Asymmetric Alkylation and Aldol Reactions of D-Mannitol-Derived Chiral Oxazolidin-2-one Derivatives

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In the preceding article, we have introduced a new chiral oxazolidin-2-one auxiliary (1) derived from a cheap D-mannitol, and demonstrated the chiral selectivity in alkylation, aldol reaction and β-lactam synthesis.1 The present work began with a search for useful chiral directing groups with which to control the chiral selectivity. Because the rigidity of cyclic structures contributes significantly to control of chirality,2 the 1,2:5,6-di-O-cyclohexylidene-D-mannitol (2) was used for the synthesis of oxazolidin-2-one chiral auxiliary (3) comparing the selectivity with the auxiliary (1) in alkylation and aldol reactions.

The 1,2:5,6-di-O-cyclohexylidene-D-mannitol (2), which was prepared from D-mannitol with cyclohexanone, boron trifluoride etherate and triethyl orthoformate in DMSO,3 was converted into the cyclic sulfate 4 via cyclic sulfite methodology.4 This cyclic sulfate is similar to epoxide in that they undergo nucleophilic displacement (SN2) readily,5 and produced 3-amino-3-deoxy-1,2:5,6-di-O-cyclohexylidene-D-altitol (5) via azide displacement, hydrolysis followed by reduction (Scheme 1). The altitol 5 was converted into the chiral auxiliary 3 in 95% yield by using diethyl carbonate with sodium methoxide.6

The N-acylated derivatives 6a-c were easily prepared in high yield by reaction of auxiliary 3 with acyl chlorides a-c using n-butyllithium in THF at -60 °C (Table 1).

As we expected, LDA mediated asymmetric alkylations of N-acyl derivatives were obtained with high diastereomeric excess through Z-enolate and re-face selectivity (Table 2).7

In most cases (entries a1-c1 except c2), the cyclohexylidene auxiliary 6 gave higher diastereomeric excess than the isopropylidene auxiliary derived from 1 (the %de in parenthesis indicates the %de from the isopropylidene auxiliary). The diastereomeric ratio was easily identified by the integration of benzyl (entries a1, b1, b2, c2) and allyl (entries a2, c1) protons in 1H NMR chemical shift as we seen in previous results. Cyclohexylidene substituent in auxiliary

Table 1. N-Acylated derivatives 6a-c from the chiral auxiliary 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Reaction time</th>
<th>Yield %</th>
<th>[α]D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(c, CHCl3)</td>
</tr>
<tr>
<td>a</td>
<td>CH3</td>
<td>30 min</td>
<td>92.2</td>
<td>+35.3 (0.6)</td>
</tr>
<tr>
<td>b</td>
<td>PhCH2</td>
<td>30 min</td>
<td>95.6</td>
<td>+33.3 (1.2)</td>
</tr>
<tr>
<td>c</td>
<td>allyl</td>
<td>30 min</td>
<td>85.0</td>
<td>+32.9 (1.1)</td>
</tr>
</tbody>
</table>

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shows bulkier and more ligid character in space than isopropylidene derivative, and gives better selectivity in alkylation. We also applied this cyclohexylidene auxiliary to the aldol reaction with benzaldehyde. “Evans” syn product was obtained by using 1 equiv of TiCl₄ via non-chelated Z-enolate, however, “non-Evans” syn aldol product was produced by using 2 equiv of TiCl₄ via chelated Z-enolate (Scheme 2). Selectivity employing 1 equiv of TiCl₄ was >99 : 1 Evans syn : non-Evans syn. The absolute configuration of 8 and the selectivity of syn:anti ratio were determined after hydrolytic cleavage of 8 to 10 by using LiOOH. The hydrolysis gave 79.4% yield of (2S,3S)-acid [α]D = -24.4 (c=0.9, CH₂Cl₂), lit. = -26.4 (c = 1.04, CH₂Cl₂) with quantitative recovery (>99%) of auxiliary 3. The ¹H NMR of the product 10 indicated the selectivity > 96 : 4 for syn:anti ratio similar to previous results.

In the same way, we found that the selectivity for non-Evans syn 9 : Evans syn 8 employing 2 equiv of TiCl₄ was >99 : 1 and for syn:anti of 11 after hydrolysis was 82 : 18. No products from endocyclic cleavage in hydrolysis reaction were observed in both cases.

In conclusion, the cyclohexylidene chiral auxiliary derived from D-mannitol shows better selectivity in asymmetric alkylations and comparable selectivity in aldol reactions compare with the isopropylidene derivative 1.

**Experimental Section**

All chemicals were purchased from commercial sources and used as received unless otherwise stated. NMR spectra were recorded at Varian Gemini-400 MHz FT-NMR for ¹H and 100 MHz for ¹³C, with the chemical shifts (δ) reported in parts per million (ppm) relative to TMS and the coupling constants (J) quoted in Hz. CDCl₃ was used as a solvent and an internal standard. Infrared spectra were recorded on a Shimadzu IR-435 spectrometer. GC-MS analyses were performed using a HP-5890/JMS-AM 150, JEOL. Flash chromatography was carried out using silica gel Merck 60 (230-400 mesh). Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F₂₅₄ (Merck, layer thickness 0.2 mm) plastic-backed silica gel plates with visualization by UV light (254 nm) or by treatment with p-anisaldehyde. Melting points were measured on a MEL-TEMP II apparatus and were uncorrected.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>RX</th>
<th>Rxn (h)</th>
<th>% yield</th>
<th>% de</th>
<th>[α]D</th>
</tr>
</thead>
<tbody>
<tr>
<td>a1</td>
<td>CH₃</td>
<td>PhCH₂Br</td>
<td>5</td>
<td>91.7</td>
<td>&gt;99 (94.0)</td>
<td>20.6 (c=1.1, CHCl₃)</td>
</tr>
<tr>
<td>a2</td>
<td>CH₃</td>
<td>allyl bromide</td>
<td>9</td>
<td>36.4</td>
<td>&gt;99 (91.6)</td>
<td>31.2 (c=1.7, CHCl₃)</td>
</tr>
<tr>
<td>b1</td>
<td>PhCH₂</td>
<td>Mel</td>
<td>9</td>
<td>45.6</td>
<td>96.9(92.6)</td>
<td>53.8 (c=1.9, CHCl₃)</td>
</tr>
<tr>
<td>b2</td>
<td>PhCH₂</td>
<td>allyl bromide</td>
<td>6</td>
<td>55.6</td>
<td>96.8(91.6)</td>
<td>75.4 (c=1.1, CHCl₃)</td>
</tr>
<tr>
<td>c1</td>
<td>allyl</td>
<td>Mel</td>
<td>20</td>
<td>46.3</td>
<td>97.1 (92.9)</td>
<td>52.2 (c=0.9, CHCl₃)</td>
</tr>
<tr>
<td>c2</td>
<td>allyl</td>
<td>PhCH₂Br</td>
<td>20</td>
<td>52.1</td>
<td>89.4(96.7)</td>
<td>29.3 (c=1.1, CHCl₃)</td>
</tr>
</tbody>
</table>

*Isolated yield. The %de in parenthesis indicates the yield from the isopropylidene auxiliary 1.

**Table 2. Asymmetric alkylation of N-acyl derivatives 6**

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**Scheme 2**
(4S,5R)-4,5-Bis(2,2-dicyclohexyl-1,3-dioxolan-4-yl)-oxazolidin-2-one (3). To a solution of 3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-D-altroitol (5) (0.63 g, 1.85 mmol) in diethyl carbonate (3.15 mL) under nitrogen atmosphere was added sodium methoxide (0.11 mL of 25% solution in MeOH, 0.46 mmol) and heated for 3 h at 70-80 °C. Diethyl carbonate was removed by evaporation and the residual solid was washed with hexane, recrystallized by MeOH to give the white solid 3 (0.64 g, 95%). Rf 0.47 (MeOH : CHCl₃ = 1 : 9); mp 170-172 °C; [α]D₂⁰ -35.8 (c 1.0, CHCl₃); νmax (film)/cm⁻¹ 3288, 2933, 2850, 1757, 1738, 1094; 1H NMR (400 MHz, CDCl₃) δ 1.40-1.66 (20H, m), 3.79 (1H, dd, J 9.3, 4.6 Hz), 3.83-3.88 (1H, m), 3.95-3.99 (1H, m), 4.13-4.19 (2H, m), 4.33-4.39 (2H, m), 4.40-4.46 (1H, m), 5.43 (1H, br s, NH); 13C NMR (100 MHz, CDCl₃) 158.1, 111.2, 110.8, 78.1, 73.9, 71.9, 67.7, 67.1, 58.3, 36.9, 36.7, 34.9, 34.6, 25.4, 25.3, 24.4 (x2), 24, 24, 21.

Typical Procedure for the Preparation of N-Acylloxazolidin-2-ones, 6a-c. To a solution of oxazolidinone (3) (1.00 g, 2.72 mmol) in THF (100 mL) under nitrogen atmosphere was added n-BuLi (2.55 mL of 1.6 M solution in Hexane, 4.08 mmol) at -60 °C and stirred for 30 min. Propionyl chloride (0.47 mL, 5.44 mmol) was added to this reaction mixture at -40 °C and stirred for 30 min. The reaction was quenched by the addition of water at 0 °C. The organic product was extracted with ethyl acetate, washed with brine, dried, concentrated and chromatographed (EtOAc : Hex = 1 : 4) to give the liquid 6a (0.10 g, 92.6%).

(4S,5R)-3-(1-Oxopropyl)-4,5-bis(2,2-dicyclohexyl-1,3-dioxolan-4-yl)-oxazolidin-2-one (6a). Rf 0.42 (EtOAc : Hex = 1 : 4); [α]D₂⁰ +35.3 (c 0.6, CHCl₃); 1H NMR (400 MHz, CDCl₃) δ 1.18 (3H, t, J 7.3 Hz.), 1.29-1.58 (20H, m), 3.92-4.06 (3H, m), 4.18 (1H, dd, J 9.2, 5.8 Hz), 4.31 (1H, dd, J 9.8, 7.0 Hz), 4.58-4.68 (2H, m), 4.73 (1H, d, J 6.7 Hz).

(4S,5R)-3-(3-Phenyl-1-oxopropyl)-4,5-bis(2,2-dicyclohexyl-1,3-dioxolan-4-yl)-oxazolidin-2-one (6c). To a solution of diisopropyl amine (0.05 mL, 0.24 mmol) in THF (2 mL) was added n-BuLi (0.22 mL of 1.6 M solution in Hexane, 0.35 mmol) and stirred for 30 min. N-Propionyl oxazolidinone (0.10 g, 0.24 mmol) in THF (2 mL) was added to this reaction mixture at -60 °C and stirred for 30 min. N-Benzyl bromide (0.11 mL, 0.94 mmol) was added to this reaction mixture at -40 °C and stirred for 2 h. The reaction was quenched by the addition of water at 0 °C. The organic product was extracted with ethyl acetate, washed with brine, dried, concentrated, and chromatographed (EtOAc : Hex = 1 : 4) to give the liquid 7a1 (0.11 g, 91.7%).
46.3%; \( R_{f} 0.59 \) (EtOAc : Hex = 1 : 4); \([\alpha]_{D}^{20} +52.2 \) (c 0.9, CHCl3); \(^1\)H NMR (400 MHz, CDCl3) \( \delta 1.25 \) (3H, d, J 6.6 Hz, \( \alpha \)-methyl), 1.37-1.59 (20H, m), 2.17 (1H, m, allyl proton), 2.40 (1H, m, allyl proton), 3.79 (1H, m), 3.87 (1H, dd, J 9.0, 6.5 Hz), 4.03 (2H, m), 4.18 (1H, dd, J 9.2, 5.9 Hz), 4.28 (1H, dd, J 9.8, 6.9 Hz), 4.58-4.66 (2H, m), 4.73 (1H, d, J 6.9 Hz), 5.01 (1H, m, =CH trans), 5.07 (1H, m, =CH cis), 5.75 (1H, m, =CH internal).

\((4S,5R,2'R')\)-3-(2-Benzyl-1-oxo-4-pentenyl)-4,5-bis-(2,2-dicyclohexyl-1,3-dioxolan-4-yl)-oxazolidin-2-one (7c2).

2.02 g (9.1, 5.9 Hz), 4.16 (1H, dd, J 9.1, 5.9 Hz), 4.20-4.25 (2H, m), 4.49 (1H, br t, J 7.2 Hz, 4.60 (1H, m), 4.67 (1H, dd, J 7.3, 0.9 Hz), 4.99 (1H, s, =CH cis), 5.03 (1H, d, J 5.9 Hz, =CH trans), 5.73 (1H, m, =CH internal) 7.18 (1H, m), 7.23-7.27 (4H, m).

\((4S,5R,2'S,3'S')\)-3-(3-Hydroxy-2-methyl-3-phenyl-1-oxo-propyl)-4,5-bis-(2,2-dicyclohexyl-1,3-dioxolan-4-yl)-oxazolidin-2-one (8).

To a solution of (\(4S,5R\))-3-(1-oxopropyl)-4,5-bis-(2,2-dicyclohexyl-1,3-dioxolan-4-yl)-oxazolidin-2-one (6a) (0.15 g, 0.35 mmol) in CHCl3 (5 mL) under nitrogen atmosphere was added TiCl4 (0.39 mL in 1.0 M solution in CHCl3, 0.39 mmol) at -60 °C and stirred for 5 min. TMEDA (0.13 mL, 0.89 mmol) was added to this reaction mixture at -60 °C and stirred for 30 min. Benzaldehyde (0.07 mL, 0.71 mmol) was added to this reaction mixture at -60 °C and stirred for 2 h. The reaction was quenched by the addition of 50% aqueous NH4Cl at 0 °C. The organic product was extracted with ethyl acetate, washed with brine, dried and concentrated to give the product (8) (53 mg, 65.8%). \( R_{f} 0.51 \) (EtOAc : Hex = 1 : 2). \(^1\)H NMR (400 MHz, CDCl3) \( \delta 1.27 \) (3H, d, J 6.9 Hz, \( \alpha \)-methyl), 1.34-1.57 (20H, m), 3.33 (1H, d, J 9.0 Hz), 3.83-3.93 (3H, m), 4.01-4.14 (3H, m), 4.92 (1H, dd, J 5.0, 2.8 Hz), 7.24-7.32 (5H, m).

\((4S,5R,2'R,3'R')\)-3-(2-Dibromo-3-hydroxy-3-methyl-1-oxo-propyl)-4,5-bis-(2,2-dicyclohexyl-1,3-dioxolan-4-yl)-oxazolidin-2-one (9).

To a solution of (\(4S,5R\))-3-(1-oxopropyl)-4,5-bis-(2,2-dimethyl-1,3-dioxolan-4-yl)-oxazolidin-2-one (6a) (0.15 g, 0.35 mmol) in CHCl3 (7 mL) under nitrogen atmosphere was added TiCl4 (0.71 mL in 1.0 M solution in CHCl3, 0.71 mmol) at -60 °C and stirred for 5 min. EtN (0.07 mL, 0.53 mmol) was added to this reaction mixture at -60 °C and stirred for 30 min. Benzaldehyde (0.07 mL, 0.71 mmol) was added to this reaction mixture at -60 °C and stirred for 2 h. The reaction was quenched by the addition of water at 0 °C. The organic product was extracted with ethyl acetate, washed with brine, dried and concentrated to give the product (9) (41 mg, 21.9%). \( R_{f} 0.43 \) (EtOAc : Hex = 1 : 2); \(^1\)H NMR (400 MHz, CDCl3) \( \delta 0.96 \) (3H, d, J 6.9 Hz, \( \alpha \)-methyl), 1.37-1.60 (20H, m), 3.51 (1H, d, J 4.7 Hz), 3.95-4.12 (4H, m), 4.15-4.21 (2H, m), 4.32-4.37 (1H, m), 4.67-4.70 (2H, m), 4.88 (1H, dd, J 7.1, 1.1 Hz), 7.24-7.37 (3H, m), 7.46 (2H, d, J 6.9 Hz).

\textit{syn-(2S,3S)}- and \textit{anti-(2R,3S)}-3-Hydroxy-2-methyl-3-phenylpropanoic acid (10). To a solution of (\(4S,5R,2'S,3'S'\))-3-(3-hydroxy-2-methyl-3-phenyl-1-oxopropyl)-4,5-bis-(2,2-dicyclohexyl-1,3-dioxolan-4-yl)-oxazolidin-2-one (8) (100 mg, 0.19 mmol) in THF (2.9 mL) and H2O (0.95 mL) was added 30% H2O2 (1.07 g, 0.94 mmol) and LiOH-H2O (16 mg, 0.38 mmol) at 0 °C and stirred for 30 min. Solid sodium sulfite and saturated NaHCO3 solution were added to the reaction mixture until pH 10. THF in the reaction mixture was evaporated. The mixture was diluted with water (2.5 mL), extracted with CH2Cl2. washed with brine, dried and concentrated to give the auxiliary (3) (70 mg, 100%).

The water layer was acidified with the addition of 1 N HCl solution until pH 2, and extracted with EtOAc, washed with brine, dried, concentrated and chromatographed to give the acids (10) (27 mg, 79.4%). \( R_{f} 0.19 \) (EtOAc : Hex = 1 : 2); \([\alpha]_{D}^{20} -24.4 \) (c 0.9, CHCl3); [lit.\(^{10}\) \([\alpha]_{D}^{20} = -26.4 \) (c 1.04, CHCl3)]. \(^1\)H NMR (400 MHz, CDCl3) \( \delta 1.14 \) (3H, d, J 9.0 Hz, \( \alpha \)-methyl), 2.83 (1H, m, \( \alpha \)-H), 4.75 (0.01H, d, J 8.8 Hz, anti CHOH), 5.18 (0.99H, d, J 4.0 Hz, syn CHOH). 5.42 (2H, br s, OH and CO2H), 7.35 (5H, s, aromatic). \(^1\)H NMR integration afforded a ratio syn:anti = 96 : 4. The data were consistent with those reported in the literature.\(^{10}\)

\textit{syn-(2R,3R)}- and \textit{anti-(2S,3R)}-3-Hydroxy-2-methyl-3-phenylpropanoic acid (11). Prepared from (9) (41 mg, 0.08 mmol) as same as above procedure and gave the acids (11) (10 mg, 71.9%) and the auxiliary (3) (28 mg, 100%). \( R_{f} 0.19 \) (EtOAc : Hex = 1 : 2); \([\alpha]_{D}^{20} +26.5 \) (c 0.35, CHCl3); [lit.\(^{10}\) \([\alpha]_{D}^{20} = -26.4 \) (c 1.04, CHCl3)]. \(^1\)H NMR (400 MHz, CDCl3) \( \delta 4.75 \) (0.04H, d, J 8.8 Hz, anti CHOH), 5.18 (0.96H, d, J 4.0 Hz, syn CHOH). \(^1\)H NMR integration afforded a ratio syn:anti = 82 : 18.

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