Enantioselective Diels-Alder Cycloadditions in the Synthesis of Two Enantiomeric Sets of Chiral Polyhydroxylated Pipecolic Acid Derivatives.

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Experimental Procedures

General Methods. 2H-Azirine 5 was prepared in situ from α-azido t-butyl acrylate. All other reagents were purchased and used without further purification. Solvents employed in reactions were dried: CH₂Cl₂ was freshly distilled under CaH₂ and toluene was submitted to simple distillation to remove the head fraction. Petroleum ether 40-60ºC used in flash chromatography was previously distilled, and all other solvents were used as purchased. Glassware was dried prior to use. Compounds were purified by dry flash chromatography, using silica 60 <0.063 mm as the stationary phase and water pump vacuum. TLC plates (Silica Gel 60 F254, Macherey-Nagel) were visualized either at UV lamp or in I₂. ¹H NMR and ¹³C NMR were run on a Varian Unity Plus 300, or Brucker Avance III 400 or Bruker BioSpin GmbH spectrometers. Infrared spectra were recorded on a Bomem MB 104. Samples were run as nujol mulls and oils as thin films. Melting points are uncorrected. MS spectra were recorded on a VG Autospec M. spectrometer.

(2S,6R)-t-Butyl 2-(hydroxymethyl)-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate (-)-7 and (2R,6S)-t-butyl 2,6-bis(hydroxymethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (+)-8

Solution A: a solution of Me₂Zn 1.2 M in toluene (0.991 mL; 1.19 mmol) was added to a solution of penta-2,4-dien-1-ol (0.10 g; 1.19 mmol) in dry toluene (6 mL) at 0 ºC, and the mixture stirred for 5 min. Solution B: a solution of MeMgBr 1.4 M in toluene/THF (0.849 mL; 1.19 mmol) was added to a solution of (S)-BINOL (0.340 g; 1.19 mmol) in dry toluene (6 mL) at 0 ºC, and mixture stirred for 5 min. Solution A was diluted with dry toluene (10 mL), added to solution B, stirred for 5 min and then refrigerated at -78 ºC. To this mixture was added a solution of t-butyl 2H-azirine-3-carboxylate (0.168 g; 1.19 mmol) in dry toluene (10 mL) during 5 min. The temperature was allowed to rise gradually to - 20 ºC and the reaction mixture was transferred into a freezer for 24 h and kept stirring. A new portion of t-butyl 2H-azirine-3-carboxylate (0.168 g; 1.19 mmol) was added, and the reaction stirred for another 7 days. The reaction was quenched with saturated solution of NaHCO₃ (1 mL), filtered through a pad of Celite®, and the Celite® washed with EtOAc (2 × 20 mL). The filtrates were combined and concentrated
under reduced pressure giving an orange oil. The crude mixture was purified by “dry-
flash” chromatography (silica, petroleum ether / diethyl ether, increasing polarity). (S)-
BINOL was recovered with petroleum ether (3): ether (1) (0.250 g; 74%); the minor
isomer (+)-8 with petroleum ether (1)/ diethyl ether (3) (0.063 g; 22%), and major
isomer (-)-7 with diethyl ether (0.130 g; 49%) as orange oils.

**Major isomer (-)-7:** \([\alpha]_{D}^{20} -54.4\) (conc. 2.0 % in CHCl₃). \(\nu_{\text{max}}\) (Nujol) 3234, 1731, 1659
\(\text{cm}^{-1}\). \(\delta_{H}\) (400 MHz, CDCl₃) 1.47 (9H, s, 3 × CH₃), 1.93 (1H, s, H-1’), 2.01 (1H, s, H-1’), 2.58-2.65 (1H, m, H-5), 2.65-2.73 (1H, m, H-5), 3.60 (1H, dd, J 10.8, 8.4 Hz, H-2’),
3.67 (1H, dd, J 11.2, 4.8 Hz, H-2’), 3.78-3.80 (1H, m, H-2), 5.27-5.31 (1H, dm, J 10.4
Hz, H-4), 5.73-5.79 (1H, m, H-3) ppm. \(\delta_{C}\) (100 MHz, CDCl₃) 22.6 (C-5), 27.7 (C-1’),
27.9 (3 × CH₃), 38.5 (C-6), 56.7 (C-2), 65.0 (C-2’), 81.4 (Cq, t-Bu), 121.8 (C-4), 124.4
(C-3), 171.4 (C=O) ppm. HRMS (ESI): calcd for C₁₂H₂₀NO₃: 226.1438; found:
226.1435.

**Minor isomer (+)-8:** \([\alpha]_{D}^{20} +51.4\) (conc. 1.8 % in CHCl₃). \(\nu_{\text{max}}\) (neat) 3407, 1725, 1642
\(\text{cm}^{-1}\). \(\delta_{H}\) (400 MHz, CDCl₃) 1.47 (9H, s, 3 × CH₃), 2.13 (1H, dm, J 16.8 Hz, H-3), 2.50-
2.70 (2H, br s, 2 × OH), 2.62 (1H, dddd, J 16.8, 5.8, 2.5, 1.0 Hz, H-3), 3.46 (1H, d, J 9.8
Hz, H-2’), 3.54 (1H, dd, J 10.8, 4.4 Hz, H-6’), 3.65 (1H, dd, J 11.0, 3.8 Hz, H-6’), 3.66
(1H, d, J 10.0 Hz, H-2’), 3.91-3.96 (1H, m, H-6), 5.57 (2H, dm, J 10.0 Hz, H-5), 5.79
(1H, ddt, J 10.2, 5.8, 2.2 Hz, H-4) ppm. \(\delta_{C}\) (100 MHz, CDCl₃) 27.9 (3 × CH₃), 32.4 (C-
3), 40.6 (C-2’), 53.6 (C-6), 61.1 (C-2), 65.3 (C-6’), 82.3 (Cq, t-Bu), 124.1 (C-4), 126.8
(C-5), 171.6 (C=O) ppm. HRMS (ESI): calcd for C₁₂H₂₂NO₄: 244.1549; found:
244.1520.

**Solution A:** a solution of Me₂Zn 1.2 M in toluene (0.991 mL; 1.19 mmol) was added to
a solution of penta-2,4-dien-1-ol (0.10 g; 1.19 mmol) in dry toluene (6 mL) at 0 °C, and
stirred for 5 min. **Solution B:** a solution of MeMgBr 1.4 M in toluene/THF (0.849 mL;
1.19 mmol) was added to a solution of (R)-BINOL (0.340 g; 1.19 mmol) in dry toluene
(6 mL) at 0 °C, and stirred for 5 min. Solution A was diluted with dry toluene (10 mL),
added to solution B, stirred for 5 min, and then refrigerated at -78 ºC. To this mixture was added a solution of \textit{t}-butyl 2\textit{H}-azirine-3-carboxylate (0.168 g; 1.19 mmol) in dry toluene (10 mL) during 5 min. The temperature was allowed to rise gradually to -20 ºC and the reaction mixture was transferred into a freezer for 24 h and kept stirring. A new portion of \textit{t}-butyl 2\textit{H}-azirine-3-carboxylate (0.168 g; 1.19 mmol) was added, and the reaction stirred for another 7 days. The reaction was quenched with saturated solution of NaHCO$_3$ (1 mL), filtered through a pad of Celite®, and the Celite® washed with EtOAc (2 × 20 mL). The filtrates were combined and concentrated under reduced pressure giving an orange oil. The crude oil was purified by “dry-flash" chromatography (silica, petroleum ether / diethyl ether). (\textit{R})-BINOL was recovered with petroleum ether (3) : ether (1) (0.246 g; 72 %); the minor isomer (-)-8 with petroleum ether (1) diethyl ether (3) (0.081 g; 28 %) and major isomer (+)-7 with diethyl ether (0.127 g; 47 %) as orange oils.

**Major isomer** (+)-7: $\left[\alpha\right]_D^{20} +78.0$ (conc. 0.75 % in CHCl$_3$)

**Minor isomer** (-)-8: $\left[\alpha\right]_D^{20} -45.6$ (conc. 1.5 % in CHCl$_3$)

**Camphanoate derivative of compound (-)-7**

To a solution of (-)-7 (0.011 g; 0.045 mmol) in dry CH$_2$Cl$_2$ (6 mL) was added DMAP (4 mg), triethylamine (98 μL) and (S)-camphanic acid chloride (22 mg; 0.09 mmol). The reaction was stirred at rt for 40 min. The solvent was removed by reduced pressure; the residuum was dissolved in ethyl acetate (10 mL), filtered through a pad of silica and washed with ethyl acetate (2 × 10 mL). The filtrate was concentrated, giving a yellow oil (0.018 g; 96 %), which proved by $^1$H NMR to be an unique diastereomer.

$\delta_H$ (400 MHz, C$_6$D$_6$) 0.75 (3H, s, CH$_3$), 0.86 (3H, s, CH$_3$), 0.92 (3H, s, CH$_3$), 1.26 (2H, dt, $J$ 10.0, 4.8 Hz, H-8’), 1.34 (9H, s, 3×CH$_3$), 1.72 (1H, ddd, $J$ 13.6, 9.0, 5.0 Hz, H-9’), 1.81 (1H, s, H-1’), 2.07 (1H, s, H-1’), 2.10 (1H, ddd, $J$ 13.4, 10.2, 4.9 Hz, H-9’), 2.31 (1H, dd, $J$ 18.4, 6.5 Hz, H-5), 2.74 (1H, dtd, $J$ 18.4, 3.3, 2.3, 1.3 Hz, H-5), 3.65 (1H, br s, H-2), 3.87 (1H, dd, $J$ 11.2, 4.4 Hz, H-2’), 4.27 (1H, dt, $J$ 12.7, 6.4 Hz, H-2’), 4.94 (1H, dm, $J$ 10.4 Hz, H-3), 5.36 (1H, dddd, $J$ 10.3, 6.6, 3.0, 2.2 Hz, H-4) ppm.

**Camphanoate derivative of compound (+)-7**
To a solution of (+)-7 (0.025 g; 0.11 mmol) in dry CH₂Cl₂ (13.5 mL) was added DMAP (9 mg), triethylamine (178 μL) and (S)-camphanic acid chloride (50 mg; 0.22 mmol). The reaction was stirred at rt for 30 min. The solvent was removed at reduced pressure and the residuum was dissolved in ethyl acetate (10 mL), filtered through a short pad of silica, and washed with ethyl acetate (2 × 10 mL). Filtrate was concentrated, giving a yellow oil (0.019 g; 41 %), which proved by ¹H NMR to be a single diastereomer.

δ_H (400 MHz, C₆D₆) 0.76 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.91 (3H, s, CH_3), 1.26 (2H, dt, J 10.0, 4.8 Hz, H-8’), 1.33 (9H, s, 3×CH₃), 1.72 (1H, ddd, J 13.6, 9.0, 5.0 Hz, H-9’), 1.82 (1H, s, H-1’), 2.05 (1H, s, H-1’), 2.10 (1H, ddd, J 13.4, 10.2, 4.9 Hz, H-9’), 2.31 (1H, dd, J 18.4, 6.5 Hz, H-5), 2.74 (1H, dddd, J 18.4, 3.3, 2.3, 1.3 Hz, H-5), 3.66 (1H, br s, H-2), 3.87 (1H, dd, J 11.2, 4.4 Hz, H-2’), 4.28 (1H, dd, J 11.1, 6.9 Hz, H-2’), 4.94 (1H, dm, J 10.4 Hz, H-3), 5.36 (1H, dddd, J 10.3, 6.6, 3.0, 2.2 Hz, H-4) ppm.

**Conversion of (+)-8 into (-)-7**

To a solution of a 3:1 mixture of (+)-8 and (-)-7 (0.122 g; 0.50 mmol) in acetone (1.6 mL) and water (0.2 mL) was added N-methylmorpholine (81 μL; 0.75 mmol), and the reaction mixture stirred for 3h at rt, then diluted with CH₂Cl₂ (10 mL) and washed with water (2 × 10 mL). The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure, giving compound (-)-7 (0.112 g; 99 %).

**((S))-Diethyl 3-(hydroxymethyl)pyridazine-1,2(3H,6H)-dicarboxylate (-)-9**

**Solution A:** a solution of Me₂Zn 1.2 M in toluene (991 μL; 1.19 mmol) was added to a solution of penta-2,4-dien-1-ol (0.100 g; 1.19 mmol) in dry toluene (6 mL) at 0 ºC, and stirred for 5 min. **Solution B:** a solution of MeMgBr 1.4 M in toluene/THF (849 μL; 1.19 mmol) was added to a solution of (S)-BINOL (0.340 g; 1.19 mmol) in dry toluene (6 mL) at 0 ºC, and stirred for 5 min. Solution A was diluted with dry toluene (10 mL), added to solution B, stirred for 5 min, and then refrigerated at -78 ºC. To this mixture was added a solution of diethyl azodicarboxylate (543 μL; 1.19 mmol) in dry toluene (10 mL). The temperature was allowed to rise gradually to rt and the reaction mixture was stirred for 18h. The reaction was quenched with saturated solution of NaHCO₃ (1
mL), filtered through a pad of Celite®, and the Celite® washed with EtOAc (3 × 20 mL). The filtrates were combined and concentrated under reduced pressure giving a yellow oil. The crude oil was purified by “dry-flash” chromatography (silica, petroleum ether / diethyl ether). (S)-BINOL was recovered with petroleum ether (1) : ether (1) (0.200 g; 69 %) and product (-)-9 with diethyl ether (0.225 g; 73 %) as a yellow oil.

\([\alpha]_D^{20} -23.4\) (conc. 1.25 % in CHCl₃). \(\nu_{\text{max}}\) (neat) 3483, 1707 cm\(^{-1}\). \(\delta_H\) (400 MHz, CDCl₃)* 1.23-1.30 (12H, m, 4 × CH₃, A+B), 2.58 (1H, br s, OH), 3.35 (1H, dd, J 12.3, 9.5 Hz, H-3’, A), 3.45 (1H, dd, J 12.0, 9.8 Hz, H-3’, B), 3.56-3.69 (2H, m, 2 ×H-3’, A+B), 3.77 (1H, dd, J 13.5, 4.3 Hz, H-6, A), 3.91 (1H, br s, H-6, B), 4.11-4.26 (8H, m, 4 × CH₂, A+B), 4.30 (1H, tdd, J 6.0, 3.9, 2.2 Hz, H-6, B), 4.34-4.44 (1H, m, H-6, A), 4.72 (2H, br s, H-3, A+B), 5.66-5.88 (4H, m, H-4 + H-5, A+B) ppm. \(\delta_C\) (100 MHz, CDCl₃)** 14.3 (CH₃, A), 14.4 (CH₃, B), 42.2 (C-6, A), 43.6 (C-6, B), 55.9 (C-3, A), 56.9 (C-3, B), 61.9 (C-3’, A+B), 62.6, 62.7, 62.8, 62.9 (CH₂, A+B), 123.4, 124.2, 124.6, 125.2 (C-4 or C-5, A+B), 154.9, 155.7, 156.2, 156.3 (C=O, A+B) ppm. HRMS (ESI): calcd for C₁₁H₁₈N₂NaO₅: 281.1108; found: 281.1109.

* \(^1\)H NMR analysis showed a 1:1 mixture of rotamers A and B, due to inversion of the nitrogen atoms lone pair within the six membered ring.

** \(^1\)C NMR also showed peak duplication.

\((2S,3S,4R,6S)-r\)-Butyl 3,4-dihydroxy-2-(hydroxymethyl)-1-azabicyclo[4.1.0]heptane-6-carboxylate (+)-10

To a solution of (+)-7 (0.075 g; 0.33 mmol) in acetone (1.60 mL) and water (0.20 mL) was added NMO (0.057 g; 0.49 mmol) and solution of OsO₄ 4% in water (35 μL; 0.06 mmol), and stirred at rt for 7h. The reaction was quenched with aqueous solution of Na₂S₂O₃ 5 % (7.40 mL), and stirred for 10 minutes. The solvent was removed by reduced pressure; the residuum obtained was washed with ethanol (3 × 20 mL), filtered through a short column of silica and concentrated yielding a brown solid which by \(^1\)H NMR spectrum proved to be a 5:1 mixture of isomers. The mixture was washed with diethyl ether and filtered under vacuum, giving the major isomer (+)-10 as a beige solid (0.057 g; 66 %).
[α]_D^{20} +73.3 (conc. 1 % in THF). mp = 161-163 °C. ν_{max} (nujol) 3334, 3187, 1726 cm⁻¹.

δ_H (400 MHz, THF-d₄) 1.40 (9H, s, 3×CH₃), 1.77 (1H, d, J 1.6 Hz, H-1’), 1.93 (1H, dd, J 14.8, 4.0 Hz, H-5), 1.97 (1H, d, J 1.2 Hz, H-1’), 2.83 (1H, dd, J 14.8, 4.0 Hz, H-5), 3.21-3.28 (1H, m, H-3 or H-4), 3.28-3.34 (1H, m, H-3 or H-4), 3.65 (1H, dd, J 5.9, 3.6 Hz, H-2), 3.69 (1H, br d, J 3.2 Hz, OH), 3.73 (1H, br d, J 5.6 Hz, OH), 3.74-3.82 (3H, m, 2×H-2’+OH) ppm. δ_C (100 MHz, THF-d₄) 28.0 (3×CH₃), 30.3 (C-5), 35.3 (C-1’), 36.0 (C-6), 57.1 (C-3 or C-4), 64.3 (C-2’), 66.7 (C-2), 67.6 (C-3 or C-4), 80.1 (Cq, t-Bu), 172.5 (C=O) ppm. HRMS (ESI): calcd for C₁₂H₂₁NO₅: 259.1420; found: 259.1429.

(2S,3S,4R,6S)-3,4-Dihydroxy-2-(hydroxymethyl)-1-azabicyclo [4.1.0]heptane-6-carboxylic acid (+)-12

To a solution of (+)-10 (0.009 g; 0.035 mmol) in 1,4-dioxane (2 mL) was added NaOH (1M, 3 mL) and stirred at rt for 10 min. The reaction mixture was filtrated through a column of resin-H⁺ (Dowex 50 WX8 16-40 Mesh) and filtered was concentrated by reduced pressure, giving the product as yellow oil ((+)12; 0.003 g; 43 %).

[α]_D^{20} +52.8 (conc. 0.6 % in MeOH). ν_{max} (neat) 3422, 1653 cm⁻¹. δ_H (400 MHz, D₂O) 1.86 (1H, s, H-1’), 1.95 (1H, s, H-1’), 2.29 (1H, dd, J 15.2, 3.6 Hz, H-3), 2.63 (1H, dd, J 15.2, 4.4 Hz, H-3), 3.33-3.41 (1H, m, H-6), 3.50 (1H, dd, J 9.0, 2.2 Hz, H-4 or H-5), 3.81 (1H, dd, J 12.0, 6.4 Hz, H-6’), 3.88-3.93 (2H, m, H-6’ + H-4 or H-5) ppm. δ_C (100 MHz, D₂O) 30.7 (C-3), 33.8 (C-1’), 38.8 (C-2), 55.6 (C-6), 62.1 (C-6’), 65.8 (C-4 or C-5), 66.1 (C-4 or C-5), 179.9 (C=O) ppm. HRMS (ESI): calcd for C₉H₁₃NO₅: 203.0794; found: 203.0801.

(2S,4R,5S,6S)-4,5-Dihydroxy-2,6-bis(hydroxymethyl)piperidine-2-carboxylic acid (+)-13

To a solution of (+)-10 (0.010 g; 0.04 mmol) in 1,4-dioxane (2 mL) was added NaOH (1M; 3 mL) and the mixture was stirred at rt for 10 min. Resin-H⁺ (Dowex 50 WX8 16-40 Mesh) was added and the mixture stirred for 1 h. The resin was filtered off and filtrate was concentrated by reduced pressure, giving a brown oil ((+)13; 0.003 g; 35 %).
$[\alpha]_D^{20} +44.4$ (conc. 0.6 % in MeOH). $\nu_{\text{max}}$ (neat) 3435, 1646, 1212 cm$^{-1}$. $\delta_H$ (400 MHz, D$_2$O) 2.19 (1H, dd, $J$ 15.2, 2.4 Hz, H-3), 2.74 (1H, dd, $J$ 15.2, 4.0 Hz, H-3), 3.64 (2H, s, H-2$'$), 3.88 (1H, dd, $J$ 11.0, 2.6 Hz, H-5), 3.91 (1H, dd, $J$ 12.2, 6.2 Hz, H-6$'$), 3.99-4.04 (1H, m, H-6), 4.10 (1H, dd, $J$ 12.4, 3.2 Hz, H-6$'$), 4.18-4.22 (1H, m, H-4) ppm. $\delta_C$ (100 MHz, D$_2$O) 33.8 (C-3), 38.1 (C-2$'$), 51.8 (C-6), 55.4 (C-6$'$), 60.9 (C-2), 63.1 (C-4), 63.3 (C-5), 169.0 (C=O) ppm. HRMS (ESI): calcd for C$_8$H$_{15}$NO$_6$: 221.0899; found: 221.0902.