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

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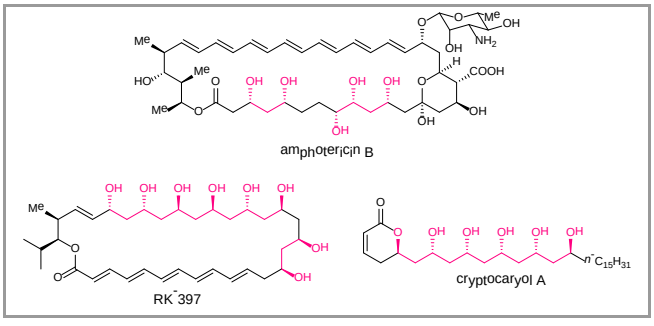
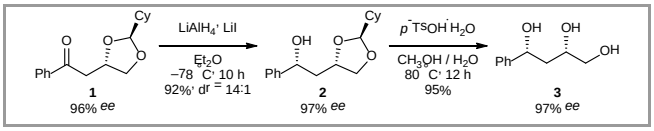
Stereoselective reduction of β-(1,3-dioxan-4-yl)ketones is an important step in the efficient synthesis of chiral 1,3-polyols, a typical structure of polyketides. In this study, we carried out investigations to optimize the conditions for diastereoselective reduction.

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

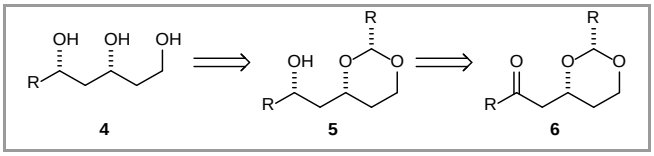
Optically active acetals are useful chiral auxiliaries for controlling the reaction at a proximal prochiral center.[1] Especially, the reduction of ketones bearing a chiral acetal, followed by deacetalization, is an efficient route to chiral polyols, which are prevalent in a wide range of natural products 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 $LiAlH_4$ in the presence of LiI (Scheme 2).[2,3] 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.[4] 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).[5] Thus, to expand our study on stereoselective polyol synthesis, we optimized the diastereoselective reduction of β-(1,3-dioxan-4-yl)ketones.



Scheme 1 Chiral polyols in bioactive compounds.



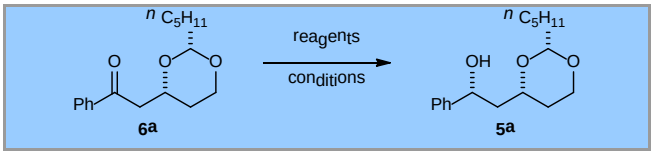
Scheme 2 Synthesis of chiral 1,2,4-triol **3**.



Scheme 3 Retrosynthetic analysis of 1,3,5-triols.

We selected 2-((2*R**,4*R**)-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 $LiAlH_4$ did not improve diastereoselectivity (Table 1, entry 6–14), other reducing agents were subsequently investigated (Table 1, entry 15–20); diastereoselectivity was improved on using $LiBH_4$ (Table 1, entry 20). The diastereoselectivity was further improved on using the Lewis acids with $LiBH_4$; $Ti(O\textit{i}\text{-}Pr)_4$ resulted in better diastereoselectivity than LiI (Table 1, entry 21), and $EuCl_3$ was the most effective additive among those we investigated (Table 1, entry 22). In order to establish a highly reproducible method, a solution of $LiBH_4$ in Et_2O prepared beforehand was used, and similarly good results were obtained (Table 1, entry 23).

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



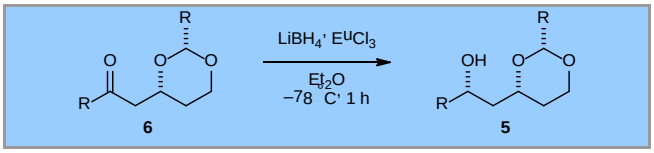
Entry	Reagent	Condition	Conv. (%)[b]	dr[c]
1	$LiAlH_4$ (1 equiv), LiI (3 equiv)	Et_2O, –78 °C, 10 h	97	5.3:1
2	$LiAlH_4$ (1 equiv)	Et_2O, –78 °C, 10 h	90	2.7:1
3	$LiAlH_4$ (1 equiv), LiI (3 equiv)	THF, –78 °C, 10 h	49	1.6:1
4	$LiAlH_4$ (1 equiv),	CPME[d], –60 °C,	87	3.6:1

	LiI (3 equiv)	24 h		
5	$LiAlH_4$ (1 equiv), LiI (3 equiv)	toluene, –78 °C, 14 h	<1	—
6	$LiAlH_4$ (1 equiv), $LiBF_4$ (3 equiv)	Et_2O, –78 °C, 5 h	94	2.7:1
7	$LiAlH_4$ (1 equiv), $ZnCl_2$ (3 equiv)	Et_2O, –78 °C, 10 h	73	1.7:1
8	$LiAlH_4$ (1 equiv), CuI (3 equiv)	Et_2O, –78 °C, 10 h	89	2.8:1
9	$LiAlH_4$ (1 equiv), $MgBr_2$ (3 equiv)	Et_2O, –78 °C, 10 h	83	1.6:1
10	$LiAlH_4$ (1 equiv), $MnCl_2$ (3 equiv)	Et_2O, –78 °C, 5 h	98	2.6:1
11	$LiAlH_4$ (1 equiv), $CaCl_2$ (3 equiv)	Et_2O, –78 °C, 5 h	96	2.4:1
12	$LiAlH_4$ (1 equiv), $LaCl_3$ (3 equiv)	Et_2O, –78 °C, 5 h	98	2.6:1
13	$LiAlH_4$ (1 equiv), $CeCl_3$ (3 equiv)	Et_2O, –78 °C, 5 h	47	2.3:1
14	$LiAlH_4$ (1 equiv), AgOTf (3 equiv)	Et_2O, –78 °C, 5 h	35	2.4:1
15	$NaBH_4$ (2 equiv), LiI (3 equiv)	Et_2O, –78 °C, 5 h	<1	—
16	$NaBH_4$ (2 equiv), LiI (3 equiv)	MeOH, –78 °C, 5 h	71	2.5:1
17	DIBAL (2 equiv), LiI (3 equiv)	Et_2O, –78 °C, 5 h	62	2.9:1
18	Red-Al® (2 equiv), LiI (3 equiv)	Et_2O, –78 °C, 5 h	98	2.1:1
19	L-Selectride® (2 equiv), LiI (3 equiv)	Et_2O, –78 °C, 5 h	96	2.0:1
20	$LiBH_4$ (2 equiv), LiI (3 equiv)	Et_2O, –78 °C, 5 h	59	7.3:1
21	$LiBH_4$ (2 equiv), $Ti(Oi\text{-}Pr)_4$ (3 equiv)	Et_2O, –78 °C, 5 h	99	10:1
22	$LiBH_4$ (2 equiv), $EuCl_3$ (3 equiv)	Et_2O, –78 °C, 5 h	99	15:1
23	$LiBH_4$ (2 equiv),[e] $EuCl_3$ (3 equiv)	Et_2O, –78 °C, 1 h	99	13:1

[a] Reactions were run using **6a** (0.10 mmol) and the reagents under the conditions in the solvent (0.050 M).
[b] Conversions are determined by ^{1}H NMR.
[c] Diastereomeric ratios were determined by ^{1}H NMR.
[d] CPME = cyclopentyl methyl ether.
[e] A solution of $LiBH_4$ in Et_2O (1.0 M) was used.

Subsequently, the effects of substituents on the acetal carbon were investigated under the optimized conditions.[6] A substrate containing the bulky isopropyl group was also tolerated, yielding the corresponding product quantitatively with high diastereoselectivity (Table 2, entry 2); however, the cyclohexyl group resulted in lower diastereoselectivity (Table 2, entry 3). An acetal bearing the phenylethyl group also exhibited high diastereoselectivity (Table 2, entry 4). On the other hand, a substrate with no substituent on the acetal carbon exhibited modest diastereoselectivity, indicating that the presence of the substituent was important for high diastereoselectivity; the stereochemistry of the acetal carbon, which enables both substituents of the 1,3-dioxane to locate at the equatorial positions and stabilizes the conformation, also seems to help the effective coordination of the substrates to the Lewis acid (Table 2, entry 5). A substrate containing the 2-naphthyl ketone group also yielded the corresponding product in good diastereomeric ratio (Table 2, entry 6). The relative configurations of the major diastereomer **5f** were determined by X-ray analysis (see Supporting Information for details), and the configurations of all other examples were assigned analogously.

Table 2. Effects of the Substituent on the Acetal Carbon[a]



Entry	R, R’	5	Conv. (%)[b]	dr[c]
1	Ph, n-C_5H_{11}	**5a**	99	13:1
2	Ph, i-Pr	**5b**	99	12:1
3	Ph, Cy	**5c**	89	7.1:1
4	Ph, $PhCH_2CH_2$	**5d**	99	11:1
5	Ph, H	**5e**	99	2.1:1
6[d]	2-naphthyl, n-C_5H_{11}	**5f**	99	11:1

[a] Reactions were run using **6** (0.10 mmol), $LiBH_4$ (0.10 mmol, 1 M solution in Et_2O), and $EuCl_3$ (0.30 mmol) in Et_2O (0.050 M).
[b] Conversions are determined by ^{1}H NMR.
[c] Diastereomeric ratios were determined by ^{1}H NMR.
[d] Reaction was run using **6f** (0.3mmol), $LiBH_4$ (0.30 mmol, 1 M solution in Et_2O), and $EuCl_3$ (0.90 mmol) for 2.5 h in Et_2O (0.050 M).

In summary, we have accomplished highly diastereoselective reduction of β-(1,3-dioxan-4-yl)ketones using $LiBH_4$ in the presence of $EuCl_3$. 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.

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(6) **Procedure for Reduction of 2-((2*R**,4*R**)-2-Pentyl-1,3-dioxan-4-yl)-1-phenylethanone (6a)**
To a 20-mL flask were added sequentially 2-((2*R**,4*R**)-2-pentyl-1,3-dioxan-4-yl)-1-phenylethanone (**6a**, 0.10 mmol), Et_2O (1.8 mL), and $EuCl_3$ (0.30 mmol). After the mixture was stirred under Ar atmosphere at –78 °C for 0.5 h, a solution of $LiBH_4$ in Et_2O (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 Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (silica gel, hexane–EtOAc (v/v = 5/1)) gave (*R**)-2-((2*R**,4*R**)-2-pentyl-1,3-dioxan-4-yl)-1-phenylethanol (**5a**).
(*R)-2-((2*R**,4*R**)-2-Pentyl-1,3-dioxan-4-yl)-1-phenylethanol (5a)**
Colorless oil; yield: 99 %, dr = 13:1; TLC: R_f = 0.37 (hexane–EtOAc, 3:1).
IR (neat): 3462, 2953, 2925, 2858, 1465, 1378, 1364, 1139, 1087, 1028, 760, 700, 665 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$) 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 (ddt, *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).
^{13}C NMR (125.7 MHz, $CDCl_3$) 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.
HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{27}O_3$: 279.1955; found: 279.1945.