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Acyloin Rearrangement of α-Hydroxy Acetals: Application to the Methyl L-Mycaroside Synthesis

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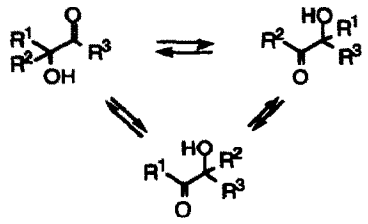
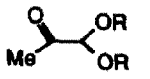
Abstract: Acid treatment of α-hydroxy acetals induced 1,2-alkyl, aryl, or alkenyl migration. An alkenyl migration product was utilized as a starting material of methyl L-mycaroside synthesis.

Acyloin rearrangement of α-hydroxy ketones and α-hydroxy aldehydes has long been known as one of the classical reactions. Since the product of this reaction is also α-hydroxy ketone, however, the reaction is subjected to an equilibration as shown in Scheme 1, and hence, the applicability of the reaction to synthetic purpose is limited only to cases where the stability differences among those isomers are large enough to give one isomer predominantly.[1] This might be a reason that the acyloin rearrangement has been studied mostly in steroid[2] or other ring system with conformational rigidity.[3] We envisioned that, if we could reduce the chance of the



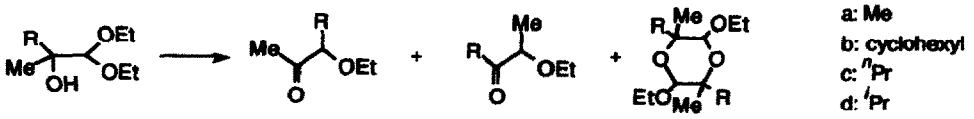
Scheme 1



1 R = Et or Bzl

equilibration, and control the migratory aptitude of the migrant, the reaction could be utilizable as a synthetic method. We thought that α-hydroxy acetal could conform to the requirement, since the primary product of the acyloin rearrangement is α-alkoxy ketone, which would have less tendency of further rearrangement than α-hydroxy ketone.[4]

The requisite α-hydroxy acetals **2** and **6** were prepared by the Grignard reaction of **1**, which are easily available by the isomerization of dihydroxyacetone in ethanol or in benzyl alcohol.[5] When **2a** - **2f** were treated with acids under conditions specified in Table 1, 1,2-alkyl or aryl migration occurred to produce **3** and **4** (Scheme 2). As shown in runs 3 and 12, the reaction with *p*-toluenesulfonic acid in benzene at room temperature gave only dimerization products **5** without any alkyl migration, while the reaction at reflux temperature in the same solvent induced the alkyl migration (runs 2 and 11).



Scheme 2

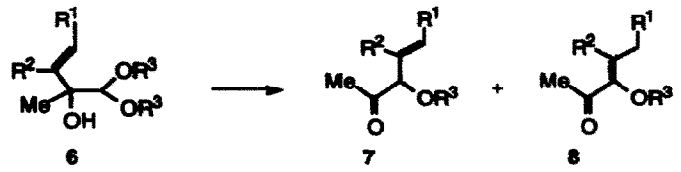
Table 1. Acid-Induced 1,2-Alkyl Migration of 2

Run	Starting material	Promoter		Cond[a]		Product and yield (%)		
		Acid	Equivalent	Solvent	Time (h)	3	4	5[b]
1	2a	$AlCl_3$	2	C	2	30	0	
2	2b	TsOH	0.3	A	2	73	0	
3	2b	TsOH	0.3	B	2	0	0	90
4	2b	$AlCl_3$	3	C	2	55	18	
5	2b	$AlBr_3$	3	C	2	63	6	
6	2b	$EtAlCl_2$	3	C	24	70	4	
7	2b	$TiCl_4$	3	C	2	44	11	
8	2b	$TiCl_2(O^iPr)_2$	3	C	2	38	5	
9	2c	$AlCl_3$	3	C	2	55	0	
10	2d	TsOH	0.3	A	2	43	0	
11	2d	TsOH	0.3	B	2	0	0	95
12	2d	$AlCl_3$	3	C	2	70	0	
13	2d	$TiCl_4$	3	C	2	50	0	
14	2e	$AlCl_3$	3	C	2	62	0	
15	2e	$TiCl_4$	3	C	2	49	0	
16	2f	TsOH	0.5	A	1	80	0	
17	2f	$AlCl_3$	1.5	C	2	79	0	
18	2f	$TiCl_4$	2	C	2	52	0	

a) A: Benzene, reflux; B: Benzene, rt; C: CH_2CH_2, −78 °C ~ rt. b) Diastereomer mixture.

As evident from the table, methyl group is reluctant to migrate, although small amounts of methyl migration products were identified in runs 4 - 9. Aluminum trihalides usually gave the best results for the 1,2-migration, while $EtAlCl_2$ required longer reaction time (run 6). Triethylaluminum was totally ineffective. Titanium(IV) chloride was inferior to AlX_3, since the yields were usually lower and some chlorinated by-products were always identified in the product.

Alkenyl groups underwent the 1,2-migration smoothly without any methyl migration, as shown in Scheme 3 and Table 2. When *p*-toluenesulfonic acid was used as a promoter, further double bond isomerization proceeded to produce α,β-enone 8, particularly in benzene (run 22). The double bond isomerization was slow in hexane (run 23), although it was still appreciable with longer reaction time (run 24). Contrastively, no double bond isomerization was observed in Lewis acid-induced reactions even after longer reaction period.



	R^1	R^2	R^3
a:	H	H	Et
b:	H	H	Bzl
c:	Me	H	Bzl
d:	H	Me	Et
e:	H	Me	Bzl
f:	Me	Me	Bzl

Scheme 3

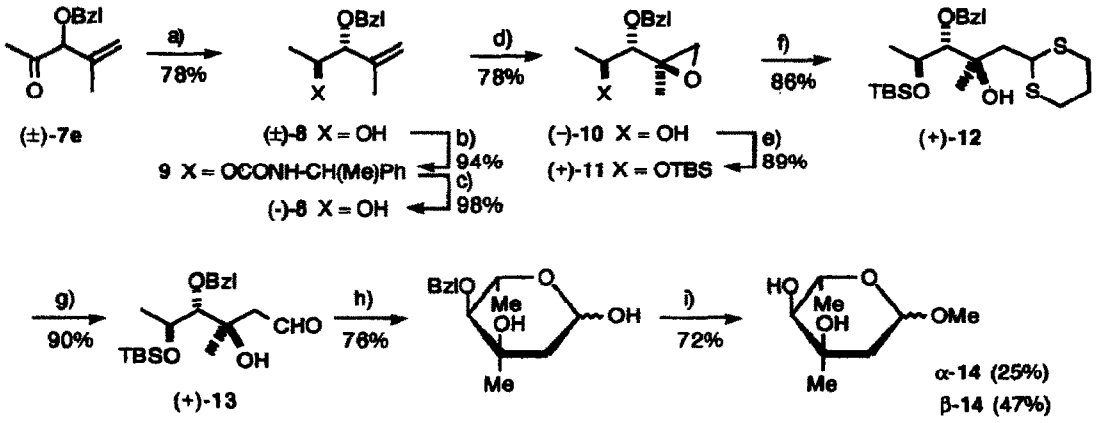
Table 2. Acid-Induced 1,2-Alkenyl Migration of 6

Run	Starting material	Promoter		Cond[a)]		Product and yield (%)	
		Acid	Equivalent	Solvent	Time (h)	7	8
19	6a	$AlCl_3$	4	C	18	37	0
20	6b	$AlCl_3$	4	C	24	20	0
21	6c	$AlCl_3$	2	D	2	86	0
22	6d	TsOH	0.3	A	10 min	40	30
23	6d	TsOH	0.3	E	10 min	49	2
24	6d	TsOH	0.5	E	2	2	30
25	6d	$TiCl_4$	1.5	C	2	47	0
26	6e	$AlCl_3$	2	D	1	83	0
27	6f	$AlCl_3$	2	D	2	71	0

a) A and C: same as the corresponding footnotes in Table 1; D: Ether, −78 °C ~ rt; E: Hexane, −78 °C ~ rt.

The products 7 have a unique structural feature of α-alkoxy-β,γ-enone, which is generally accessible only with difficulty.[6] This structure unit is characteristic in that it is ether having vinyl and carbonyl groups attached to a chiral center. We expected it could be a convenient building block for the natural product synthesis by manipulating these functional groups. As a demonstration for the synthetic application, we accomplished a methyl mycaroside synthesis from 7e as shown in Scheme 4. Mycarose is a representative of 2,6-dideoxy saccharides which are important constituents of several antibiotics, and many homologues with various stereochemistries and branched carbon skeletons are known.[7]

Reduction of 7e with $LiAlH_4$ in ether afforded 8 with *anti*/*syn* ratio of 19 : 1, and the major isomer was isolated in pure state by column chromatography. Resolution of the racemic alcohol was effected by condensing with (−)-(*S*)-1-methylbenzyl isocyanate, followed by $LiAlH_4$ treatment. The (−)-alcohol obtained from crystalline carbamate 9 (mp 79.5 - 82 °C) was found to be optically pure by NMR analysis of its (*R*)-MTPA-ester. Epoxidation of (−)-8 by *t*-butyl hydroperoxide in the presence of vanadium catalyst afforded a diastereomer mixture of epoxide with *anti*/*syn* ratio of 5.6 : 1. The major *anti*-isomer (−)-10 was isolated by column chromatography.[8] Silyl protection and succeeding reaction with dithiane gave (+)-12, from which (+)-13 was prepared. Deprotection of the silyl group followed by Pd/C-catalyzed hydrogenation in methanol afforded methyl L-mycaroside 14. Column chromatography afforded α-isomer (25%) {$[\alpha]^{18}_D = -120$ ° (c = 0.2, CH_2Cl_2), lit:[9] $[\alpha]^{20}_D = -138$ ° (c = 0.2, CH_2Cl_2)} and β-isomer (47%) {$[\alpha]^{18}_D = +39$ ° (c = 1, $CHCl_3$), lit:[10] $[\alpha]^{25}_D = +54$ ° (c = 2.3, $CHCl_3$), lit:[11] $[\alpha]^{25}_D = -52.8$ ° (c = 1, $CHCl_3$) for β-D-isomer)}. Both anomers showed identical NMR spectra with those of reported.[9, 11] The accomplishment of the synthesis confirms the stereochemistries of all the intermediates.



a) $LiAlH_4$ / Et_2O; b) (-)-(*S*)-1-methylbenzyl isocyanate / neat; c) $LiAlH_4$ / THF;
d)TBHP / $VO(acac)_2$ / CH_2Cl_2; e) TBSCl / imidazole / DMF; f) 1,3-dithiane / ^nBuLi / THF / HMPA;
g) HgO / $HgCl_2$ / H_2O-MeCN; h) TBAF / THF; i)10%-Pd / C / MeOH

Scheme 4

Typical Experimental Procedure of 1,2-Alkenyl Migration: To a suspension of $AlCl_3$ (585 mg, 4.4 mmol) in diethyl ether (80 ml) was added a solution of **6e** (687 mg, 2.2 mmol) in ether (20 ml) at −78 °C under nitrogen atmosphere. The mixture was slowly warmed up to rt, and stirred for 1 h. The reaction mixture was quenched with $NaHCO_3$ aqueous solution, and the product was extracted with ether. After dried over $MgSO_4$, solvent was removed, and the residue was purified by column chromatography to afford **7e** (375 mg, 83% yield).

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