Supplementary Material (ESI) for Chemical Communications


# Controlling the formation of 1 out of 64 stereoisomers using organocatalysis

**Søren Bertelsen, Rasmus Lyng Johansen and Karl Anker Jørgensen***

*Danish National Research Foundation: Center for Catalysis, Department of Chemistry*
*Aarhus University, DK-8000 Aarhus C, Denmark*
*kaj@chem.au.dk*

# Supporting Information

## Contents

# Experimental Section

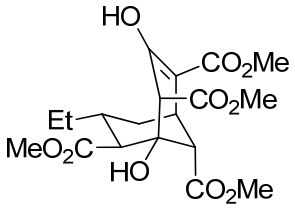
**General.** The $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm relative to $CHCl_3$ ($\delta = 7.26$) for $^{1}H$ NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for $^{13}C$ NMR. Purification of reaction products was carried out by flash chromatography (FC) using silica gel 60 (230-400 mesh from Merck). The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Chiralcel AD column. Optical rotation was measured on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a micromass LCT spectrometer using electrospray ($ES^+$) ionisation techniques.

**Materials.** Commercially available starting materials and solvents were used without further purification.

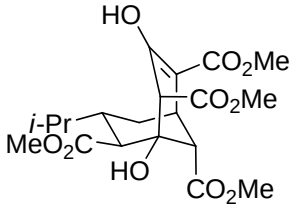
**General Procedures.**

**One-pot reaction:** In a standard reaction, dimethyl 3-oxopentanedioate (0.50 mmol) was added at room temperature to a stirred solution of catalyst (0.025 mmol), $PhCO_2H$ (0.025 mmol) and aldehyde (0.25 mmol) in toluene (125 μL). After complete consumption of the aldehyde (as monitored by $^{1}H$ NMR spectroscopy), methanol (1.0 mL) and piperidine (0.05 mmol) was added and the reaction was stirred at 40 $^{o}C$ until full conversion of dimethyl 3-oxopentanedioate (as indicated by TLC). Evaporation and column chromatography (eluent: 5 % $Et_2O$ in $CH_2Cl_2$) afforded the pure products. Recrystallizations were done in MeOH.

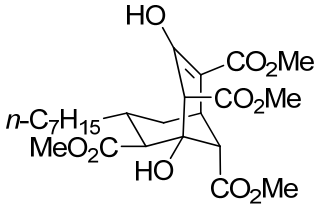
**Analytical and Spectroscopic Data**



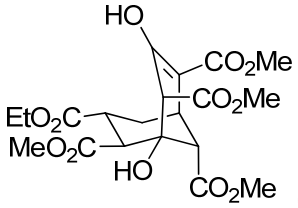

**(1*R*,4*R*,5*R*,6*S*,7*R*,9*S*)-Tetramethyl 7-ethyl-3,5-dihydroxybicyclo[3.3.1]non-2-ene-2,4,6,9-tetracarboxylate 4a.** The product was obtained following the standard procedure and purified by FC. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak AD Column (hexane/*i*-PrOH (80/20)): flow rate 1.0 mL/min: $\tau_{minor} = 6.9$ min, $\tau_{major} = 10.8$ min (94% ee). $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 1H), 4.53 (s, 1H), 4.50 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.55 (m, 2H), 2.79 (d, $J = 12.0$ Hz, 1H), 1.82-1.55 (m, 2H), 1.35-1.25 (m, 1H), 1.15-1.00 (m, 2H), 0.79 (t, $J = 7.4$ Hz, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 173.5, 173.2, 170.8, 170.3, 167.6, 101.9, 72.0, 56.4, 52.5, 52.3, 52.0, 51.8 (2C), 46.5, 33.9, 31.5, 30.5, 26.6, 10.6. MS (TOF $ES^+$): $[M+Na]^+$ calcd for $C_{19}H_{26}NaO_{10}$ 437.1424; found 437.1418. $[\alpha]^{20}_D = +114.9$ (*c* 1.02, $CH_2Cl_2$).




**(1*R*,4*R*,5*R*,6*S*,7*S*,9*S*)-Tetramethyl 3,5-dihydroxy-7-isopropylbicyclo[3.3.1]non-2-ene-2,4,6,9-tetracarboxylate 4b.** The product was obtained following the standard procedure and purified by FC. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak AD Column (hexane/*i*-PrOH (80/20)): flow rate 1.0 mL/min: $\tau_{minor}$ = 6.1 min, $\tau_{major}$ = 11.3 min (96% ee). $^1$H NMR (400 MHz, $CDCl_3$) δ 11.97 (s, 1H), 4.54 (s, 1H), 4.47 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 3.57-3.53 (m, 2H), 2.98 (d, *J* = 12.5 Hz, 1H), 1.76 (tt, *J* = 12.5, 3.6 Hz, 1H), 1.56-1.41 (m, 2H), 1.21-1.12 (m, 1H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.5, 173.2, 170.8, 170.3, 167.7, 101.8, 72.2, 54.2, 52.5, 52.3, 51.9, 51.8, 51.7, 46.6, 37.7, 31.2, 28.8, 24.3, 21.0, 15.8. MS (TOF ES$^+$): $[M+Na]^+$ calcd for $C_{20}H_{28}NaO_{10}$ 451.1580; found 451.1572. $[\alpha]^{20}_D$ = +123.9 (*c* 1.02, $CH_2Cl_2$).

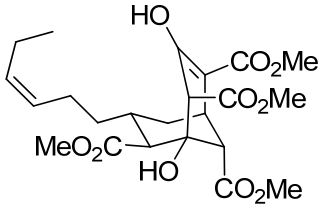



**(1*R*,4*R*,5*R*,6*S*,7*R*,9*S*)-Tetramethyl 7-heptyl-3,5-dihydroxybicyclo[3.3.1]non-2-ene-2,4,6,9-tetracarboxylate 4c.** The product was obtained following the standard procedure and purified by FC. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak AD Column (hexane/*i*-PrOH (80/20)): flow rate 1.0 mL/min: $\tau_{minor}$ = 6.3 min, $\tau_{major}$ = 10.0 min (95% ee). $^1$H NMR (400 MHz, $CDCl_3$) δ 11.97 (s, 1H), 4.52 (s, 1H), 4.48 (s, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 3.54 (m, 2H), 2.77 (d, *J* = 12.0 Hz, 1H) 1.80-1.63 (m, 2H), 1.30-1.00 (m, 13H), 0.85 (t, *J* = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.5, 173.2, 170.8, 170.3, 167.6, 101.8, 72.0, 56.7, 52.5, 52.3, 51.9, 51.8 (2C), 46.5, 33.9, 32.7, 31.7, 31.6, 31.1, 29.6, 29.0, 26.1, 22.5, 14.0. MS (TOF ES$^+$): $[M+Na]^+$ calcd for $C_{24}H_{36}NaO_{10}$ 507.2206; found 507.2208. $[\alpha]^{20}_D$ = +79.2 (*c* 1.01, $CH_2Cl_2$).

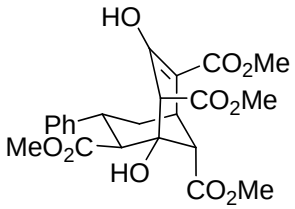



**(1*S*,2*S*,3*R*,5*R*,8*R*,9*S*)-3-Ethyl 2,6,8,9-tetramethyl 1,7-dihydroxybicyclo[3.3.1]non-6-ene-2,3,6,8,9-pentacarboxylate 4d.** The product was obtained following the standard procedure and purified by FC. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak AD Column (hexane/*i*-PrOH (80/20)): flow rate 1.0 mL/min: $\tau_{minor}$ = 10.6 min, $\tau_{major}$ = 17.8 min (89% ee). $^1$H NMR (400 MHz, $CDCl_3$) δ 12.02 (s, 1H), 4.63 (s, 1H), 4.15-4.04 (m, 2H), 3.99 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 3.58-3.54 (m, 2H), 3.43 (d, *J* = 12.3 Hz, 1H),

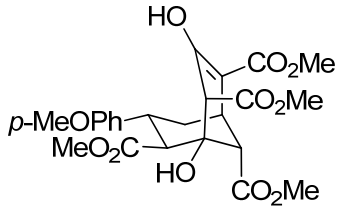
2.81 (dt, *J* = 12.6, 4.6 Hz, 1H), 1.95-1.87 (m, 1H), 1.65-1.54 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.2, 172.7, 172.6, 170.6, 169.5, 167.4, 101.2, 71.5, 61.1, 52.8, 52.6, 52.4 (2C), 52.1, 51.0, 46.1, 38.9, 31.4, 28.7, 14.0. $[M+Na]^+$ calcd for $C_{20}H_{26}NaO_{12}$; 481.1322; found 481.1318. $[\alpha]^{20}_D$ = +95.3(*c* 1.01, $CH_2Cl_2$).



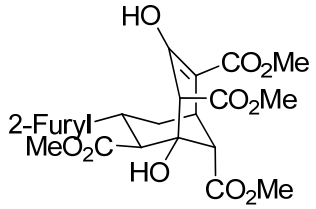

**(1*R*,4*R*,5*R*,6*S*,7*R*,9*S*)-Tetramethyl 7-((Z)-hex-3-enyl)-3,5-dihydroxybicyclo[3.3.1]non-2-ene-2,4,6,9-tetracarboxylate 4e.** The product was obtained following the standard procedure and purified by FC. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak AD Column (hexane/*i*-PrOH (80/20)): flow rate 1.0 mL/min: $\tau_{minor}$ = 5.8 min, $\tau_{major}$ = 8.2 min (94% ee). $^1$H NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 1H), 5.36-5.27 (m, 1H), 5.22-5.12 (m, 1H), 4.52 (s, 1H), 4.48 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 3.56-3.52(m, 2H), 2.80 (d, *J* = 12.1 Hz, 1H), 2.05-1.67 (m, 6H), 1.31-1.02 (m, 3H), 0.91 (t, *J* = 7.5, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.5, 173.1, 170.8, 170.3, 167.6, 132.1, 128.0, 101.8, 72.0, 56.6, 52.5, 52.3, 51.9, 51.8 (2C), 46.5, 33.8, 32.3, 31.5, 31.0, 23.8, 20.4, 14.3. MS (TOF ES$^+$): $[M+Na]^+$ calcd for $C_{23}H_{32}NaO_{10}$; 491.1893; found 491.1895 $[\alpha]^{20}_D$ = +95.2(*c* 1.01, $CH_2Cl_2$).



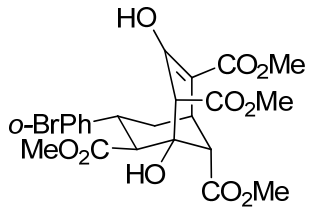

**(*1R,4R,5S,6S,7R,9S*)-Tetramethyl 3,5-dihydroxy-7-phenylbicyclo[3.3.1]non-2-ene-2,4,6,9-tetracarboxylate 4f.** The product was obtained following the standard procedure and purified by FC. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak AD Column (hexane/*i*-PrOH (80/20)): flow rate 1.0 mL/min: $\tau_{minor}$ = 9,5 min, $\tau_{major}$ = 20.3 min (94% ee). $^1$H NMR (400 MHz, $CDCl_3$)[1] δ 12.10 (s, 1H), 7.28-7.12 (m, 5H), 4.53 (s, 1H), 4.52 (s, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.67 (d, *J* = 2.8 Hz, 1H), 3.61 (q, *J* = 3.0, 1H), 3.44 (s, 3H), 3.41 (s, 1H), 2.99 (dt, J = 12.3, 4.9 Hz, 1H), 1.79-1.64 (m, 2H).$^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.4, 172.1, 170.8, 170.1, 167.7, 141.2, 128.4 (2C), 127.5 (2C), 127.0, 101.7, 72.0, 56.3, 52.6, 52.4, 52.1, 52.0, 51.7, 46.4, 39.6, 33.7, 32.0. MS (TOF ES$^+$): $[M+Na]^+$ calcd for $C_{23}H_{26}NaO_{10}$ 485.1424; found 485.1408. $[\alpha]^{20}_D$ = +105.7 (*c* 1.00 $CH_2Cl_2$).




**(*1R,4R,5S,6S,7R,9S*)-Tetramethyl 3,5-dihydroxy-7-(4-methoxyphenyl)bicyclo[3.3.1]non-2-ene-2,4,6,9-tetracarboxylate 4g.** The product was obtained following the standard procedure and purified by FC. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak AD Column (hexane/*i*-PrOH (80/20)): flow rate 1.0 mL/min: $\tau_{minor}$ = 22.7 min, $\tau_{major}$ = 67.1 min (91% ee). $^1$H NMR (400 MHz, $CDCl_3$) δ 12.08 (s, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 4.50 (d, *J* = 4.3 Hz, 2 H), 3.85 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.65 (d, *J* = 3.0 Hz, 1H), 3.59 (q, *J* = 6.3 Hz, 1H), 3.45 (s, 3H), 3.35 (d, *J* = 12.5 Hz, 1H), 2.93 (dt, *J* = 12.2, 4.8 Hz, 1H), 1.75-1.59 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.5, 172.2, 170.9, 170.2, 167.7, 158.4, 133.2, 128.6 (2C), 113.8 (2C), 101.8, 72.1, 56.7, 55.2, 52.6, 52.4, 52.1, 52.0, 51.8, 46.4, 38.8, 33.8, 32.0. MS (TOF ES$^+$): calcd for $C_{24}H_{28}NaO_{11}$ 515.1529; found 515.1520. $[\alpha]^{20}_D$ = +123.6(*c* 1.04, $CH_2Cl_2$).




**(1*R*,4*R*,5*R*,6*S*,7*R*,9*S*)-Tetramethyl 7-(furan-2-yl)-3,5-dihydroxybicyclo[3.3.1]non-2-ene-2,4,6,9-tetracarboxylate 4h.** The product was obtained following the standard procedure and purified by FC. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak AD Column (hexane/*i*-PrOH (80/20)): flow rate 1.0 mL/min: $\tau_{minor}$ = 13.9 min, $\tau_{major}$ = 22.5 min (90% ee). $^1$H NMR (400 MHz, $CDCl_3$) δ 12.06 (s, 1H), 7.27 (s, 1H), 6.23-6.21 (m, 1H), 6.00 (d, *J* = 3.2 Hz, 1H), 4.66 (s, 1H), 4.54 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.64 (br s, 2H), 3.61 (s, 3H), 3.29 (d, *J* = 12.5 Hz, 1H), 3.16 (dt, *J* = 12.4, 4.2 Hz, 1H), 1.89-1.64 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.4, 172.2, 170.8 170.1, 167.6, 154.7, 141.5, 110.0, 105.5, 101.4, 71.8, 54.6, 52.6, 52.5, 52.1, 52.0, 51.8, 46.2, 33.5, 31.5, 31.1. MS (TOF ES$^+$): calcd for $C_{21}H_{24}NaO_{11}$ 475.1216; found 475.1219. $[\alpha]^{20}_D$ = +91.3 (*c* 1.01, $CH_2Cl_2$).




**(*1R,4R,5S,6S,7R,9S*)-Tetramethyl 7-(2-bromophenyl)-3,5-dihydroxybicyclo[3.3.1]non-2-ene-2,4,6,9-tetracarboxylate 4i.** The product was obtained following the standard procedure and purified by FC. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak AD Column (hexane/*i*-PrOH (80/20)): flow rate 1.0 mL/min: $\tau_{minor}$ = 10.9 min, $\tau_{major}$ = 15.2 min (96% ee). $^1$H NMR

(400 MHz, $CDCl_3$) δ 12.13 (s, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.25-7.21 (m, 2H), 7.03 (ddd, *J* = 8.8, 6.2, 2.8 Hz, 1H), 4.58 (s, 1H), 4.34 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 3.71-3.60 (m, 3H), 3.56-3.54 (m, 1H), 3.53 (s, 3H), 1.85 (dt, *J* = 13.7, 2.9 Hz, 1H), 1.33 (ddd, *J* = 14.4, 11.6, 3.0 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 173.4, 171.8, 170.8, 169.9, 167.5, 140.7, 133.1, 128.2, 127.7, 126.9, 124.6, 101.5, 72.3, 54.1, 52.6 (2C), 52.4, 52.1, 52.0, 46.4, 37.7, 33.3, 32.1. MS (TOF $ES^+$): calcd for $C_{23}H_{25}BrNaO_{10}$ 563.0529; found 563.0524. $[\alpha]^{20}_D$ = +70.7 (*c* 1.01, $CH_2Cl_2$).

## X-Ray data for compound 4i

Crystal data for [**4i**]: $C_{23}H_{25}BrO_{10}$, M = 540.06, orthorhombic, Space group P 21 21 2 (no. 112), a = 15.9364(7) Å, b = 15.936(0) Å, c = 18.6763(10) Å, V = 4743.2(3) $Å^3$, T = 293 K, Z = 8, Dc = 1.516 g $cm^{-3}$, μ(Mo Kα, λ = 0.71073 Å) = 1.789 $mm^{-1}$, 16280 reflections collected, 5229 unique [Rint = 0.0296], which were used in all calculations. Refinement on F2, final R(F) = 0.044, Rw(F2) = 0.0808. Flack parameter x = -0.010(7). The crystal was very weakly diffracting which is the reason for the low resolution of the data set. All non-H atoms were treated anisotropic.

## References

[1] K. Aoyagi, H. Nakamura, Y. Yamamoto, *J. Org. Chem.* 1999, **64**, 4148.