Novel Synthesis of Chiral 5-Cyanomethyl-3,4-dihydroxy-2-iodomethyltetrahydrofuran from 3-Diphenylmethyl-5-(1,2-dihydroxy-3-butenyl)isoxazolines via Iodoetheration Reaction

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3-Butenyl-isoxazolines were known as good precursors for the syntheses of new types of 5-cyanomethyl-2-iodomethyltetrahydrofuran derivatives. 5-Cyanomethyl-2-iodomethyltetrahydrofuran was synthesized from isoxazolines by electrophilic iodoetheration using iodine or iodine monochloride, which was the first example of electrophilic cleavage of isoxazoline ring by iodoetheration reaction. From the combination of this reaction and diastereoselective formation of isoxazoline in the support of magnesium chelation effect, we synthesized 5-cyanomethyl-3-hydroxy-2-iodomethyltetrahydrofuran from syn-5-(1-hydroxy-3-butenyl)isoxazolines with diastereoselectivity. We expected better diastereoselectivity could be achieved by adding one more hydroxyl group at the 2-position of butenyl group in isoxazoline close to the reaction center. First, we prepared chiral 3-diphenylmethyl-5-(1,2-dihydroxy-3-butenyl)isoxazolines (3) by 1,3-dipolar cycloaddition reaction of diphenylacetohydroximoyl chloride (1) with (3R,4R)-1,5-hexadiene-3,4-diol (2a) and meso-1,5-hexadiene-3,4-diol (2b) by the aid of magnesium chelation effect, and after O-protection of isoxazolines, iodoetheration was examined to synthesize chiral 5-cyanomethyl-3,4-dihydroxy-2-iodomethyltetrahydrofurans 6.

Diphenylacetohydroximoyl chloride (1), precursor of diphenylacetonitrile oxide was reacted with (3R,4R)-1,5-hexadiene-3,4-diol (2a) in the presence of ethylmagnesium bromide as shown in Scheme 1. The more ethylmagnesium bromide was used, the more diadduct 4a was formed in this reaction. When 2.2 equiv of ethylmagnesium bromide was used, the best result of 3a was obtained (Entry 3 in Scheme 1). In case of meso-1,5-hexadiene-3,4-diol (2b), however, only 47% of 3b was obtained (Entry 4 in Scheme 1). The isolated 3a was a single stereoisomer that thought to be syn-isomer of 5-position and a-position due to the magnesium chelation effect, but 3b must be a racemic mixture of syn-isomers according to which double bond was reacted.

The hydroxyl groups of 3a were protected with TBDMS and MOM group, and then reacted with iodine mono-chloride in dichloromethane to give 5-cyanomethyl-3,4-dihydroxy-2-iodomethyltetrahydrofurans 6 in moderate yields as shown in Scheme 2. 5a (P=TBDMS) afforded only trans-6a (P=TBDMS) without any trace of cis-6a (P=TBDMS), while 5a (P=MOM) afforded a mixture of two isomers (trans/cis, 5/1). As we expected, the bulkier TBDMS group showed better diastereoselectivity in iodoetheration. We examined the energy minimizations of trans-{}

### Scheme 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>2</th>
<th>EtMgBr(eq.)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt; (3)</th>
<th>3 : 4&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a (R&lt;sub&gt;1&lt;/sub&gt;=OH, R&lt;sub&gt;2&lt;/sub&gt;=H)</td>
<td>6.0</td>
<td>44 (3a)</td>
<td>2 : 1</td>
</tr>
<tr>
<td>2</td>
<td>2a (R&lt;sub&gt;1&lt;/sub&gt;=OH, R&lt;sub&gt;2&lt;/sub&gt;=H)</td>
<td>3.0</td>
<td>65 (3a)</td>
<td>5 : 1</td>
</tr>
<tr>
<td>3</td>
<td>2a (R&lt;sub&gt;1&lt;/sub&gt;=OH, R&lt;sub&gt;2&lt;/sub&gt;=H)</td>
<td>2.2</td>
<td>76 (3a)</td>
<td>9 : 1</td>
</tr>
<tr>
<td>4</td>
<td>2b (R&lt;sub&gt;1&lt;/sub&gt;=H, R&lt;sub&gt;2&lt;/sub&gt;=OH)</td>
<td>2.2</td>
<td>47 (3b)</td>
<td>3 : 1</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields. <sup>b</sup>Isolated ratio.
6a and cis-6a with other protection group by MM2. TBDMS-Protected 6a showed about 1 kcal difference between trans-6a and cis-6a, and MOM-protected 6a showed almost no difference between two isomers. Interestingly, 3b derived from meso-1,5-hexadiene-3,4-diol (2b) was protected with TBDMS group and the iodoetheration of 5b (P=TBDMS) with iodine monochloride afforded 1:1 mixture of trans-6b (P=TBDMS) and cis-6b (P=TBDMS). In the MM2 calculation, cis-6b (P=TBDMS) was more stable by 1.6 kcal than trans-6b (P=TBDMS). The individual five isomers of 6 such as trans-6a (P=TBDMS), trans-6a (P=MOM), cis-6a (P=MOM), trans-6b (P=TBDMS), and cis-6b (P=TBDMS) were separated, and the assignments of each proton and the relative stereochemistry of each isomer were confirmed by COSY and NOE experiment. For example, when methylene protons attached to iodine in trans-6b (P=TBDMS) appeared at 3.22 ppm was irradiated, protons on 4,5-positions (3.93-4.04 ppm) and 2,3-positions (4.28-4.34 ppm) showed 9.52% and 2.13% NOE respectively. However, when methylene protons attached to iodine in cis-6b (P=TBDMS) appeared at 3.28 ppm was irradiated, only protons on 4,5-positions (4.17-4.23 ppm) showed 5.45% NOE with 0.75% NOE of methylene attached to CN group. The weak NOE between two methylene groups was thought to be a critical evidence of cis-form. The configurations of other tetrahydrofurans 6 were confirmed by the same experiments.

As a conclusion, 3-diphenylmethyl-5-(1,2-dihydroxy-3-butenyl)isoxazoline was prepared diastereoselectively by 1,3-dipolar cycloaddition reaction of diphenylacetonitrile oxide with chiral 1,5-hexadiene-3,4-diol in the support of magnesium chloride reaction. Iodoetheration of O-protected 3-diphenylmethyl-5-(1,2-dihydroxy-3-butenyl)isoxazolines afforded the corresponding 5-cyanomethyl-3,4-diol (O-protected-hydroxyl)-2-isomethyldihydrofurans with good diastereoselectivity. From these reactions, new series of highly substituted chiral tetrahydrofurans could be synthesized.

**Experimental Section**

**General.** Unless otherwise specified, all reagents were purchased from commercial sources and were used without further purification. $^1$H NMR spectra were obtained with a Bruker AMX-500. All chemical shifts are reported in ppm downfield from internal tetramethylsilane and coupling constants are given in Hz. IR spectra were taken by a Jasco FT-IR spectrophotometer. MS spectra were recorded by EI method and HRMS spectra were measured on a Jeol JMX-DX 303 mass spectrometer. Chromatographic separations were carried out on a silica gel column (Merck silica gel 60).

**Typical procedure of 1,3-dipolar cycloaddition (Entry 3 in Scheme 1):** To a solution of (3R,4R)-1,5-hexadiene-3,4-diol (2a, 114 mg, 1.0 mmol) in dichloromethane (20 mL) was added ethylmagnesium bromide (3.0 M solution in diethyl ether, 0.74 mL, 2.2 mmol) at 0 °C and the reaction mixture was stirred for 30 min at this temperature. Diphenylacetoxyhydroximoyl chloride (246 mg, 1.0 mmol) in dichloromethane (5 mL) was added slowly by a syringe at 0 °C. The reaction mixture was stirred for 2 h at rt and saturated ammonium chloride solution (10 mL) was poured into the reaction mixture. The organic layer was extracted with dichloromethane (50 mL), washed with brine, dried over MgSO$_4$, and concentrated by a rotary evaporator. The residue was separated with silica gel chromatography (t-hexane/ethyl acetate, 2/1) to give 3a (246 mg, 76%) as a white solid.

**Scheme 2**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant</th>
<th>5</th>
<th>Yield (%) of 6</th>
<th>trans : cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a (R=OH, R'=H)</td>
<td>5a (R=OP, R=H, P=TBDMS)</td>
<td>69</td>
<td>trans only</td>
</tr>
<tr>
<td>2</td>
<td>3a (R=OH, R'=H)</td>
<td>5a (R=OP, R=H, P=MOM)</td>
<td>60</td>
<td>5 : 1</td>
</tr>
<tr>
<td>3</td>
<td>3b (R=H, R'=OH)</td>
<td>5b (R=OP, R=H, P=TBDMS)</td>
<td>68</td>
<td>1 : 11</td>
</tr>
</tbody>
</table>

*Isolated yields (trans-6 + cis-6).
1H), 4.34-4.50 (m, 2H), 4.71 (dd, 2H, J = 11.4, 7.6 Hz), 4.74 (dd, 2H, J = 11.5, 4.3 Hz); 13C NMR (CDCl3, 125 MHz) δ 18.3, 56.3, 56.4, 76.8, 77.1, 80.5, 80.8, 81.6, 96.8, 97.4, 117.1; IR (neat) 2922, 2851, 1466, 1151, 1021 cm−1; MS m/z 371 (M+), 310, 248, 119, 182.

cis-6a (P–MOM): 1H NMR (500 MHz, CDCl3) δ 2.67 (d, 2H, J = 7.0 Hz), 3.22-3.33 (m, 2H), 3.44 (s, 6H), 4.28-4.32 (m, 2H), 4.40-4.52 (m, 2H), 4.70-4.80 (m, 4H); 13C NMR (CDCl3, 125 MHz) δ 18.3, 56.3, 56.4, 76.8, 77.2, 80.5, 80.8, 81.6, 96.8, 97.4, 117.1; IR (neat) 2926, 2852, 2249, 1465, 1150, 1022 cm−1; MS m/z 371 (M+), 310, 248, 119, 182.

trans-6b (P–TBDMS): 1H NMR (500 MHz, CDCl3) δ 0.12 (s, 3H), 1.14 (s, 6H), 0.15 (s, 3H), 0.91 (s, 9H), 0.93 (s, 9H), 2.68 (dd, 1H, J = 17.3, 4.8 Hz), 2.84 (dd, 1H, J = 17.3, 7.6 Hz), 3.22 (dd, 2H, J = 5.2 Hz). 3.93-4.04 (m, 2H), 4.28-4.34 (m, 2H), 13C NMR (CDCl3, 125 MHz) δ = 4.8, −4.4, −4.3, −4.2, 7.5, 18.0, 18.3, 19.8, 25.9, 26.0, 72.9, 76.5, 76.9, 83.4, 118.3; IR (neat) 2929, 2857, 2250, 1471, 1253, 1161, 1.051 cm−1; MS m/z 512 (M+), 454, 398, 270, 241, 171.

 cis-6b (P–TBDMS): 1H NMR (500 MHz, CDCl3) δ 0.15 (s, 12H), 0.94 (s, 18H). 2.70-2.76 (m, 2H), 3.28 (d, 2H, J = 6.0 Hz), 4.17-4.23 (m, 2H), 4.26-4.29 (m, 2H); 13C NMR (CDCl3, 125 MHz) δ = 4.8, −4.6, −4.5, −4.1, 3.6, 18.4, 18.5, 20.8, 26.1, 26.2, 73.9, 74.3, 76.0, 81.9, 118.3; IR (neat) 2929, 2858, 2250, 1471, 1254, 1164, 1054 cm−1; HRMS calcd for C20H24NO4Si3H4: 511.143503, found 511.141785.

References


