A NOVEL SYNTHESIS OF A 2,8-DIOXABICYCLO[3.2.1]OCTANE SKELETON FROM A 2,5-DIALKYLTETRAHYDROFURAN DERIVATIVE

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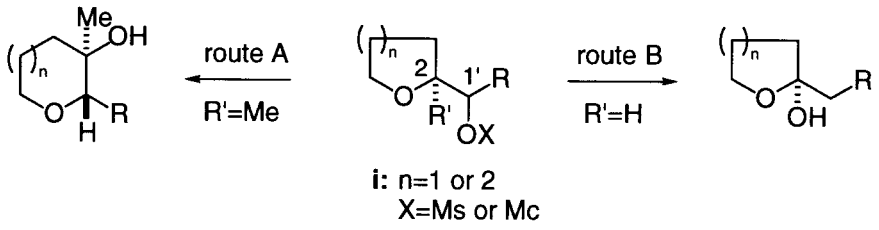
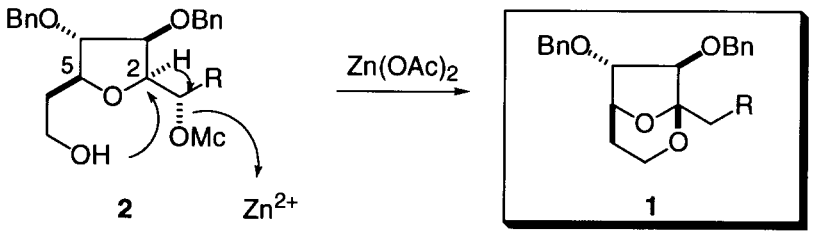
Abstract - A unique method for the construction of 6,7-dihydroxy-2,8-dioxabicyclo[3.2.1]octane, a core component of zaragogic acids, was developed based on zinc acetate-mediated rearrangement reaction of a 2,5-dialkyltetrahydrofuran derivative having a 1'-monochlate on the C2-side chain.

The 2,8-dioxabicyclo[3.2.1]octane system (**1**) is often found in natural products; as a representative example, zaragogic acids, powerful squalene synthase inhibitors, include the 5,6-bicyclic acetal system as a core component.[1] In relation to total synthesis of these natural products,[2] many approaches to such a unique ring system have been reported.[1,3] The synthetic examples reported so far have mainly relied on acid-catalyzed internal acetalization of ketones having a 1,3-diol moiety. On the other hand, several unique methods for the construction of this system have also been developed.[4] Recently, we developed a novel rearrangement-ring expansion[5a-d] (Scheme 1, route A) and/or rearrangement-ring opening reaction[5e] (Scheme 1, route B) of cyclic ethers (**i**), having a C1'-leaving group (mesylate or monochlate[6]) on the C2-side chain, with zinc acetate.

Scheme 1

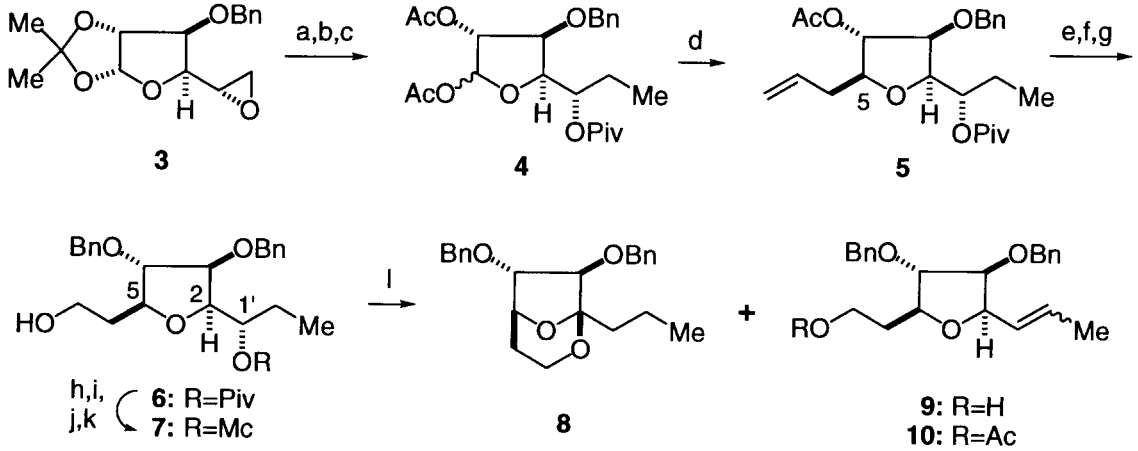


Scheme 2



Based on these results, we anticipated that if this reaction could be applied to a cyclic ether (**2**) with a hydroxyethyl group at the C5-position, an intramolecular rearrangement-cyclization would take place to produce the 2,8-dioxabicyclo[3.2.1]octane derivative (**1**) (Scheme 2). We now report a unique and unprecedented method for the construction of 5,6-bicyclic acetal (**1**) from the tetrahydrofuran derivative (**2**). To examine this unique route for the construction of the 5,6-bicyclic acetal system (**1**), we chose a 2,3-dibenzyloxytetrahydrofuran (**7**) as the requisite substrate, which has a hydroxyethyl group at the C5-position and a 1'-monochlate[6] on the C2-side chain. The synthesis started with the known epoxide (**3**),[7] prepared from D-glucose (Scheme 3). The epoxide (**3**) was converted into a 2:3 mixture of the α- and β-diacetates (**4**)[8] by the addition of Me_2CuLi, protection of the hydroxyl group, and acylation. The mixture **4**, without separation, was subjected to the next stereoselective *C*-allylation (Table 1). The best

Scheme 3



Reagents and conditions: (a) Me_2CuLi, ether, -78 °C (88%); (b) PivCl, DMAP, pyridine-CH_2Cl_2, rt; (c) Ac_2O-AcOH-H_2SO_4 (15:15:1), 0 °C (78%, 2 steps); (d) allylTMS, TMSOTf, CH_2Cl_2, -15~0 °C (93%); (e) K_2CO_3, MeOH, rt (96%); (f) BnBr, NaH, Bu_4NI, DMF, 0 °C; (g) O_3, MeOH, CH_2Cl_2; $NaBH_4$ (75%, 2 steps); (h) TrCl, 2,6-lutidine, CH_2Cl_2, rt; (i) $LiAlH_4$, ether, 0 °C; (j) McCl, 2,6-lutidine, CH_2Cl_2, rt; (k) 5%HCl-MeOH-CH_2Cl_2, rt (79% from **6**); (l) 4 equiv. of $Zn(OAc)_2$, DMF, 100 °C (32% for **8**, ~17% for **9**).

Table 1. *C*-Allylation of the Furanose Derivatives (**4**) with Allyltrimethylsilane

Run	Conditions[a]	Ratio[b] (β/α)	Yield (%)
1.	BF_3·Et_2O, CH_2Cl_2, 0 °C→rt, 18 h	6/1	68[c]
2.	BF_3·Et_2O-TMSOTf (1:1), MeCN, 0 °C, 2 h	2/1	77
3.	BF_3·Et_2O-TMSOTf (1:1), CH_2Cl_2, 0 °C→rt, 18 h	12/1	79[c]
4.	TMSOTf,[d] CH_2Cl_2, -10 °C→rt, 18 h	12/1	83
5.	TMSOTf, CH_2Cl_2, -15→0 °C, 2 d	19/1	93

[a]5.0 Equiv. of allyltrimethylsilane and 1.0 equiv. of Lewis acid were employed. [b]The ratio was determined by the ^{1}H-NMR analyses. [c]12~14% of deacetylated product (β/α = 9/2~3/2) was also isolated. [d]0.3 Equiv. of the reagent was employed.

Figure 1

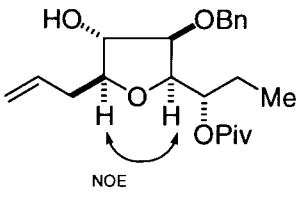


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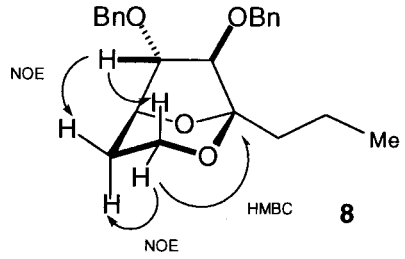
Figure 2



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result (Table 1, Run 5) was obtained using allyltrimethylsilane (5 equiv.) in the presence of TMSOTf (1 equiv.) in CH_2Cl_2 at −15 ~ 0 °C, stereoselectively giving the *C*-allyl derivative (**5**) in 93 % yield (β/α = 19/1). The newly formed C5-stereochemistry of **5** was determined by the NOE experiments of the corresponding 4-hydroxy derivative (**11**) (Figure 1), which was prepared from **5** by treatment with K_2CO_3 in MeOH. After hydrolysis and benzylation, **5** was subject to ozonolysis followed by reductive work-up with $NaBH_4$, giving an alcohol (**6**). The alcohol (**6**) was converted into a monochlate (**7**) in 79% overall yield by a four -step sequence: (1) tritylation of the alcohol; (2) $LiAlH_4$ reduction of the pivalate; (3) sulfonylation[6] with $ClCH_2SO_2Cl$ (MeCl); and (4) hydrolysis of the trityl group.

With the requisite substrate (**7**) in hand, our attention was focused on the conversion of the tetrahydrofuran (**7**) into the 5,6-bicyclic acetal system. The reaction of **7** with $Zn(OTf)_2$ and $Sc(OTf)_3$ provided a complex mixture, while $Zn(OAc)_2$ gave a promising result.[5d] After several examinations, the best result was obtained using DMF as the solvent (Table 2, Run 4). Treatment of **7** with 4 equiv. of $Zn(OAc)_2$ in DMF at 100 °C furnished the desired 2,8-dioxabicylo[3.2.1]octane (**8**)[9] in 32% yield along with an olefin (**9**) (~17%).[10] The structure of **8** was confirmed by ^1H NMR, NOE, and HMBC analyses (Figure 2).

Table 2. $Zn(OAc)_2$-Mediated Rearrangement of **7**[a]

Run	Solvent	Temp.(°C)	Yield (%)		
			8	**9**	**10**
1.	aq. AcOH	80	10	-	16
2.	AcOH	100	-	-	41
3.	2-Methoxyethanol	100	10	-	-
4.	DMF	100	32	17	-
5.	DMSO	100	trace	23	-
6.	HMPA	100	11	-	-

[a]4.0 Equiv. of $Zn(OAc)_2$ was employed.

In conclusion, a novel method for the construction of the 2,8-dioxabicyclo[3.2.1]octane derivative (**8**) from 2,5-dialkyltetrahydrofuran (**7**) was demonstrated based on the $Zn(OAc)_2$-mediated rearrangement reaction.

ACKNOWLEDGMENTS

This work was supported in part by Special Project Funding for Basic Science (Essential Reaction) from RIKEN. We thank Dr. H. Koshino for the NMR spectral measurements, Ms. K. Harata for the mass

spectral measurements.

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8. All new compounds were fully characterized by IR, NMR, and high-resolution mass spectra.
9. **8**: $[\alpha]_D^{24}$ +3.3° (*c* 0.40, $CHCl_3$), ^1H (400 MHz, $CDCl_3$) δ 1.32 (m, 4-Heq), 2.23 (m, 4-Hax), 3.91 (m, 3-Heq), 3.93 (m, 7-H), 3.98 (d, J = 2.0 Hz, 6-H), 4.20 (ddd, J = 12, 12, and 3.9 Hz, 3-Hax), 4.31 (br s, 5-H); ^{13}C (100MHz, $CDCl_3$) δ 28.7 (C-4), 60.3 (C-3), 77.7 (C-5), 86.0 (C-6), 88.4 (C-7), 105.3 (C-1). HRMS Calcd. for $C_{23}H_{29}O_4$ (MH^+) 369.2066, found 369.2068.
10. A trace amount of **8** was obtained from the C-1' epimer of **7** under the same conditions.

Received, 22nd October, 1999