Supporting information

An enantioselective desymmetrisation approach to C9-substituted trans-hydrindene rings based on a diastereotopic group-selective intramolecular Diels-Alder reaction.

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A) Synthesis of 3-[(2E,7E)-6-((E)-buta-1,3-dienyl)-deca-2,7,9-trienoyl]-oxazolidin-2-one (11)

To a solution of oxalyl chloride (754 µL, 6.8 mmol) in CH₂Cl₂ (3.4 mL) at -78 °C was added DMSO (963 µL, 13.6 mmol). After 20 min, a solution of alcohol 9 (417 mg, 2.3 mmol) in CH₂Cl₂ (1 mL) was added. After 2.5 h, TEA (1.9 mL, 13.6 mmol) was added. The reaction mixture was warmed up to 0 °C. After 30 min at this temperature, the reaction mixture was concentrated *in vacuo*. The resulting residue was suspended in THF and filtered through a glass frit followed by rinsing with THF. The filtrate was concentrated *in vacuo* to afford an orange oil which was used in the next step without further purification.

To a solution of phosphonate 10 (1.4 g, 5.1 mmol) in THF (5 mL) at 0 °C was added NaHMDS (1 M in THF, 5.1 mL, 5.1 mmol). The bright yellow solution was stirred for 5 min at the same temperature and was warmed up to room temperature. A solution of crude aldehyde, as obtained above, in THF (1 mL) was added. The orange solution was stirred for 2 h. The reaction was quenched with phosphate buffer pH 7.2 (10 mL) and diluted with AcOEt (10 mL). The layers were separated and the aqueous layer was extracted with AcOEt (2 × 10 mL). The combined organic layers were washed with 1 M aqueous NaHSO₄ (1 × 10 mL), water (1 × 10 mL), saturated aqueous NaHCO₃ (1 × 10 mL), brine (1 × 10 mL) and dried over anhydrous MgSO₄. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 2:1) to afford 11 as a yellow oil (347 mg, 52% from 9).

IR (film): $\nu_{\text{max}}$ 2923 (w), 1773 (s), 1681 (m), 1633 (m), 1603 (w), 1360 (s), 1219 (s), 1004 (s) cm⁻¹;

$^1$H NMR (300 MHz; CDCl₃): δ$_H$ 7.24 (1 H, d, $J$ 15.5, CH=CH-C=O), 7.12 (1 H, dt, $J$ 15.5 and 6.4, CH=CH-C=O), 6.31 (2 H, dt, $J$ 16.9 and 10.2, 2× CH₂=CH-H), 6.05 (2 H,
dd, $J$ 15.3 and 10.3, 2× CH$_2$=CH-CH), 5.57 (2 H, dd, $J$ 15.3 and 7.7, 2× CH$_2$=CH-CH=CH), 5.14 (2 H, dd, $J$ 17.0 and 1.7, 2× CH=CH$_{cis}$H$_{trans}$), 5.01 (2 H, dd, $J$ 10.2 and 1.7, 2× CH=CH$_{cis}$H$_{trans}$), 4.42 (2 H, t, $J$ 8.0, CH$_2$-N), 4.06 (2 H, t, $J$ 8.1, CH$_2$-O), 2.81 (1 H, quint, $J$ 7.4, CH-CH$_2$-CH$_2$), 2.28 (2 H, q, $J$ 7.3, CH$_2$-CH=CH) and 1.62 (2 H, q, $J$ 7.5, CH-CH$_2$-CH$_2$) ppm;

$^{13}$C NMR (75 MHz; CDCl$_3$): δC 165.2 (1 × s), 153.4 (1 × s), 150.9 (1 × d), 136.8 (2 × d), 136.1 (2 × d), 131.3 (2 × d), 120.2 (1 × d), 116.1 (2 × t), 62.0 (1 × t), 45.0 (1 × d), 42.6 (1 × t), 32.9 (1 × t), 30.3 (1 × t) ppm;

MS (Cl) $m/z$ 288 ((M+H)$^+$, 26%), 201 (30), 172 (18), 146 (92), 91 (100); HRMS (ES) for C$_{17}$H$_{21}$NO$_3$Na (M+Na)$^+$ calcd 310.1413 found 310.1417.
B) The IMDA process

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{H} \\
11 & \quad \text{cis} \quad \text{H} \\
12 & \quad \text{trans} \quad \text{H}
\end{align*}
\]

Under thermal conditions:

To a solution of 11 (284 mg, 0.99 mmol) in anhydrous toluene (20 mL) in a sealed tube was added BHT (2 mg, 0.01 mmol). The solution was degassed with a nitrogen stream. The reaction was heated at 150 °C for 24 h. The solvent was removed and the residue was purified by column chromatography (neat CH\(_2\)Cl\(_2\)) to afford the product as a white solid (227 mg, 80%) in a 70:30 ratio of 12/13.

Under achiral Lewis-acid catalysed conditions:

To a solution of 11 (40 mg, 0.14 mmol) in anhydrous CH\(_2\)Cl\(_2\) (4.6 mL) at -78 °C was added Me\(_3\)Al (2 M in hexane, 100 µL, 0.20 mmol). The bright yellow solution was immediately warmed up to -30 °C. After 4 h at this temperature, the reaction was diluted with Et\(_2\)O (5 mL) and quenched with saturated aqueous solution of Rochelle’s salt (5 mL). After the phase separation, the aqueous phase was extracted with Et\(_2\)O (2 × 5 mL). The combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous MgSO\(_4\). After removing the solvent *in vacuo*, the residue was purified by column chromatography (CH\(_2\)Cl\(_2\)/MeOH 99.5:0.5) to afford 12/13 as a white solid (24 mg, 59%) as a 78:22 ratio of 12/13.

With the chiral bis(oxazoline) catalyst:

To a solution of 11 (60 mg, 0.21 mmol) in anhydrous CH\(_2\)Cl\(_2\) (5.2 mL) was added a solution of [Cu(S,S)-bis(tert-butyloxazoline)](SbF\(_6\))\(_2\) (0.014 M in CH\(_2\)Cl\(_2\), 1.5 mL, 0.02 mmol). The reaction was stirred at room temperature for 24 h. The solvent
was removed and the residue was purified by column chromatography (neat CH$_2$Cl$_2$) to afford 2 as a white solid (34 mg, 56%) in a 82:18 ratio of 12/13.

The diastereoisomers were separated by reverse phase HPLC (X-Terra Prep RP$_{18}$ column 5µm 19×100 mm, mobile phase 50-55% 1% aqueous NH$_3$ in CH$_3$CN and the detection was performed at 230 nm).

**Data for the major isomer 12:**

mp 94 °C;
IR (film): $\nu_{\text{max}}$ 2961 (w), 2911 (w), 2864 (w), 1784 (s), 1688 (s), 1650 (w), 1604 (w), 1385 (s), 1200 (s) cm$^{-1}$;
$^1$H NMR (400 MHz; C$_6$D$_6$): $\delta_H$ 6.33 (1 H, dt, $J$ 17.1 and 10.0, H$_{12}$), 6.02 (1 H, dd, $J$ 15.0 and 11.0, H$_{11}$), 5.84 (1 H, d, $J$ 9.5 and 2.0, H$_2$), 5.55 (1 H, m, H$_3$), 5.41 (1 H, dd, $J$ 15.0 and 8.5, H$_{10}$), 5.07 (1 H, dd, $J$ 17.0 and 2.0, H$_{13}$)$_{\text{trans}}$, 4.95 (1 H, dd, $J$ 10.0 and 2.0, H$_{13}$)$_{\text{cis}}$, 4.20 (1 H, td, $J$ 10.6 and 6.0, H$_3$), 3.08-2.97 (4 H, m, H$_{14}$, H$_{15}$), 2.62 (1 H, m, H$_4$), 2.34 (1 H, m, H$_4$), 2.09-1.97 (2 H, m, H$_9$, H$_6$), 1.93 (1 H, m, H$_8$), 1.82 (2 H, m, H$_1$), 1.74 (1 H, m, H$_7$), 1.39-1.24 (2 H, m, H$_7$, H$_8$) ppm;
$^{13}$C NMR (100 MHz; C$_6$D$_6$): $\delta_C$ 175.9 (1 × s, C$_{17}$), 154.2 (1 × s, C$_{16}$), 139.0 (1 × d, C$_{10}$), 138.2 (1 × d, C$_{12}$), 132.0 (1 × d, C$_{11}$), 128.9 (1 × d, C$_{2}$), 126.9 (1 × d, C$_{3}$), 115.7 (1 × t, C$_{13}$), 61.7 (1 × t, C$_{15}$), 49.7 (1 × d, C$_{6}$), 47.2 (1 × d, C$_{9}$), 46.4 (1 × d, C$_{1}$), 44.2 (1 × d, C$_{5}$), 42.9 (1 × t, C$_{14}$), 31.2 (1 × t, C$_{4}$), 30.9 (1 × t, C$_{7}$), 27.8 (1 × t, C$_{8}$) ppm;
ES (Cl) $m/z$ 288 ((M+H)$^+$, 82), 201 (22), 173 (8), 91 (100);
HRMS (EI) for C$_{17}$H$_{21}$NO$_3$ (M)$^+$ calcd 287.1521 found 287.1525.
Partial data for the minor isomer 13:

IR (film): $\nu_{\text{max}}$ 2961 (w), 2911 (w), 2864 (w), 1784 (s), 1688 (s), 1650 (w), 1604 (w), 1385 (s), 1200 (s) cm$^{-1}$;

$^1$H NMR (400 MHz; C$_6$D$_6$): $\delta_H$ 6.36 (1 H, dt, $J = 17.1$ and 10.2, H$_{12}$), 6.08 (1 H, dd, $J = 15.0$ and 10.0, H$_{11}$), 5.87 (1 H, d, $J = 9.5$, H$_2$); 5.17 (1 H, d, $J = 16.6$, H$_{13\text{trans}}$), 5.01 (1 H, d, $J = 10.5$ and 1.5, H$_{13\text{cis}}$) and 4.27 (1 H, td, $J = 9.5$ and 6.5, H$_3$) ppm;

$^{13}$C NMR (100 MHz; C$_6$D$_6$): $\delta_C$ 175.9 (1 × s, C$_{17}$), 154.2 (1 × s, C$_{16}$), 138.8 (1 × d, C$_{10}$), 138.2 (1 × d, C$_{12}$), 129.3 (1 × d, C$_{11}$), 128.9 (1 × d, C$_2$), 126.9 (1 × d, C$_3$), 115.7 (1 × t, C$_{13}$), 61.7 (1 × t, C$_{15}$); 48.1 (1 × d, C$_6$), 44.4 (1 × d, C$_9$), 43.9 (1 × d, C$_1$), 43.2 (1 × d, C$_5$), 42.9 (1 × t, C$_{14}$), 31.3 (1 × t, C$_7$); 31.2 (1 × t, C$_4$) and 28.6 (1 × t, C$_8$) ppm;

MS (CI) $m/z$ 288 ((M+H)$^+$, 82%), 201 (22), 173 (8), 91 (100);

HRMS (EI) for C$_{17}$H$_{21}$NO$_3$ (M)$^+$ calcd 287.1521 found 287.1525.

Comparison with literature $^1$H NMR data to establish the $trans$ ring junction in the minor diastereoisomer

<table>
<thead>
<tr>
<th>entry</th>
<th>cycloadduct</th>
<th>$^1$H NMR of H5 in CDCl$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>$\delta$ 3.92, td, $J = 10.2$, 6.0 Hz</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>$\delta$ 3.91, td, $J = 10.6$, 6.2 Hz</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>$\delta$ 3.91, td, $J = 10.8$, 6.2 Hz$^a$</td>
</tr>
</tbody>
</table>

Mixture after IMDA reaction
C) Mosher's ester analysis

\[
\begin{align*}
\text{LiBH}_4, \text{EtOH} & \quad \text{THF, rt, 18 h} \quad 91\% \\
\text{O} & \quad \text{H} \\
\text{H} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{OH} & \quad \text{12/13} \\
& \quad \text{16} \\
\text{OH} & \quad \text{17} \\
1) (S)-\text{MTPA, DMF, oxalyl chloride, hexane, rt} \\
2) \text{TEA, DMAP} \\
& \quad \text{CDCl}_3
\end{align*}
\]

Racemic Mosher ester

Non racemic Mosher ester