Diastereoselective Reduction of β-(1,3-Dioxan-4-yl)ketones

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Stereoselective reduction of β-(1,3-dioxan-4-yl)ketones is an important step in the efficient synthesis of chiral 1,3-polyols, a typical structure of polyketides. In this study, we carried out investigations to optimize the conditions for diastereoselective reduction.

Key words: diastereoselective reduction, chiral acetal, 1,3-dioxane, 1,3-polyol, polyketide

Optically active acetals are useful chiral auxiliaries for controlling the reaction at a proximal prochiral center. Especially, the reduction of ketones bearing a chiral acetal, followed by deacetalization, is an efficient route to chiral polyols, which are prevalent in a wide range of natural products and bioactive agents (Scheme 1). Indeed, we recently demonstrated the synthesis of a chiral 1,2,4-triol, a structure found in the antifungal agent, amphotericin B, from a ketone bearing the 1,3-dioxolane moiety. In this synthesis, highly diastereoselective reduction was accomplished using LiAlH4 in the presence of LiI (Scheme 2). In this context, a method for the synthesis of 1,3-polyols is in even greater demand, as they are found in a vast range of polyketides and are regarded as a valued structure in drug discovery. However, previous studies on the reduction of β-(1,3-dioxan-4-yl)ketones, despite providing a useful template for the construction of a stereodefined 1,3-polyol motif, showed insufficient stereoselectivity (Scheme 3).

Thus, to expand our study on stereoselective polyol synthesis, we optimized the diastereoselective reduction of β-(1,3-dioxan-4-yl)ketones.

We selected 2-((2R*,4R*)-2-pentyl-1,3-dioxan-4-yl)-1-phenylethanone (6a) as the substrate for our investigations (Table 1). Initially, we used the reaction conditions from our previous synthesis (Scheme 2); however, the stereoselectivity was much lower than the previous case (Table 1, entry 1). Although the addition of Lewis acid was found to be effective (Table 1, entries 1 and 2), these reagents lowered both the selectivity and reactivity when used with other solvents (Table 1, entries 3–5). Since the use of other Lewis acids with LiAlH4 did not improve diastereoselectivity (Table 1, entry 6–14), the ability to establish diastereoselectivity was further improved on using LiBH4 (Table 1, entry 20). The diastereoselectivity was further improved on using the Lewis acids with LiBH4; Ti(Oi-Pr)4 resulted in better diastereoselectivity than LiAlH4 (Table 1, entry 21), and EuCl3 was the most effective additive among those we investigated (Table 1, entry 22). In order to establish a highly reproducible method, a solution of LiBH4 in Et2O prepared beforehand was used, and similarly good results were obtained (Table 1, entry 23).

Table 1. Diastereoselective Reduction of 2-((2R*,4R*)-2-pentyl-1,3-dioxan-4-yl)-1-phenylethanone (6a)*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Condition</th>
<th>Conv. (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiAlH4 (1 equiv), LiI (3 equiv)</td>
<td>Et2O, –78 °C, 10 h</td>
<td>97</td>
<td>5.3:1</td>
</tr>
<tr>
<td>2</td>
<td>LiAlH4 (1 equiv)</td>
<td>Et2O, –78 °C, 10 h</td>
<td>90</td>
<td>2.7:1</td>
</tr>
<tr>
<td>3</td>
<td>LiAlH4 (1 equiv), LiI (3 equiv)</td>
<td>THF, –78 °C, 10 h</td>
<td>49</td>
<td>1.6:1</td>
</tr>
<tr>
<td>4</td>
<td>LiAlH4 (1 equiv), CPME4, –60 °C</td>
<td></td>
<td>87</td>
<td>3.6:1</td>
</tr>
</tbody>
</table>

*The date will be inserted once the manuscript is accepted.
A solution of LiBH₄ in Et₂O (1.0 M) was used.

c Diastereomeric ratios were determined by 1H NMR.

b Conversions are determined by 1H NMR.

die conditions in the solvent (0.050 M).

a Reactions were run using

<table>
<thead>
<tr>
<th>Entry</th>
<th>R, R’</th>
<th>5</th>
<th>Conv. (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph, n-C₅H₁₁</td>
<td>5a</td>
<td>99</td>
<td>13:1</td>
</tr>
<tr>
<td>2</td>
<td>Ph, i-Pr</td>
<td>5b</td>
<td>99</td>
<td>12:1</td>
</tr>
<tr>
<td>3</td>
<td>Ph, Cy</td>
<td>5c</td>
<td>89</td>
<td>7:1:1</td>
</tr>
<tr>
<td>4</td>
<td>Ph, n-C₃H₇</td>
<td>5d</td>
<td>99</td>
<td>11:1</td>
</tr>
<tr>
<td>5</td>
<td>Ph, CH₂CH₂</td>
<td>5e</td>
<td>99</td>
<td>2:1:1</td>
</tr>
<tr>
<td>6</td>
<td>2-naphthyl, n-C₃H₇</td>
<td>5f</td>
<td>99</td>
<td>11:1</td>
</tr>
</tbody>
</table>

6° Diastereometric ratios were determined by ¹H NMR.

In summary, we have accomplished highly diastereoselective reduction of β-(1,3-dioxan-4-y)ketones using LiBH₄ in the presence of EuCl₃. The resulting product is a useful synthetic precursor to chiral polyols, which are found in a range of valuable bioactive compounds. Further studies on the application of this method to asymmetric synthesis of chiral polyols are currently underway in our laboratory and will be reported in due course.
Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References


(6) Procedure for Reduction of 2-((2R*,4R*)-2-Pentyl-1,3-dioxan-4-yl)-1-phenylethanol (6a)

To a 20-mL flask were added sequentially 2-((2R*,4R*)-2-pentyl-1,3-dioxan-4-yl)-1-phenylethanol (6a, 0.10 mmol), Et2O (1.8 mL), and EuCl3 (0.30 mmol). After the mixture was stirred under Ar atmosphere at –78 °C for 0.5 h, a solution of LiBH4 in Et2O (0.2 mmol, 1.0 M, 0.2 mL) was added. The resulting mixture was additionally stirred at –78 °C for 1 h. The reaction was quenched by 1 M aqueous NaOH, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na2SO4, and concentrated in vacuo. Purification by flash column chromatography (silica gel, hexane–EtOAc (v/v = 5/1)) gave (R*)-2-((2R*,4R*)-2-pentyl-1,3-dioxan-4-yl)-1-phenylethanol (5a).

(R*)-2-((2R*,4R*)-2-Pentyl-1,3-dioxan-4-yl)-1-phenylethanol (5a)

Colorless oil; yield: 99 %, dr = 13:1; TLC: Rp = 0.37 (hexane–EtOAc, 3:1).

IR (neat): 3462, 2953, 2925, 2858, 1465, 1378, 1139, 1087, 1028, 760, 700, 665 cm⁻¹.

1H NMR (500 MHz, CDCl3) δ 7.47–7.33 (m, 4H), 7.27 (m, 1H), 4.97 (dd, J = 9.5, 3.5 Hz, 1H), 4.58 (t, J = 5.5 Hz, 1H), 4.09 (ddd, J = 11.5, 5.0, 1.0 Hz, 1H), 3.92 (tt, J = 11.0, 2.5 Hz, 1H), 3.75 (dt, J = 12.0, 2.5, 1.0 Hz, 1H), 2.04 (m, 1H), 1.80–1.72 (m, 2H), 1.67–1.62 (m, 2H), 1.44–1.38 (m, 3H), 1.35–1.27 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H).

13C NMR (125.7 MHz, CDCl3) δ 144.4, 128.6, 127.7, 126.0, 102.3, 74.1, 66.7, 45.4, 35.2, 31.9, 31.7, 24.0, 22.8, 14.3.