149.23 (+), 167.09 (+).

IR (KBr): ν = 3480, 3365, 2953, 2865, 1709, 1610, 1437, 1278, 1105, 1057, 777 cm^{-1}.

LRMS (EI): 272 (2, M^+), 254 (41), 226 (20). 225 (14), 218 (22), 213 (16), 195 (34), 192 (17), 191 (45), 181 (12), 168 (16), 167 (100), 166 (22), 165 (47), 163 (32), 157 (55), 154 (11), 153 (20), 152 (28), 141 (13), 132 (11), 131 (16), 128 (13), 122 (13), 115 (21), 109 (14), 91 (16), 81 (23), 55 (11).

HRMS (EI): calcd for [$C_{17}H_{20}O_3$]: 272.1412; found: 272.1414.

Anal: calcd for [$C_{17}H_{20}O_3$]: C, 74.97; H, 7.40. Found: C, 75.05; H, 7.29.

Crystallographic Data. Crystal data for (*S*)-(-)-1-phenylethylamine salt of ketoacid **1a** ($C_{24}H_{29}NO_3$, M_r = 379.50): crystal size 0.50 x 0.10 x 0.10 mm^3, orthorhombic, space group $P2_12_12_1$, a = 6.165(2) Å, b = 7.090(2) Å, c = 45.81(2) Å, V = 2002(1) Å^3, Z = 4, ρ_{calcd} = 1.259 g cm^{-3}; $2\Theta_{max}$ = 50º, 10295 measured, 2904 unique and 2166 observed reflections [$I \geq 3\sigma(I)$], μ = 0.082, max./min. transmission: 1.000/0.7636; 281 parameters, R_1 = 0.055 [$I \geq 3\sigma(I)$], wR_2 = 0.103 (all data); max., min. residual electron density 0.24, -0.26 e$^-$ Å^{-3}. Same salt photolyzed to 70% conversion ($C_{24}H_{29}NO_3$, M_r = 379.50): crystal size 0.50 x 0.10 x 0.10 mm^3, orthorhombic, space group $P2_12_12_1$, a = 6.163(5) Å, b = 7.104(4) Å, c = 46.29(3) Å, V = 2026.67(3) Å^3, Z = 4, ρ_{calcd} = 1.244 g cm^{-3}; $2\Theta_{max}$ = 51.1º, 10526 measured, 2319 unique and 2217 observed reflections [$I \geq 2\sigma(I)$], μ = 0.081, max./min. transmission: 1.000/0.4525; 276 parameters, R_1 = 0.053 [$I \geq 2\sigma(I)$], wR_2 = 0.138 (all data); max., min. residual electron density 0.22, -0.20 e$^-$ Å^{-3}. Same salt photolyzed to 93% conversion ($C_{24}H_{29}NO_3$, M_r = 379.50): crystal size 0.50 x 0.10 x 0.10 mm^3, orthorhombic, space group $P2_12_12_1$, a = 6.1652(18) Å, b = 7.0925(14) Å, c = 46.969(9) Å, V = 2053.8(8) Å^3, Z = 4, ρ_{calcd} = 1.227 g cm^{-3}; $2\Theta_{max}$ = 50.0º, 7785 measured, 2696 unique and 2180 observed reflections [$I \geq 2\sigma(I)$], μ = 0.08, max./min. transmission: 1.000/0.5693; 281 parameters, R_1 = 0.050 [$I \geq 2\sigma(I)$], wR_2 = 0.140 (all data); max., min. residual electron density 0.22, -0.24 e$^-$ Å^{-3}. (*S*)-(-)-1-phenylethylamine salt **2c** recrystallized from methanol ($C_{24}H_{29}NO_3$, M_r = 379.50): crystal size 0.35 x 0.15 x 0.05 mm^3, monoclinic, space group $P2_1$, a = 12.2557(9) Å, b = 6.9907(4) Å, c = 12.6665(9) Å, β = 105.869(3)º, V = 1043.9(1) Å^3, Z = 2, ρ_{calcd} = 1.207 g cm^{-3}; $2\Theta_{max}$ = 55.6º, 9374 measured, 4275 unique and 3411 observed reflections [$I \geq 2\sigma(I)$], μ = 0.079, max./min. transmission: 1.000/0.7769; 268 refined parameters, R_1 = 0.0406 [$I \geq 2\sigma(I)$], wR_2 = 0.0968 (all data); max., min. residual electron density 0.14, -0.18 e$^-$ Å^{-3}. All structures were obtained using a Rigaku/ADSC CCD diffractometer, μ(MoKα) = 0.82

cm^{-1}, λ = 0.7107 Å, T = 173 K. Data was collected using ϕ (0.0 to 190.0º) and ω (-26.0 to 23.0º) oscillations and was corrected for Lorentzian polarization and absorption Structures were solved using direct methods (SIR97 or SIR92) and refined using full-matrix least squares (teXsan or SHELXL-97); carbon-bound hydrogen atoms were calculated, nitrogen-bound hydrogen atoms were refined. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-206313, CCDC-206314, CCDC-206315, and CCDC-206316. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[1] S. Beckman, H. Geiger, *Chem. Ber.* **1961**, *94*, 48.