Supplementary information

for

Asymmetric synthesis of 2-azabicyclo[3.3.1]nonanes by a microwave-assisted organocatalyzed tandem desymmetrization and intramolecular aldolization

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II) Copies of $^1$H NMR and $^{13}$C NMR spectra of compounds 1-5
I) Experimental section

General procedures. $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ solution. Chemical shifts are reported as δ values (ppm) relative to internal Me$_4$Si. Infrared spectra were recorded on a Nicolet 320 FT-IR spectrophotometer. TLC was performed on SiO$_2$ (silica gel 60 F$_{254}$, Merck). The spots were located by UV light, a 1% KMnO$_4$ aqueous solution or a 1.5% K$_2$PtCl$_6$ aqueous solution. Chromatography refers to flash chromatography and was achieved on SiO$_2$ (silica gel 60, SDS, 230–400 mesh). All reactions were carried out under an argon atmosphere. Drying of the organic extracts during the work-up of reactions was performed over anhydrous Na$_2$SO$_4$. HPLC analyses for the determination of enantiomeric excess were carried out using a DAICEL CHIRALPAK IC column (250×4.6 mm I.D., 5 µm; Chiral Technologies Europe) on a Waters model 2487 Dual Absorbance Detector and set at the wavelength of 290 nm. The chromatog. resoln. of compound 4 was achieved using CH$_2$Cl$_2$/MeOH 99:1 as the mobile phase in an isocratic run. Microwave irradiation experiments were performed using a single-mode Discover System from CEM Corporation using standard Pyrex vessel (capacity 10 mL).

$\textit{N}$-(2,2-Diethoxyethyl)-4-aminocyclohexanone ethylene acetal (2)

A mixture of cyclohexanedione monoethylene acetal (5 g, 31.05 mmol), 2,2-diethoxyethylamine (5.70 mL, 38.42 mmol) and molecular sieves (8 g) in CH$_2$Cl$_2$ (60 mL) was stirred at rt for 4 h. The reaction mixture was filtered on a celite pad and concentrated to yield the corresponding imine. $^1$H NMR (CDCl$_3$, 300 MHz): δ 1.22 (t, 6H, $J = 7.1$ Hz, CH$_3$), 1.84 (m, 4H), 2.46 (m, 4H), 3.50 (d, 2H, $J = 5.40$ Hz), 358 (m, 2H), 3.72 (m, 2H), 3.99 (s, 4H), 4.74 (t, 1H, $J = 5.4$ Hz); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 15.3 (CH$_3$), 25.3 (CH$_2$), 34.0 (CH$_2$), 34.9 (CH$_2$), 36.2 (CH$_2$), 62.5 (CH$_2$), 64.3 (CH$_2$), 102.8 (CH), 107.9 (C), 172.6 (C=N). The residue was dissolved in MeOH (100 mL) and treated with NaBH$_4$ (2.3 g, 62.09 mmol) at 0 ºC then at rt overnight. Finally the mixture was concentrated, brine was added and the aqueous extracted with CH$_2$Cl$_2$. The organics were dried and concentrated to yield amine 2 in a quantitative yield and enough pure to be used in the next step without further purification. An analytical sample was obtained by chromatography (CH$_2$Cl$_2$-CH$_2$Cl$_2$/MeOH 97:3). 2: IR (NaCl, neat): 3325, 2973, 2935, 2877, 1446, 1376, 1343, 1275, 1107, 1063, 1036, 922, 854, 733, 664 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 1.21 (t, 6H, $J = 7.2$ Hz, CH$_3$), 1.37 (brs, 1H, NH), 1.45 (m, 2H), 1.55 (td, 2H, $J = 12.6$, 3.6 Hz), 1.77 (m, 2H), 1.87 (m, 2H), 2.54 (tt, 1H, $J = 9.6$, 3.6 Hz), 2.74 (d, 2H, $J = 5.6$ Hz), 3.54 (dq, 2H, $J = 9.2$, 7.2 Hz), 3.70 (dq, 2H, $J = 9.2$, 7.2 Hz), 3.93 (s, 4H), 4.58 (t, 1H, $J = 5.6$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 15.3 (CH$_3$), 30.1 (CH$_2$), 32.9 (CH$_2$), 49.5 (CH$_2$), 55.0 (CH), 62.2 (CH$_2$), 64.1 (CH$_2$), 64.2 (CH$_2$), 102.4 (CH), 108.6 (C). HRMS (ESI-TOF): Calcd for C$_{14}$H$_{28}$NO$_4$ 274.2012 (M$^+$+1). Found 274.2012.
\(N-(2,2\text{-Diethoxyethyl})-N-(\text{methoxycarbonyl})-4\text{-aminocyclohexanone ethylene acetal} (3)\)

A mixture of amine 2 (8.5 g, 31.05 mmol), methyl chloroformate (4.85 mL, 62.1 mmol) and \(K_2CO_3\) (8.58 g, 62.1 mmol) in \(CH_3CN\) (200 mL) was stirred at rt overnight. The solvent was then removed, brine was added and the aqueous extracted with \(CH_2Cl_2\). The organics were dried, concentrated and the residue purified by chromatography (\(CH_2Cl_2\)-\(CH_2Cl_2/MeOH 99:1\)) to yield 3 as a colourless oil (8.74 g, 85%) .

**IR** (NaCl, neat): 2974, 2947, 2879, 1700, 1452, 1344, 1287, 1247, 1158, 1100, 1064, 982, 930, 812, 774 cm\(^{-1}\); \(^1H\) NMR (CDCl\(_3\), 400 MHz): \(\delta\) 1.20 (t, 3H, \(J = 7.0\) Hz, \(CH_3\)), 1.54-1.94 (m, 8H), 3.25 (brs, 2H), 3.52 (brs, 2H), 3.71 (brs, 5H), 3.92 (s, 4H), 4.62 (brs, 1H); \(^{13}C\) NMR (CDCl\(_3\), 100 MHz): \(\delta\) 15.3 (\(CH_3\)), 27.5 and 27.9 (\(CH_2\)), 34.0 (\(CH_2\)), 46.9 and 48.0 (\(CH_2\)), 52.4 (\(CH_3\)), 55.7 (CH), 63.3 (\(CH_2\)), 64.3 (\(CH_2\)) 101.5 and 102.0 (CH), 107.8 (C), 156.6 (CO).

**HRMS** (ESI-TOF) Calcd for \(C_{16}H_{29}NO_6\)Na 354.1887 (M\(^+\)+Na). Found: 354.1887.

\(N-(\text{Methoxycarbonyl})-N-(2\text{-oxoethyl})-4\text{-aminocyclohexanone} (1)\)

A solution of carbamate 3 (2 g, 6 mmol), THF (30 mL) and 5% HCl (60 mL) was stirred at rt for 10 min then it was extracted with \(CH_2Cl_2\). The organics were dried and concentrated to yield ketoaldehyde 1 (1.2 g, 95%) enough pure to be used in the next step without further purification. An analytical sample was obtained by chromatography (\(CH_2Cl_2/AcOEt 1:1\)).

**IR** (NaCl, neat): 2956, 2875, 2832, 2717, 1700, 1453, 1369, 1328, 1296, 1222, 1191, 1134, 1097, 997, 953, 775 cm\(^{-1}\); \(^1H\) NMR (CDCl\(_3\), 400 MHz): \(\delta\) 1.74 (brs, 2H), 2.09 (m, 2H), 2.39-2.60 (m, 4H), 3.72 and 3.80 (2s, 3H, \(CH_3\)), 3.90 and 3.97 (2s, 2H), 4.41 and 4.63 (2brs, 1H), 9.56 (s, 1H, CHO); \(^{13}C\) NMR (CDCl\(_3\), 100 MHz): \(\delta\) 29.7 and 30.1 (\(CH_2\)), 39.6 (\(CH_2\)), 52.2 and 52.6 (\(CH_2\)), 53.1 (\(CH_3\)), 53.4 (CH), 156.0 and 156.6 (CO), 198.0 (CHO), 208.8 (CO); HRMS (ESI-TOF) Calcd for \(C_{10}H_{15}NO_4\)Na 236.0893 (M\(^+\)+Na). Found: 236.0893.

\((1RS, 4SR, 5SR)-4\text{-Hydroxy-2-methoxycarbonyl-2-azabicyclo[3.3.1]nonan-6-one (rac-4)}\)

A solution of carbamate 3 (1 g, 3 mmol), THF (20 mL) and 10% HCl (40 mL) was stirred at rt for 4 h. The mixture was then extracted with \(CH_2Cl_2\), the organics were dried and the solvent removed to yield rac-4 (0.56 g, 87%). An analytical sample was obtained by chromatography (\(CH_2Cl_2/AcOEt 1:1\)).

**IR** (NaCl, neat): 3413, 3008, 2953, 2926, 2872, 1698, 1450, 1403, 1341, 1300, 1263, 1217, 1192, 1121, 1106, 1087, 1037, 978, 942, 753 cm\(^{-1}\); \(^1H\) NMR (CDCl\(_3\), 400 MHz, gCOSY): \(\delta\) 1.90-2.24 (m, 4H), 2.46 (dt, 1H, \(J = 18, 8.4\) Hz, H-7ax), 2.59 (ddd, 1H, \(J = 18, 9.2, 4.8\) Hz, H-7eq), 2.82 (brs, 1H, H-5), 2.89 (t, 1H, \(J = 12.4\) Hz, H-3ax), 3.24 and 3.27 (2d, 1H, \(J = 5.6\) Hz, OH), 3.73 (s, 3H, \(CH_3\)), 3.98 (brs, 1H, H-4), 4.23 and 4.37 (2dd, 1H, \(J = 13.2, 6\) Hz, H-3eq), 4.45 and
4.61 (2brs, 1H, H-1); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta\) 27.7 and 28.6 (C-9), 29.4 and 29.9 (C-8), 38.3 (C-7), 43.4 and 43.7 (C-1), 45.9 and 46.1 (C-3), 49.4 (C-5), 52.8 (CH\textsubscript{3}), 67.4 and 67.7 (C-4), 156.0 (CO), 212.3 and 213.2 (C-6). HRMS (ESI-TOF) Calcd for C\textsubscript{10}H\textsubscript{16}NO\textsubscript{2} 214.1073 (M\textsuperscript{+}+H). Found 214.1074.

(1\textsuperscript{R},4\textsuperscript{S},5\textsuperscript{S})-4-Hydroxy-2-methoxycarbonyl-2-azabicyclo[3.3.1]nonan-6-one (4).

In a 10 mL vessel was placed ketoaldehyde 1 (0.1 g, 0.47 mmol), catalyst C (43 mg, 0.12 mmol, 25%), acetonitrile (1 ml) and water (0.08 mL, 4.4 mmol). The mixture was subsequently heated with stirring to 100 \(^\circ\)C using microwave irradiation for 15 min. After concentration, the reaction mixture was purified by chromatography (CH\textsubscript{2}Cl\textsubscript{2}/AcOEt 1:1) to give 4 (70 mg, 70%) as a viscous colourless oil: HPLC (Daicel Chiralpak IC, CH\textsubscript{2}Cl\textsubscript{2}/MeOH 99:1, 1 mL min\textsuperscript{-1}, \(\lambda = 290\) nm; major isomer \(t = 8.48\) min, minor isomer 9.63 min, 70% ee).

4: \([\alpha]_{D}^{23} = -74\) (c = 1.7, CHCl\textsubscript{3}).

Methyl 3-Formyl-4-hydroxy-2-azabicyclo[2.2.2]octane -2-carboxylate (rac-5).

A mixture of ketoaldehyde 1 (0.1 g, 0.47 mmol), CH\textsubscript{2}Cl\textsubscript{2} (25 mL), K\textsubscript{2}CO\textsubscript{3} (0.2 g, 3.6 mmol), THF (10 mL) and H\textsubscript{2}O (25 ml) was shaken for about 4 minutes then it was extracted with CH\textsubscript{2}Cl\textsubscript{2}. The organics were dried and concentrated to yield pure isoquinuclidine rac-5 as a colourless viscous oil (88 mg, 88%). An analytical sample was obtained by chromatography (CH\textsubscript{2}Cl\textsubscript{2}/AcOEt 1:1). IR (NaCl, neat): 3416, 2954, 2917, 2872, 2722, 1733, 1680, 1453, 1396, 1336, 1249, 1193, 1141, 1104, 1037, 1007, 957, 772, 734 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz, gCOSY): \(\delta\) 1.50-2.16 (m, 8H), 2.62 and 2.79 (2brs, 1H, OH), 3.70 and 3.75 (2s, 3H, CH\textsubscript{3}), 3.94 and 4.03 (2brs, 1H, H-3), 4.10 and 4.24 (2brs, 1H, H-1), 9.71 and 9.72 (2d, 1H, \(J = 1.2\) Hz, CHO); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta\) 25.9 and 26.3 (CH\textsubscript{2}), 26.4 and 26.6 (CH\textsubscript{2}), 28.9 and 29.0 (CH\textsubscript{2}), 33.0 and 33.3 (CH\textsubscript{2}), 43.7 and 44.3 (C-1), 52.8 and 52.9 (CH\textsubscript{3}), 68.4 and 68.8 (C-3), 71.3 and 71.4 (C-4), 154.9 and 155.9 (CO), 204.2 and 204.4 (CHO); HRMS (ESI-TOF) Calcd for C\textsubscript{10}H\textsubscript{15}NO\textsubscript{4}Na 236.0893 (M\textsuperscript{+}+Na). Found 236.0893.

Resolution of (±±±±)-rac-4

To a solution of (±)-rac-4 (0.08 g, 0.35 mmol) in pyridine (2 mL) was added a solution of (S)-O-acetyl mandeloyl chloride (0.225 g, 1.06 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (2mL) dropwise at -5 \(^\circ\)C and the mixture was stirred at this temperature for 3h. The reaction mixture was then quenched with water, extracted with CH\textsubscript{2}Cl\textsubscript{2} and the organics were dried and concentrated. After chromatography (hexane/AcOEt 1:1) the two diastereomers were obtained almost pure with other intermediate fractions, overall yield 82%.
(1S,4R,5R)-4.AcMA (less polar)

IR (NaCl, neat): 3067, 2953, 2873, 1747, 1700, 1495, 1448, 1342, 1300, 1230, 1107, 1047, 957, 754, 698 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, 55 °C, gCOSY): δ 1.90-2.07 (m, 3H), 2.18 (m, 1H), 2.20 (s, 3H, CH₃), 2.43 (ddd, 1H, J = 18, 11.2, 8.4 Hz, H-7ax), 2.52 (dd, 1H, J = 18, 8 Hz, H-7eq), 2.83 (brs, 1H, H-5), 3.23 (dd, 1H, J = 14, 10 Hz, H-3ax), 3.73 (s, 3H, CH₃), 4.31 (brs, 1H, H-3eq), 4.44 (brs, 1H, H-1), 5.10 (dt, 1H, J = 9.2, 7.2 Hz, H-4), 5.85 (s, 1H, CHAr), 7.34-7.45 (m, 5H, ArH); ¹³C NMR (CDCl₃, 100 MHz): δ 20.5 (CH₃), 29.9 (C-8), 30.7 (C-9), 38.7 (C-7), 43.7 (C-3), 44.3 (C-1), 47.2 (C-5), 52.9 (CH₃), 69.2 (C-4), 74.5 (CHAr), 127.5, 128.8, 129.3 (CHAr), 133.3 (ipso-C), 156.0 (CO), 167.8 (CO), 170.3 (CO), 206.8 (C-6); HRMS (ESI-TOF) calcd for C₂₀H₂₃NO₇Na 412.1367 (M⁺+Na). Found 412.1364.

(1R,4S,5S)-4.AcMA (more polar)

IR (NaCl, neat): 3067, 2953, 2874, 1752, 1700, 1448, 1408, 1341, 1300, 1234, 1106, 1084, 1047, 958, 752, 698 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, 55 °C, gCOSY): δ 1.90-2.08 (m, 3H), 2.15 (m, 1H), 2.15 (s, 3H, CH₃), 2.33 (ddd, 1H, J = 17.6, 12, 8.8 Hz, H-7ax), 2.56 (dd, 1H, J = 17.6, 8 Hz, H-7eq), 2.98 (brs, 1H, H-5), 3.01 (dd, 1H, J = 14.4, 10.4 Hz, H-3ax), 3.71 (s, 3H, CH₃), 4.21 (dd, 1H, J = 13.6, 7.6 Hz H-3eq), 4.43 (brs, 1H, H-1), 5.08 (dt, 1H, J = 8.8, 7.2 Hz, H-4), 5.92 (s, 1H, CHAr), 7.34-7.46 (m, 5H, ArH); ¹³C NMR (CDCl₃, 100 MHz): δ 20.5 (CH₃), 29.8 (C-8), 30.7 (C-9), 38.6 (C-7), 43.4 (C-3), 44.3 (C-1), 47.2 (C-5), 52.9 (CH₃), 69.3 (C-4), 74.3 (CHAr), 127.5, 128.8, 129.3 (CHAr), 133.8 (ipso-C), 155.9 (CO), 167.7 (CO), 169.9 (CO), 207.0 (CO); HRMS (ESI-TOF) calcd for C₂₀H₂₃NO₇Na 412.1367 (M⁺+Na). Found 412.1364.
II) Copies of $^1$H NMR and $^{13}$C NMR spectra of compounds 1-5
Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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![Chemical Structure](image)

**Supplementary Material**

**ESI** / nOES / NMR-600

**1H1** / Temp: 300 K / W: 300000000000

**Data**: 09/11/09 / Exp.: F.DIANA

**Pulse Sequence**: nOES
**rac-5**

(S10)

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