Diastereoselective Reduction of 2-Acyl-1,3-dioxanes Derived from *D*-Glucose

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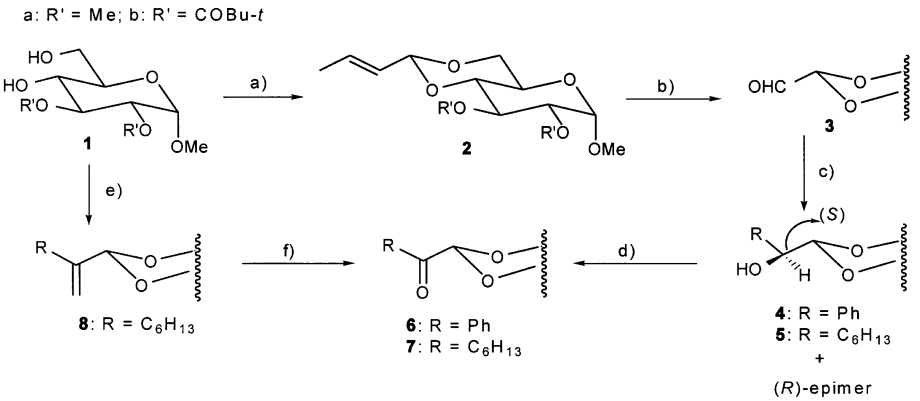
The diastereoselective addition of organometallic reagents to carbonyl compounds bearing a chiral auxiliary is a useful method for asymmetric synthesis. Especially, various types of 2-acyl-1,3-oxathianes,[1] 1,3-oxazines,[2] 1,3-oxazolidines[3] or 1,3-dioxolanes[4] have been employed for the asymmetric synthesis of α-hydroxy aldehydes. Recently, Bailey reported the highly diastereoselective additions of Grignard reagents to 2-acyl-1,3-dioxanes derived from simple 1,3-diols.[5] This report prompted us to disclose our own results on the diastereoselective reduction of 2-acyl-1,3-dioxanes derived from *D*-glucose.

Aromatic and aliphatic ketones used for our study were prepared according to Scheme 1. The known diol **1a**[6] was condensed with crotonaldehyde to give acetal **2a**, which was converted to aldehyde **3a** upon treatment with ozone/Me_2S. The resulting crude **3a** was allowed to react with PhMgBr and $C_6H_{13}MgBr$ in ether to give the (*R*)-carbinols **4a** and **5a** in 60% de and 65% de, respectively. Subsequent oxidation with Jones reagent gave ketones **6a** and **7a**. Similarly, ketone **6b** was prepared starting from diol **1b**.[2] Remarkably, the addition of PhMgBr (ether, -78 °C) to aldehyde **3b** was highly diastereoselective, giving the (*R*)-carbinol **4b** in 96% de. Aliphatic ketones could be also prepared in a different way: diols **1a** or **1b** were condensed with α-substituted acrolein[7] to provide alkenes **8a** or **8b**, which were converted to ketones **7a** or **7b** *via* ozonolysis. Ketone **7a** prepared in two different ways showed the identical spectroscopic properties.

After securing ketones, we studied the diastereoselectivity in the reduction of these ketones, as shown in Table 1. Scanning the Table 1 reveals that high degree of diastereoselectivity can be obtained with a suitable reducing agent, except aliphatic ketone **7a** having *O*-methyl groups. For example, bulky reducing agents such as L-Selectride® (entry 7) and LiAlH(OBu-*t*)$_3$ (entry 8) showed excellent selectivity of 96% de in the reduction of phenyl ketones **6a** and **6b**, respectively. Curiously, L-Selectride® was nonselective in the reduction of **6b**. Also, aliphatic ketone **7b** was reduced with LiAlH(OBu-*t*)$_3$ or Bu_4NBH_4 in 80% de (entries 8, 12). DIBAL-H (diisobutylaluminum hydride) gave the alcohol having the opposite configuration in the case of ketone **6b** (entry 10).

It is necessary to hydrolyze the acetal group to retrieve α-hydroxy aldehyde derivative and also determine the absolute configuration of the new stereogenic center created in the reduction reaction. To this end, the alcohol **4a** obtained from L-Selectride® reduction was protected with benzyl group and the resulting benzyl ether was subjected to various deprotection conditions. Unfortunately, the acid-catalyzed hydrolysis using various reagents was unsuccessful.[8] Also, the oxidative deprotection using ozone[9] could not cleave the acetal group. Therefore, we resorted to the following indirect method. Each of (*R*)- and (*S*)-2-benzyloxyphenylacetaldehyde[10] was condensed with diol **1a** to give the benzyl ether of **4a**. Comparison of the ^{1}H NMR spectra of the benzyl ethers of **4a** revealed that benzyl ether from L-Selectride® reduction was identical to that derived from (*S*)-mandelic acid, thus establishing the (*S*)-configuration of the carbinol carbon. Similarly, the carbinol carbon generated at the LiAlH(OBu-*t*)$_3$ reduction of ketone **6b** was found to have the (*S*)-



Scheme 1. a) crotonaldehyde, *p*-TsOH, benzene, reflux, 1 h, 72% (**2a**), 85% (**2b**); b) O_3, CH_2Cl_2, -78 °C then Me_2S, 90% (**3a**), 95% (**3b**); c) PhMgBr or $C_6H_{13}MgBr$, ether, -78 °C, 0.5 h, 85% (**4a**), 96% (**4b**), 85% (**5a**); d) Jones reagent, acetone, 37% (**6a**), 40% (**6b**), 45% (**7a**); e) H_2C=C(R)CHO, *p*-TsOH, benzene, reflux, 3 h, 42% (**8a**), 45% (**8b**); f) O_3, CH_2Cl_2, -78 °C then Me_2S, 66% (**7a**), 75% (**7b**).

Table 1. Diastereoselectivity in the reduction of 2-Acyl-1,3-dioxanes derived from *D*-Glucose[a,b]

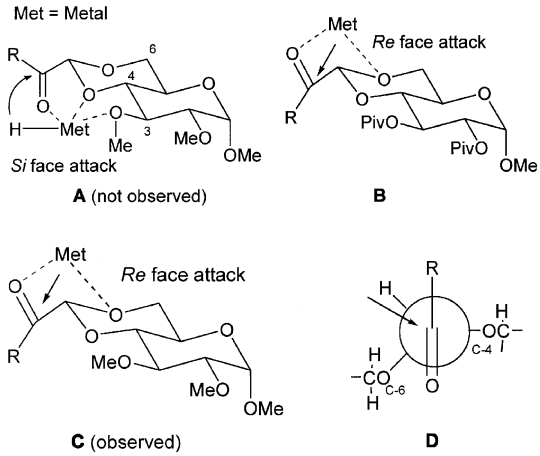
Entry	Reducing agents	Conditions	Ketone **6a**	Ketone **6b**	Ketone **7a**	Ketone **7b**[c]
1	$NaBH_4$	EtOH, 20 °C, 1 h	50	40	30	20
2	$LiBH_4$	THF, 0 °C, 2 h	70	20	40	20
3	$Zn(BH_4)_2$	Ether, 0 °C, 1 h	50	30	35	10
4	$LiAlH_4$	Ether, -78 °C, 2 h	70	decomposed	35	decomposed
5	$LiAlH_4$	THF, -78 °C, 2 h	65	decomposed	35	decomposed
6	L-Selectride®	Ether, -78 °C, 2 h	80	0	20	60
7	L-Selectride®	THF, -78 °C, 2 h	96	0	0	20
8	$LiAlH(OBu\text{-}t)_3$	Ether, -78 °C, 2 h	80	96	0	80
9	$LiAlH(OBu\text{-}t)_3$	THF, -78 °C, 2 h	75	96	10	50
10	DIBAL-H	Toluene, -78 °C, 2 h	30	-60[d]	-10[d]	-10[d]
11	BH_3SMe_2	THF, 0 °C, 1 h	20	0	20	20
12	Bu_4NBH_4	CH_2Cl_2, 20 °C, 3 h	20	60	10	80

[a]Diastereoselectivity was determined by ^{1}H-NMR spectroscopy. [b]Isolated yields were greater than 90%. [c]The absolute configuration of the carbinol product was inferred from the stereochemical model **B**. [d]Minus sign indicates the formation of (*R*)-isomer as a major product.

configuration, based on the comparison of the ^{1}H NMR spectrum of benzyl ethers of **4b**. Also, the $LiAlH_4$ reduction of hexyl ketone **7a** gave the (*S*)-alcohol as a major product, based on the comparison of ^{1}H-NMR spectrum of its benzyl ether with that from (*R*)- and (*S*)-2-benzyloxyoctanal.

We expected at the beginning of this study that two types of ketones differentiated by protective groups may behave to chelating reducing agents in different ways. In ketones with *O*-methyl groups, the oxygen atom of the carbonyl may form a tridentate chelate **A** with one oxygen atom of the acetal and C-3 *O*-methyl group, permitting *Si* face attack.[4a] On the other hand, the bulkiness and the electron-attracting nature of the pivaloyl group may disable the formation of such a tridentate chelate, instead leading to a formation of chelate **B** where the C-6 oxygen atom takes part in chelation. Then, (*R*)-epimer will be formed.

Formation of (*S*)-carbinol in the reduction of **6a** and **7a** clearly disapproves the formation of a tridentate chelate **A** and instead suggests the involvement of C-6 oxygen atom in chelation as in model **C**. It is likely that C-3 *O*-methyl group hinders the formation of complex **A** due to the steric hindrance. It has been reported that Bu_4NBH_4, diborane and DIBAL-H, which are both non-chelating agents, reduce chiral 2-acyl-1,3-oxathianes in the same sense of stereodirection according to the dipolar model.[11] In the present case, stereochemical outcomes observed in the reduction with these three reagents do not seem to be explained by single stereochemical model, because these reagents do not show the same sense of stereodirection (entries 10-11). However, in the case of Bu_4NBH_4 reduction a Felkin-Anh model **D**, which is similar to models **B** or **C**, can be evoked to explain the formation of (*S*)-alcohol. In this model, the relative bulkiness around C-4 and C-6 oxygen atoms will be important in deciding which is the larger group.[12] It is obvious that compared to ketones having *O*-methyl groups, ketones having *O*-pivaloyl group will have the larger difference in steric bulkiness around C-4 and C-6 oxygen atoms, which in turn makes the C-4 oxygen atom behave to a greater extent as a larger one. This fact is manifested by the higher diastereoselectivity observed in the reduction of ketones **6b** and **7b** than in the reduction of ketones **6a** and **7a**.



In conclusion, the present study shows that chiral 2-acyl-1,3-dioxanes derived from *D*-glucose can be reduced stereoselectively with suitable reducing agents. The direction of diastereoselective reduction can be explained in terms of Crams chelate models **B** or **C** invoking the participation of C-6 oxygen atom rather than C-3 oxygen atom when chelating agents such as L-Selectride® and $LiAlH(OBu\text{-}t)_3$ are used. Involvement of C-6 oxygen atom in chelation clearly disapproves the tridentate model **A**.[4a] Also, the addition of Grignard reagents to ketones was found to be highly stereoselective. We are currently studying the stereochemistry of this addition reaction.

References and Notes

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