Supporting Information

Transforming Terpene Feedstock into Polyketide Architecture

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I. GENERAL PROCEDURE

Solvents of HPLC grade were purchased from Fisher Scientific or VWR (Prolabo). Where dry solvents (diethyl ether, dichloromethane, toluene, DMF or THF) were required they were purified by Solvent Purification Systems M-BRAUN Glovebox Technology SPS-800. Technical quality solvents for column chromatography were used after short path distillation in a rotary evaporator. Unless noted below, all other compounds were reported in literature or were supplied by Aldrich, Acros or AlfaAesar, and used without further purification. Thin-layer chromatography (SiO₂, TLC) was performed on Merck TLC silica gel 60 F₂₅₄. Column chromatography was performed on Merck silica gel 60 (0.040 – 0.063 nm), using standard flash chromatographic methods. Melting points were measured on a Büchi B-540 block apparatus and are uncorrected. Optical rotations were recorded on a Perkin Elmer polarimeter 341 at 589 nm, and were reported as [α]D (concentration). The NMR spectra were recorded on Bruker DRX300 (300 MHz), DRX400 (400 MHz), DRX500 (500 MHz) or DRX600 (600 MHz) spectrometers and were referenced against the residual solvent peaks [CHCl₃: δ 7.26 ppm (¹H NMR) and 77.16 ppm (¹³C NMR)]. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, and integration. Infrared spectra were recorded on a Nicolet Impact 400D spectrometer on potassium bromide matrix (disk or film). Low resolution mass spectra were performed on a Thermo TSQ mass spectrometer, Hewlett-Packard 6890 series/Mass selective detector. High resolution mass spectra were recorded on a LTQ Orbitrap mass spectrometer coupled to an Accela HPLC-System (HPLC column: Hypersyl GOLD, 50 mm × 1 mm, 1.9 μm). All instruments are from Thermo Electron. Chiral HPLC analysis was performed using an Agilent 1200 series HPLC with a diode array detector. Chiral columns include Daicel Chiralpak IA (Chiral Technologies Eur., 25 cm × 4.6 mm I.D.) and Daicel Chiralpak IC (Chiral Technologies Eur., 25 cm × 4.6 mm I.D.). Chiral GC analysis was performed using an Agilent 6850 series GC with a FID detector on a Hydrodex-β-6TBDM (Macherey & Nagel, 25 m × 0.25 mm).

II. 1,4-Dienes from allylic acetates (conditions and optimisation)

Optimisation of the reaction conditions for the synthesis of 1,4-dienes from allylic acetates (Scheme 1: 1a → 2a)

<table>
<thead>
<tr>
<th>entry</th>
<th>mol%</th>
<th>catalyst</th>
<th>eq. $\text{MgX}$</th>
<th>X</th>
<th>T [°C]</th>
<th>solvent</th>
<th>Yield$^{[a]}$ [％]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>Li$_2$CuCl$_4$</td>
<td>1.5</td>
<td>Cl</td>
<td>0 → 20</td>
<td>THF</td>
<td>0</td>
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<tr>
<td>2</td>
<td>10</td>
<td>Li$_2$CuCl$_4$</td>
<td>1.5</td>
<td>Br</td>
<td>−30</td>
<td>THF</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>CuI</td>
<td>1.4</td>
<td>Br</td>
<td>−78</td>
<td>THF</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>CuI</td>
<td>3.0</td>
<td>Br</td>
<td>−78 → −30</td>
<td>THF/DMS=10:1</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>CuBr·SMe$_2$</td>
<td>2.0</td>
<td>Br</td>
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<td>70</td>
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<tr>
<td>6</td>
<td>20</td>
<td>CuI</td>
<td>1.5</td>
<td>Br</td>
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<tr>
<td>7</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>−30</td>
<td>THF/DMS=10:1</td>
<td>0</td>
</tr>
</tbody>
</table>

$^{[a]}$ isolated yields.

General procedure for the synthesis of 1,4-dienes from allylic acetates (Table 1)

A solution of the allylic acetate (1 mmol) in dry THF (3 mL) was treated at room temperature with copper(I)iodide (38 mg, 0.2 mmol, 20 mol%) and dimethylsulfide (0.3 mL) under argon. The heterogeneous mixture was cooled to −30 °C and became clear after few minutes. Then vinlylmagnesium bromide (1.50 mL, 1.5 mmol, 1.5 eq., 1 M in THF) was added over 20 min and stirred for additional 30 min at that temperature. For substrates with a free alcohol, one additional equivalent of vinlylmagnesium bromide was used. If the reaction was not completed, additional vinlylmagnesium bromide (0.5 mL, 0.5 mmol, 0.5 eq., 1M in THF) could be added slowly. The reaction was quenched with saturated NH$_4$Cl solution (3 mL) and diluted with water. The aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined organic layers dried over MgSO$_4$. After evaporation of the solvent the crude residue was subjected to column chromatography (conditions see below) yielding the 1,4-dienes as colourless oils.
2a: Eluent: n-pentane/ethyl acetate = 50:1, \( R_f = 0.62 \) (n-pentane/ethyl acetate = 50:1); \(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \( \delta = 1.27 \) (s, 3H), 1.31 (s, 3H), 1.60-1.73 (m, 5H), 2.09-2.24 (m, 2H), 2.72 (t, \( J = 6.3 \) Hz, 1H), 2.75-2.78 (m, 2H), 4.96 (ddt, \( J = 10.0, 3.0, 1.5 \) Hz, 1H), 5.02 (ddt, \( J = 17.2, 3.6, 1.6 \) Hz, 1H), 5.20-5.24 (m, 1H), 5.81 (ddt, \( J = 16.3, 10.0, 6.3 \) Hz, 1H); \(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \( \delta = 16.0, 18.7, 24.9, 27.4, 32.3, 36.3, 58.4, 64.2, 114.2, 122.0, 135.5, 137.2; \) \( \text{IR} \ (\text{\textit{v}} / \text{cm}^{-1}) \) 680 (w), 875 (w), 909 (m), 994 (w), 1122 (w), 1249 (w), 1378 (m), 1450 (w), 1638 (m), 2925 (m), 2962 (m); \text{HRMS} \ (\text{ESI}) \ m/z \) calculated for \( \text{C}_{12}\text{H}_{21}\text{O} \ [\text{M+H}]^+ \) 181.1587, found 181.1585.

2b: Eluent: n-pentane/ethyl acetate = 50:1, \( R_f = 0.61 \) (n-pentane/ethyl acetate = 50:1); \(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \( \delta = 1.28 \) (s, 3H), 1.31 (s, 3H), 1.54-1.71 (m, 2H), 1.74 (d, \( J = 1.0 \) Hz, 3H), 2.13-2.24 (m, 2H), 2.72 (t, \( J = 6.3 \) Hz, 1H), 2.76-2.79 (m, 2H), 4.96 (ddt, \( J = 10.4, 3.5, 1.5 \) Hz, 1H), 5.03 (ddt, \( J = 17.1, 3.5, 1.5 \) Hz, 1H), 5.22 (t, \( J = 7.3 \) Hz, 1H), 5.80 (ddt, \( J = 16.6, 10.0, 6.3 \) Hz, 1H); \(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \( \delta = 18.7, 23.4, 24.9, 27.3, 28.4, 32.1, 58.4, 64.0, 114.4, 122.9, 135.5, 137.4; \) \( \text{IR} \ (\text{\textit{v}} / \text{cm}^{-1}) \) 680 (m), 793 (w), 864 (m), 908 (s), 995 (m), 1122 (m), 1249 (w), 1323 (w), 1380 (s), 1455 (s), 1638 (m), 2926 (s), 2964 (s), 3079 (w); \text{HRMS} \ (\text{ESI}) \ m/z \) calculated for \( \text{C}_{12}\text{H}_{21}\text{O} \ [\text{M+H}]^+ \) 181.1587, found 181.1584.

2c: Eluent: cyclohexane, \( R_f = 0.73 \) (cyclohexane); \(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \( \delta = 1.62 \) (s, 3H), 1.63 (s, 3H), 1.70 (d, \( J = 0.9 \) Hz, 3H), 2.01-2.13 (m, 4H), 2.75-2.78 (m, 2H), 4.96 (ddt, \( J = 10.1, 3.5, 1.5 \) Hz, 1H), 5.03 (ddt, \( J = 17.1, 3.7, 1.8 \) Hz, 1H), 5.10-5.14 (m, 1H), 5.16-5.20 (m, 1H), 5.82 (ddt, \( J = 16.3, 10.1, 6.2 \) Hz, 1H); \(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \( \delta = 15.9, 17.7, 25.7, 26.7, 32.2, 39.7, 114.0, 121.3, 124.3, 131.4, 136.4, 137.4; \) \( \text{IR} \ (\text{\textit{v}} / \text{cm}^{-1}) \) 831 (w), 909 (s),
992 (m), 1108 (w), 1377 (m), 1441 (m), 1638 (m), 2856 (s), 2916 (s), 2969 (s), 3079 (w); HRMS (EI) m/z calculated for C_{12}H_{20} [M]^+, 164.1560, found 164.1554.

2d: Eluent: cyclohexane, R_f = 0.75 (cyclohexane); ^1H-NMR (300 MHz, CDCl_3): δ = 1.63 (s, 3H), 1.70 (s, 3H), 1.73 (q, J = 1.2 Hz, 3H), 2.03-2.12 (m, 4H), 2.74-2.89 (m, 2H), 4.96 (ddt, J = 10.1, 3.5, 1.6 Hz, 1H), 5.03 (ddt, J = 17.2, 3.7, 1.8 Hz, 1H), 5.10-5.20 (m, 2H), 5.81 (ddt, J = 16.5, 10.3, 6.3 Hz, 1H); ^13C-NMR (75 MHz, CDCl_3): δ = 17.6, 23.4, 25.7, 26.6, 31.9, 32.2, 114.2, 122.2, 124.2, 131.6, 136.4, 137.7; IR (\text{cm}^{-1}) 829 (w), 909 (s), 991 (m), 1109 (w), 1378 (m), 1448 (m), 1638 (m), 2857 (s), 2921 (s), 2968 (s), 3079 (w); HRMS (EI) m/z calculated for C_{12}H_{20} [M]^+, 164.1560, found 164.1560.

2e: Eluent: n-pentane/diethyl ether = 50:1, R_f = 0.26 (n-pentane/diethyl ether = 50:1); ^1H-NMR (400 MHz, CDCl_3): δ = 1.65 (s, 3H), 2.04 (s, 3H), 2.33 (t, J = 7.0 Hz, 2H), 2.75-2.78 (m, 2H), 4.16 (t, J = 7.0 Hz, 2H), 4.97 (ddt, J = 10.0, 3.2, 1.5 Hz, 1H), 5.02 (ddt, J = 17.2, 3.6, 1.6 Hz, 1H), 5.242-5.26 (m, 1H), 5.80 (ddt, J = 16.3, 10.3, 6.1 Hz, 1H); ^13C-NMR (75 MHz, CDCl_3): δ = 16.0, 21.0, 32.2, 38.6, 62.9, 114.4, 124.1, 132.3, 136.9, 171.1; IR (\text{cm}^{-1}) 805 (w), 911 (m), 1042 (s), 1241 (s) 1365 (m), 1384 (m), 1433 (w), 1638 (w), 1743 (s), 2963 (m), 3080 (w); HRMS (ESI) m/z calculated for C_{10}H_{17}O_2 [M+H]^+, 169.1223, found 169.1222.

2f: Eluent: n-pentane/ethyl acetate = 50:1, R_f = 0.44 (n-pentane/ethyl acetate = 50:1); ^1H-NMR (400 MHz, CDCl_3): δ = 1.62 (s, 3H), 1.71-1.78 (m, 2H), 2.05-2.09 (m, 5H), 2.74-2.77 (m, 2H), 4.05 (t, J = 6.5 Hz, 2H), 4.96 (ddt, J = 10.0, 3.0, 1.5 Hz, 1H), 5.01 (ddt,
$J = 17.2, 3.5, 1.9$ Hz, 1H), 5.17-5.21 (m, 1H), 5.79 (ddt, $J = 16.3, 10.0, 6.3$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 15.8, 21.0, 26.7, 32.2, 35.7, 64.1, 114.2, 122.1, 135.2, 137.2, 171.2$; IR ($\tilde{\nu}$/cm$^{-1}$) 606 (w), 910 (m), 994 (w), 1040 (m), 1243 (s), 1366 (m), 1386 (m) 1448 (w), 1638 (w), 1742 (s), 2956 (m), 3079 (w); HRMS (ESI) $m/z$ calculated for C$_{11}$H$_{19}$O$_2$ [M+H]$^+$, 183.1380, found 183.1378.

2g:  Eluent: $n$-pentane/ethyl acetate = 10:1, $R_f = 0.56$ ($n$-pentane/ethyl acetate = 50:1); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta = 1.76$ (d, $J = 1.0$ Hz, 3H), 2.05 (s, 3H), 2.38 (t, $J = 7.0$ Hz, 2H), 2.76-2.79 (m, 2H), 4.12 (t, $J = 7.0$ Hz, 2H), 4.97 (ddt, $J = 10.0, 3.2, 1.6$ Hz, 1H), 5.03 (ddt, $J = 17.1, 3.5, 2.0$ Hz, 1H), 5.31 (t, $J = 7.3$ Hz, 1H), 5.80 (ddt, $J = 16.3, 10.0, 6.3$ Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta = 21.0, 23.6, 31.0, 32.2, 62.6, 114.5, 125.0, 132.1, 137.2, 171.1$; IR ($\tilde{\nu}$/cm$^{-1}$) 912 (m), 995 (w), 1044 (m), 1236 (s), 1365 (m), 1383 (m), 1448 (w), 1639 (w), 1742 (s), 2970 (m); HRMS (ESI) $m/z$ calculated for C$_{10}$H$_{16}$O$_2$Na [M+Na]$^+$, 191.1043, found 191.1043.

2h:  Eluent: $n$-pentane/diethyl ether = 50:1, $R_f = 0.21$ ($n$-pentane/diethyl ether = 50:1); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta = 1.69-1.76$ (m, 5H), 2.06 (s, 3H), 2.08-2.12 (m, 2H), 2.72-2.76 (m, 2H), 4.04 (t, $J = 6.6$ Hz, 2H), 4.96 (ddt, $J = 10.1, 3.3, 1.5$ Hz, 1H), 5.02 (ddt, $J = 17.1, 3.6, 1.8$ Hz, 1H), 5.21 (t, $J = 7.1$ Hz, 1H), 5.79 (ddt, $J = 16.3, 10.1, 6.2$ Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta = 21.0, 23.2, 26.7, 27.8, 32.1, 64.1, 114.3, 123.1, 135.2, 137.4, 171.1$; IR ($\tilde{\nu}$/cm$^{-1}$) 911 (w), 995 (w), 1038 (m), 1242 (s), 1366 (m), 1450 (w), 1638 (w), 1743 (s), 2965 (m); HRMS (ESI) $m/z$ calculated for C$_{11}$H$_{19}$O$_2$ [M+H]$^+$, 183.1380, found 183.1378.
2i: Eluent: n-pentane/ethyl acetate = 5:1, \( R_f = 0.35 \) (n-pentane/ethyl acetate = 5:1); \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta = 1.50 \) (s, 1H), 1.63 (s, 3H), 1.66-1.73 (m, 2H), 2.09 (t, \( J = 7.5 \) Hz, 2H), 2.74-2.78 (m, 2H), 3.64 (t, \( J = 6.5 \) Hz, 2H), 4.95 (ddt, \( J = 10.0, 3.3, 1.8 \) Hz, 1H), 5.02 (ddt, \( J = 17.1, 3.5, 1.5 \) Hz, 1H), 5.20-5.23 (m, 1H), 5.80 (ddt, \( J = 16.6, 10.0, 6.3 \) Hz, 1H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta = 15.8, 30.7, 32.2, 35.9, 62.7, 114.2, 121.8, 136.0, 137.2 \); IR (\( \tilde{\nu} / \text{cm}^{-1} \)) 909 (m), 993 (w), 1062 (m), 1383 (w), 1434 (w), 1638 (m), 2939 (s), 2976 (m), 3079 (w), 3355 (s); HRMS (ESI) \( m/z \) calculated for C\(_9\)H\(_{17}\)O \([\text{M+H}]^+\), 141.1274, found 141.1272.

2j: Eluent: n-pentane/diethyl ether = 2:1, \( R_f = 0.41 \) (n-pentane/diethyl ether = 2:1), IR (\( \tilde{\nu} / \text{cm}^{-1} \)) = 910 (s), 1151 (w), 1181 (w), 1257 (w), 1378 (w), 1638 (m), 2928 (m), 2975(s), 3078 (w), 3446 (s); \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta = 1.25 \) (s, 3H), 1.31 (s, 3H), 1.70 (s, 3H), 1.78 (bs, 1H), 2.20 (dd, 1H, \( J = 14.6, 5.5 \) Hz), 2.32 (dd, 1H, \( J = 14.6, 6.5 \) Hz), 2.73 (d, 1H, \( J = 2.5 \) Hz), 2.79 (bt, 2H, \( J = 6.8 \) Hz), 3.10 (ddd, 1H, \( J = 6.5, 5.4, 2.5 \) Hz), 4.97 (dtt, 1H, \( J = 10.0, 3.0, 1.5 \) Hz), 5.03 (dtt, 1H, \( J = 17.1, 3.5, 1.5 \) Hz), 5.30 (tq, 1H, \( J = 7.3, 1.5 \) Hz), 5.81 (dtt, 1H, \( J = 16.9, 10.2, 6.3 \) Hz); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta = 16.6, 24.9, 27.8, 32.2, 41.7, 54.8, 64.8, 67.7, 114.5, 124.1, 132.4, 138.8 \); HRMS (ESI): \( m/z \) für C\(_{12}\)H\(_{21}\)O\(_2\) \([\text{M+H}]^+\), calculated 197.1536, found 197.1536.

III. Compound characterisation

Epoxide 1a:
To a solution of geranyl acetate (10.0 g, 51 mmol) in dichloromethane (300 mL) at 0 °C was added \textit{m}-chloroperbenzoic acid (14.0 g, 56 mmol, 1.1 eq., 70 %) portionwise and the white suspension was stirred for 3 h at room temperature. Then a 3N NaOH solution (100 mL) was added and the mixture became a clear solution. The aqueous layer was extracted with dichloromethane (3 x 30 mL) and the combined organic layers were washed with brine (200 mL), dried over MgSO$_4$, filtered and concentrated \textit{in vacuo}. The crude compound was purified by flash column chromatography (SiO$_2$, \textit{n}-pentane/diethyl ether = 20:1 \textrightarrow 10:1 \textrightarrow 5:1) and epoxide 1a was obtained as a colourless oil (9.14 g, 85 %).

$R_f = 0.44$ (\textit{n}-pentane/ethyl acetate = 5:1); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.25 (s, 3H), 1.29 (s, 3H), 1.62-1.68 (m, 2H), 1.71 (s, 3H), 2.04 (s, 3H), 2.12-2.26 (m, 2H), 2.69 (t, $J = 6.0$ Hz, 1H), 4.58 (d, $J = 7.0$ Hz, 2H), 5.38 (tq, $J = 7.2$, 1.3 Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 16.4, 18.7, 21.0, 24.8, 27.0, 36.1, 58.4, 61.2, 63.9, 118.8, 141.2, 171.0; HRMS (ESI): $m/z$ for C$_{12}$H$_{21}$O$_3$ [M+H]$^+$, calculated 213.1485, found 213.1485.

Aldehyde 3:

To a suspension of epoxide 2a (2.18 g, 12.1 mmol) in a THF/H$_2$O mixture (2:1, 60 mL) was added sodium periodate (5.17 g, 24.2 mmol, 2 eq.). The reaction mixture was stirred for 4 h and then the white precipitate was filtered through celite®, rinsed with diethyl ether (50 mL). The aqueous phase was separated and extracted with diethyl ether (2 x 50 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated \textit{in vacuo}. The crude compound was purified by flash column chromatography (SiO$_2$, \textit{n}-pentane/diethyl ether = 50:1) and compound 3 was obtained as a colourless oil (1.25 g, 77 %).

$R_f = 0.28$ (cyclohexane/ethyl acetate = 92:8); IR ($\tilde{\nu}$ / cm$^{-1}$) = 910 (w), 996 (w), 1087 (w), 1387 (w), 1639 (w), 1723 (s), 2721 (w), 2918 (m), 2975 (m), 3426 (w); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.64 (s, 3H), 2.36 (t, $J = 7.4$ Hz, 2H), 2.55 (dt, $J = 7.5$, 2.1 Hz, 2H), 2.76 (t, $J = 6.3$ Hz, 2H), 4.95-5.03 (m, 2H), 5.19-5.23 (m, 1H), 5.79 (ddt, $J = 16.9$, 10.4, 6.2 Hz, 1H); 9.78 (t, $J = 2.0$ Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 16.1, 31.8, 32.2, 42.1, 114.4, 122.5, 134.4, 136.9, 202.5; HRMS (ESI): $m/z$ for C$_9$H$_{15}$O [M+H]$^+$, calculated 139.1117, found 139.1115.

S-8
A stirred solution of aldehyde 3 (200 mg, 1.45 mmol) and D/L-Proline (51 mg, 0.44 mmol, 30 mol%) in acetonitrile (4 mL) was cooled to 0 °C and treated with N-Chlorosuccinimide (212 mg, 1.60 mmol, 1.1 eq.) portionwise. The reaction mixture was warmed to room temperature over 50 min and then recooled to 0 °C, followed by the addition of sodium borohydride (3.63 mmol, 138 mg, 2.5 eq.). After a further 10 min at 0 °C and then 5 min at room temperature, a freshly prepared solution of EtOH/aqueous KOH (6 mL, solution prepared from: 12 mL EtOH, 12.5 g KOH, 25 mL H2O) was added and the medium was stirred vigorously for 1 h. The reaction mixture was diluted with water (20 mL) and diethyl ether (10 mL) and the aqueous layer was further extracted with diethyl ether (2 x 25 mL), the organic layers dried over MgSO4 and the solvents removed under reduced pressure. Purification by column chromatography (SiO2, n-pentane/diethyl ether = 25:1) of the crude product yielded epoxide 5 as a colourless oil (85 mg, 43 %).

Rf = 0.78 (cyclohexane/ethyl acetate = 6:1); IR (\( \tilde{\nu} / \text{cm}^{-1} \)) = 748 (w), 832 (m), 912 (s), 995 (m), 1112 (m), 1406 (m), 1639 (s), 1667 (s), 2921 (s), 2980 (s), 3050 (w), 3410 (w), 3583 (w); 1H-NMR (400 MHz, CDCl3): \( \delta \) 1.71 (s, 3H), 2.20 (dd, J = 14.6, 5.5 Hz, 1H), 2.28 (dd, J = 14.6, 6.0 Hz, 1H), 2.50 (dd, J = 5.0, 3.0 Hz, 1H), 2.78-2.81 (m, 3H), 2.98-3.03 (m, 1H), 4.98 (ddt, J = 10.0, 5.0, 1.5 Hz, 2H), 5.03 (ddt, J = 17.1, 5.5, 1.8 Hz, 1H), 5.82 (ddt, J = 16.9, 10.2, 6.3 Hz, 1H); 13C-NMR (100 MHz, CDCl3): \( \delta \) 16.7, 32.2, 42.5, 46.9, 51.4, 114.5, 123.9, 132.6, 136.9; HRMS (ESI): m/z for C9H15O [M+H]+, calculated 139.1117, found 139.1115.

Epoxide 5:

1.) 30 mol% D/L-Proline
2.) 2.5 eq. NaBH4, 15 min 0°C, then EtOH/KOH 60 min rt
A single neck, round bottom flask was charged with (2R, 5S)-2-tert-butyl-3,5-dimethylimidazolidin-4-one trifluoroacetic salt 4 (1.30 g, 4.57 mmol, 23 mol%), lithium chloride (2.58 g, 59.6 mmol, 3.0 eq.), copper trifluoroacetate hydrate (2.88 g, 9.90 mmol, 50 mol%) and potassium persulfate (6.45 g, 23.9 mmol, 1.2 eq.). The solids were dissolved in acetonitrile (159 mL, 0.125 M) and water (0.8 mL, 43.7 mmol, 2.2 eq.) and cooled to 0 °C, before the aldehyde 3 (2.75 g, 19.9 mmol) was added. The green suspension was stirred at 4 °C (fridge) for 16 h, recooled to 0 °C and treated with sodium borohydride (1.88 g, 49.8 mmol, 2.5 eq.) in several portions. After 30 min at 0 °C a freshly prepared NaOH/EtOH solution (74 mL, made from 50 mL water, 24 mL, EtOH and 25 g NaOH) was added to the black suspension and the reaction mixture was stirred vigorously for additional 3 h at room temperature. The reaction mixture was diluted with water (200 mL), extracted with diethyl ether (3 x 150 mL) and the combined organic phases were dried over MgSO₄. Careful evaporation (max. 40 °C @ 230 mbar) yielded a crude oil, which was purified by column chromatography (SiO₂, n-pentane/diethyl ether = 25:1) to afford epoxide 5 as a colourless liquid (1.54 g, 56 %, 95 % ee calculated by chiral GC).

Rₓ= 0.78 (cyclohexane/ethyl acetate = 6:1); [α]D⁰ = 4.14 (CHCl₃, c = 11.41); IR (υ / cm⁻¹) = 748 (w), 832 (m), 912 (s), 995 (m), 1112 (m), 1406 (m), 1639 (s), 1667 (s), 2921 (s), 2980 (s), 3050 (w), 3410 (w), 3583 (w); ^1H-NMR (400 MHz, CDCl₃): δ 1.71 (s, 3H), 2.20 (dd, J = 14.6, 5.5 Hz, 1H), 2.28 (dd, J = 14.6, 6.0 Hz, 1H), 2.50 (dd, J = 5.0, 3.0 Hz, 1H), 2.78-2.81 (m, 3H), 2.98-3.03 (m, 1H), 4.98 (ddt, J = 10.0, 5.0, 1.5 Hz, 2H), 5.03 (ddt, J = 17.1, 5.5, 1.8 Hz, 1H), 5.82 (ddt, J = 16.9, 10.2, 6.3 Hz, 1H); ^13C-NMR (100 MHz, CDCl₃): δ 16.7, 32.2, 42.5, 46.9, 51.4, 114.5, 123.9, 132.6, 136.9; HRMS (ESI): m/z for C₉H₁₅O [M+H]⁺, calculated 139.1117, found 139.1115.

Dithiane 6:

| 2-Methyl-1,3-dithiane (2.12 g, 15.8 mmol, 1.8 eq.) was dissolved in THF (50 mL) and n-BuLi (9.88 mL, 15.8 mmol, 1.8 eq., 1.6 M in hexane) was added dropwise over 20 min. After a |
further 10 min at room temperature, epoxide 5 (1.21 g, 8.75 mmol) in THF (10 mL + 2.0 ml rinse) was introduced via cannula over 45 min. After 30 min, the reaction was quenched by addition of a saturated aqueous NH₄Cl solution (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over MgSO₄ and concentrated. The crude residue was subjected to flash column chromatography (n-pentane/diethyl ether = 5:1) yielding dithiane 6 (1.97 g, 82%) as a yellow oil.

R_f = 0.31 (cyclohexane/ethyl acetate = 6:1); [α]_D° = −36.5 (CHCl₃, c = 7.70); IR (ν / cm⁻¹) = 724 (w), 909 (m), 1012 (m), 1085 (m), 1257 (w), 1421 (m), 2925 (s), 3074 (w), 3442 (m), 3818 (w), ¹H-NMR (400 MHz, CDCl₃): δ 1.66 (s, 3H), 1.68 (s, 3H), 1.88-2.07 (m, 3H), 2.13-2.18 (m, 1H), 2.22-2.28 (m, 2H), 2.77-2.83 (m, 4H), 2.92-3.07 (m, 3H), 4.05-4.11 (m, 1H), 4.96-5.06 (m, 1H), 5.27-5.29 (m, 1H), 5.65-5.75 (m, 1H); ¹³C-NMR (100 MHz, CDCl₃): δ 16.2, 24.8, 26.6, 26.8, 28.5, 32.3, 47.1, 47.9, 48.4, 66.6, 144.5, 125.3, 133.1, 136.9; HRMS (ESI): m/z for C₁₄H₂₅OS₂ [M+H]⁺, calculated 273.1341, found 273.1342.

Methylketone 7

To a suspension of dithiane 6 (95 mg, 0.35 mmol) and calcium carbonate (1.85 mmol, 185 mg, 5 eq.) in a MeOH/acetonitrile solution (9:4) (13 mL) was added PhI(TFA)₂ (0.56 mmol, 239 mg, 1.5 eq.) in one portion at room temperature. After 10 min the reaction was quenched with a Na₂S₂O₅/NaHCO₃ solution (1:1) (10 mL) and the aqueous phase extracted with dichloromethane (3 x 15 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated. Flash column chromatography (n-pentane/diethyl ether = 2:1) gave methylketone 7 (48 mg, 75%) as a colourless oil.

R_f = 0.20 (n-pentane/diethyl ether = 2:1); [α]_D° = −25.9 (CHCl₃, c = 8.88); IR (ν / cm⁻¹) = 910 (w), 994 (w), 1078 (m), 1359 (m), 1486 (m); 1710 (s), 2388 (w), 2972 (s), 3457 (s); ¹H-NMR (400 MHz, CDCl₃): δ 1.66 (s, 3H), 2.12-2.14 (m, 5H), 2.56-2.59 (m, 2H), 2.74 (bs, 1H), 2.79 (bt, J = 6.6 Hz, 2H), 4.16-4.22 (m, 1H), 4.96-5.05 (m, 2H), 5.27 (dt, J = 7.2, 0.9 Hz, 1H), 5.75-5.85 (m, 1H); ¹³C-NMR (100 MHz, CDCl₃): δ 16.1, 30.9, 32.3, 46.9, 49.5, 65.5,
114.5, 125.4, 132.8, 138.8, 209.4; **HRMS (ESI)**: $m/z$ for $\text{C}_{11}\text{H}_{19}\text{O}_2 [\text{M}+\text{H}]^+$, calculated 183.1380, found 183.1379.

**(E)-2,2-Dimethyl-3-(3-methyl-5-phenylpent-3-enyl)oxirane (Scheme 3, Step a)**

To a solution of epoxide 1a (406 mg, 1.91 mmol) in THF (10 mL) at 0°C was added dropwise lithium tetrachlorocuprate (0.8 mL, 0.08 mmol, 4 mol%, 0.1 M in THF) and the reaction mixture was stirred for 5 min. Then a solution of phenylmagnesium chloride (2.87 mL, 5.73 mmol, 3 eq., 2M in THF) was slowly added and the reaction mixture was stirred for 1.5 h at 0°C. The reaction was quenched by addition of a saturated NH$_4$Cl solution (10 mL) and the residues of magnesium salt were dissolved by addition of water. The aqueous phase was separated and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude compound was purified by flash column chromatography (SiO$_2$, cyclohexane/ethyl acetate = 99:1) and epoxide S-1a was obtained as an oil (390 mg, 89%).

$R_f = 0.26$ (cyclohexane/ethyl acetate = 99:1); **IR** ($\tilde{\nu}$ / cm$^{-1}$) = 698 (s), 741 (s), 874 (w), 1030 (w), 1122 (m), 1249 (w), 1323 (w), 1377 (s), 1453(s), 1494 (s), 1603 (w), 2923 (s), 2961 (s), 3026 (m), 3061 (w); **$^1$H-NMR** (400 MHz, CDCl$_3$): $\delta$ 1.27 (s, 3H), 1.29 (s, 3H), 1.62-1.72 (m, 2H), 1.75 (s, 3H), 2.12-2.27 (m, 2H), 2.72 (t, $J = 6.3$ Hz, 1H), 3.38 (d, $J = 7.5$ Hz, 2H), 5.41 (tq, $J = 7.3$, 1.5 Hz, 1H), 7.17-7.20 (m, 3H), 7.27-7.31 (m, 2H); **$^{13}$C-NMR** (100 MHz, CDCl$_3$): $\delta$ 16.2, 18.7, 24.8, 27.4, 34.2, 36.2, 58.4, 64.1, 132.7, 125.7, 128.3 (4 C), 135.2, 141.5; **HRMS (ESI)**: $m/z$ for $\text{C}_{16}\text{H}_{23}\text{O} [\text{M}+\text{H}]^+$, calculated 231.1743, found 231.1743.

Aldehyde 8
To a suspension of sodium periodate (450 mg, 2.1 mmol, 3 eq.) in a THF/H2O solution (2:1, 5 mL) was added a solution of epoxide S-1a (159 mg, 0.7 mmol) dissolved in a THF/H2O solution (2:1, 1 mL) at room temperature. The reaction mixture was stirred for 7.5 h and then the white precipitate was filtered through celite®, rinsed with diethyl ether (5 mL). The aqueous phase was separated and extracted with diethyl ether (2 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO4, filtered and concentrated in vacuo. The crude compound was purified by flash column chromatography (SiO2, n-pentane/diethyl ether = 50:1 → 25:1) and compound 8 was obtained as an oil (120 mg, 91 %).

R_f = 0.44 (n-pentane/diethyl ether = 6:1); IR (ν / cm⁻¹) = 689 (w), 742 (w), 1029 (w), 1074 (w), 1266 (w), 1450 (w), 1602 (w), 1685 (w), 1724 (s), 2721 (w), 2916 (w), 3027 (w), 3061 (w); ¹H-NMR (400 MHz, CDCl₃): δ 1.74 (s, 3H), 2.39 (t, 2H, J = 7.1 Hz), 2.57 (dt, 2H, J = 7.5, 1.0 Hz), 3.37 (d, 2H, J = 7.0 Hz), 5.39 (tq, 1H, J = 7.4, 1.3 Hz), 7.15-7.21 (m, 3H), 7.27-7.31 (m, 2H), 9.78 (t, 1H, J = 1.8 Hz); ¹³C-NMR (100 MHz, CDCl₃): δ 16.3, 31.8, 34.1, 42.1, 124.1, 125.8, 128.2 (2 C), 128.4 (2 C), 134.1, 141.2, 202.4; HRMS (ESI): m/z for C₁₃H₁₇O [M+H]^+, calculated 189.1274, found 189.1273.

Hydroxyketone 9 and Enone 10

A solution of aldehyde 8 (522 mg, 2.78 mmol), D-Proline (97 mg, 0.83 mmol) and isopropanol (0.42 mL, 2 equiv.) in acetone (20 mL) was stirred for 3 days at room temperature. The reaction mixture was filtered over celite®, washed with ethyl acetate (20 mL) and the solution was concentrated in vacuo. The crude compound was purified by flash column chromatography (SiO2, n-pentane/diethyl ether 7:3 → 1:1) and compound 9 (287 mg, 42 %, 72 % ee) and enone 10 (285 mg, 45 %) were obtained as yellow oils.
Compound 9

\( R_f = 0.23 \) (n-pentane/diethyl ether = 2:1); \([\alpha]_D^{20} = -13.1 \) (CHCl₃, c = 10); IR (\( \tilde{\nu} / \text{cm}^{-1} \)) = 700 (w), 742 (w), 1072 (w), 1097 (m), 1160 (w), 1275 (s), 1361 (s), 1450 (m), 1493 (w), 1711 (s), 2857 (w), 2930 (s), 3026 (w), 3439 (s); HPLC: \( R_t = 8.36 \) min (major enantiomer), \( R_t = 7.60 \) min (minor enantiomer) (Daicel IA, n-hexane/iso-propanol = 90:10, c = 0.71 mg/mL, 1 mL/min, T = 20°C); \(^1\)H-NMR (500 MHz, CDCl₃): \( \delta \) 1.51-1.58 (m, 1H), 1.62-1.69 (m, 1H), 1.74 (s, 3H), 2.08-2.24 (m, 2H), 2.17 (s, 3H), 2.55 (dd, \( J = 17.6, 9.2 \) Hz, 1H), 2.63 (dd, \( J = 17.6, 3.1 \) Hz, 1H), 2.95 (bs, 1H), 3.37 (d, \( J = 7.3 \) Hz, 2H), 4.02-4.07 (m, 1H), 5.39 (tq, \( J = 7.4, 1.0 \) Hz, 1H), 7.17-7.20 (m, 3H), 7.27-7.30 (m, 2H); \(^{13}\)C-NMR (125 MHz, CDCl₃): \( \delta \) 16.1, 30.7, 34.2, 34.6, 35.5, 49.9, 67.3, 123.5, 125.7, 128.3 (2 C), 128.3 (2 C), 135.6, 141.6, 209.7; HRMS (ESI): m/z for C₁₆H₂₂O₂ [M+H]⁺, calculated 247.1693, found 247.1693.

Compound 10

\( R_f = 0.38 \) (n-pentane/diethyl ether = 2:1); \(^1\)H-NMR (500 MHz, CDCl₃): \( \delta \) 1.73 (s, 3H), 2.19-2.23 (m, 2H), 2.19 (s, 3H), 2.37 (dd, \( J = 17.0, 8.5 \) Hz, 2H), 3.36 (d, \( J = 9.5 \) Hz, 2H), 5.38 (dt, \( J = 9, 1.5 \) Hz, 1H), 6.06 (d, \( J = 20 \) Hz, 1H), 6.06 (td, \( J = 20, 8.5 \) Hz, 1H), 7.17-7.20 (m, 3H), 7.27-7.30 (m, 2H); \(^{13}\)C-NMR (125 MHz, CDCl₃): \( \delta \) 16.0, 26.7, 30.8, 34.2, 38.0, 124.3, 125.8, 128.3 (2 C), 128.4 (2 C), 131.5, 134.4, 141.3, 148.0, 198.7.

Oxa-Michael conditions for the conversion of 10 to 9

\[
\begin{align*}
\text{Cl}_3\text{CCOOH (20 mol%), H}_2\text{O}_2, \\
\text{dioxane, } 32 ^\circ \text{C, then P(OEt)}_3
\end{align*}
\]

Amine 11 (52 mg, 0.16 mmol, 0.1 eq.) was added to a solution of trichloroacetic acid (52.1 mg, 0.32 mmol, 0.3 eq) in 1,4-dioxane (6.4 mL). Then enone 10 (365 mg, 1.6 mmol, 1 eq.) was added followed by the addition of aqueous hydrogen peroxide (486 \( \mu \)L, 3 eq., 4.8 mmol, 30% w/w) after 20 min at ambient temperature. After 48 h at 32°C, triethylphosphite
(3 equiv., 830 mL, 3.0 mmol) was added dropwise at 0°C and the reaction mixture was stirred for 15 h at 32°C. Additional triethylphosphite (2 equiv., 554 mL, 3.2 mmol) was added and the reaction further stirred for 6 h. The reaction mixture was extracted with diethyl ether (2 x 35 mL) and the combined organic phases were washed with brine, dried over Na₂SO₄ and filtered. The resulting solution was concentrated in vacuo. The crude compound was purified by flash column chromatography (SiO₂, n-pentane/diethyl ether = 1:1) and compound 9 (177 mg, 45 %, 92 % ee) was obtained as a yellow oil.

Aldehyde 12

A reaction vial was charged with epoxide 2a (90 mg, 0.5 mmol), Rh(acac)(CO)₂ (2.6 mg, 0.01 mmol, 2 mol%), Xantphos (4,5-Bis(diphenyl-phosphino)-9,9-dimethylxanthene) (30 mg, 0.05 mmol, 10 mol%) and toluene (2 mL). The yellow solution was stirred at 60 °C for 16 h under an H₂/CO atmosphere (20 bar) and subjected directly to column chromatography (SiO₂, n-pentane/diethyl ether = 6:1). The aldehyde 12 was obtained as a colourless oil (104 mg, 99 %).

\[ R_f = 0.20 \text{ (n-pentane/diethyl ether = 6:1); IR (}\tilde{\nu}/\text{cm}^{-1}\text{) } = 680 \text{ (w), 872 (w), 1120 (m), 1380 (m), 1453 (m), 1724 (s), 2959 (s), 3494 (s), 3650 (w), 3673 (w); H-NMR (400 MHz, CDCl₃): } \delta \text{ 1.27 (s, 3H), 1.30 (s, 3H), 1.61 (s, 3H), 2.02-2.41 (m, 4H), 2.42 (dt, } J = 7.3, 1.6 \text{ Hz, 2H), 2.70 (t, } J = 6.3 \text{ Hz, 1H), 5.15 (tq, } J = 7.2, 1.3 \text{ Hz, 1H), 9.77 (t, } J = 1.8 \text{ Hz, 1H); C-NMR (100 MHz, CDCl₃): } \delta \text{ 16.0, 18.7, 22.2, 24.9, 27.2, 27.4, 36.3, 43.3, 58.3, 64.1, 123.8, 135.5, 202.7; HRMS (ESI): } m/z \text{ for C}_{13}H_{26}O_{2}N \text{ [M+NH₄]⁺, calculated 252.1958, found 252.1952.} \]
Acq. Operator : Bokelmann
Acq. Instrument : GC 6850
Injection Date : 16-Feb-10, 13:27:38
Location : Vial 2
Inj : 1
Inj Volume : 1 μl

Acq. Method : C:\CHEM32\2\METHODS\PHILIPP.M
Last changed : 2/16/2010 1:23:29 PM by Bokelmann
(modified after loading)

Analysis Method : C:\CHEM32\2\METHODS\AT_MERKS.M
Last changed : 6/30/2010 10:41:54 AM by Bokelmann
(modified after loading)

Sample Info : MN Hydrodex-β-6TDBM
80°C
0.9ml/min He
100:1 split
Data File C:\CHEM32\\DATA\PHILIPP\FW232.D
Sample Name: FW232

Acq. Operator : Bokelmann
Acq. Instrument : GC 6850 Location : Vial 1
Injection Date : 17-Feb-10, 09:51:10 Inj : 1
            :                      Inj Volume : 1 μl
Acq. Method : C:\CHEM32\METHODS\PHILIPP.M
Last changed : 2/16/2010 2:09:55 PM by Bokelmann
Analysis Method : C:\CHEM32\METHODS\AT_MERKS.M
Last changed : 6/30/2010 11:13:43 AM by Bokelmann
            : (modified after loading)
Sample Info : MN Hydrodex-β-6TDBM
            : 80°C
            : 0.9ml/min He
            : 100:1 split

[Graph of FID1 A (PHILIPPFW232.D)]