

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

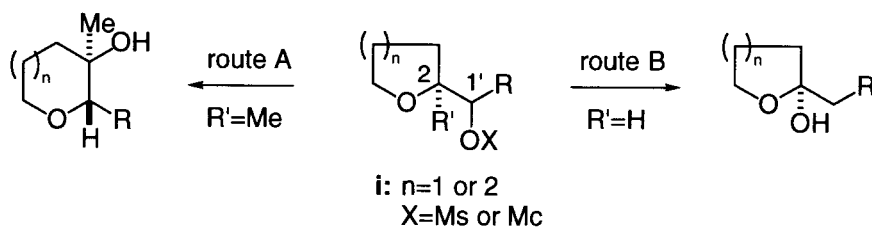
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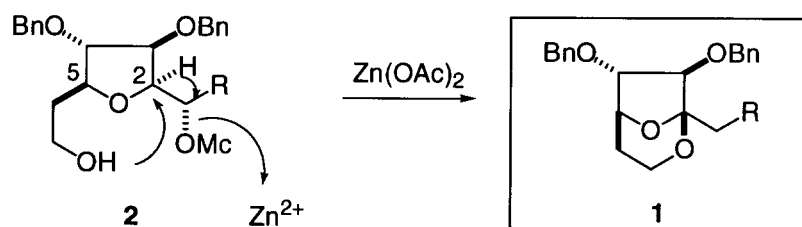
Abstract - A unique method for the construction of 6,7-dihydroxy-2,8-dioxabicyclo[3.2.1]octane, a core component of zaragolic acids, was developed based on zinc acetate-mediated rearrangement reaction of a 2,5-dialkyltetrahydrofuran derivative having a 1'-monochlate on the C2-side chain.

The 2,8-dioxabicyclo[3.2.1]octane system (**1**) is often found in natural products; as a representative example, zaragolic 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^{5c} (Scheme 1, route B) of cyclic ethers (**i**), having a C1'-leaving group (mesylate or monochlate⁶) on the C2-side chain, with zinc acetate.

Scheme 1

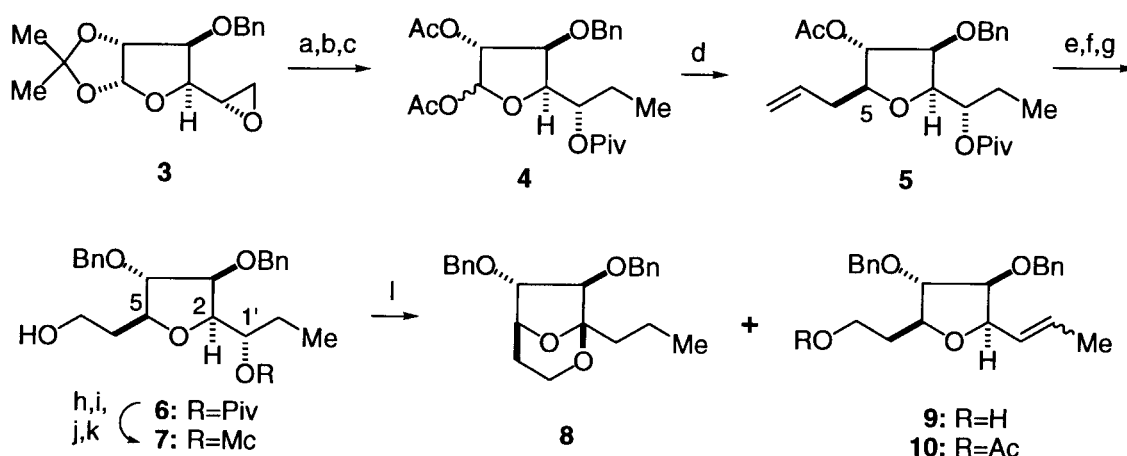


Scheme 2



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'-monochlate⁶ 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 , $-15\sim 0^\circ\text{C}$ (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 $\text{Zn}(\text{OAc})_2$, 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.	$\text{BF}_3\cdot\text{Et}_2\text{O}$, CH_2Cl_2 , $0^\circ\text{C}\rightarrow\text{rt}$, 18 h	6/1	68 ^c
2.	$\text{BF}_3\cdot\text{Et}_2\text{O}$ -TMSOTf (1:1), MeCN, 0°C , 2 h	2/1	77
3.	$\text{BF}_3\cdot\text{Et}_2\text{O}$ -TMSOTf (1:1), CH_2Cl_2 , $0^\circ\text{C}\rightarrow\text{rt}$, 18 h	12/1	79 ^c
4.	TMSOTf, ^d CH_2Cl_2 , $-10^\circ\text{C}\rightarrow\text{rt}$, 18 h	12/1	83
5.	TMSOTf, CH_2Cl_2 , $-15\rightarrow 0^\circ\text{C}$, 2 d	19/1	93

^a5.0 Equiv. of allyltrimethylsilane and 1.0 equiv. of Lewis acid were employed. ^bThe ratio was determined by the ^1H -NMR analyses. ^c12~14% of deacetylated product ($\beta/\alpha = 9/2\sim 3/2$) was also isolated. ^d0.3 Equiv. of the reagent was employed.

Figure 1

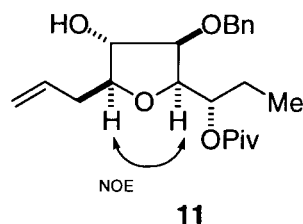
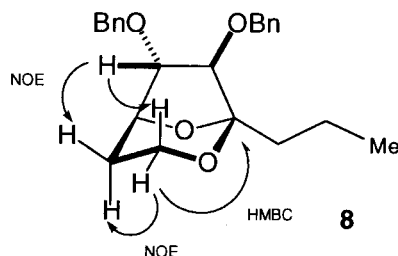


Figure 2



result (Table 1, Run 5) was obtained using allyltrimethylsilane (5 equiv.) in the presence of TMSOTf (1 equiv.) in CH_2Cl_2 at $-15 \sim 0^\circ\text{C}$, stereoselectively giving the C-allyl derivative (**5**) in 93 % yield ($\beta/\alpha = 19/1$). 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) sulfonylation⁶ with $\text{ClCH}_2\text{SO}_2\text{Cl}$ (McCl); 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 $\text{Zn}(\text{OTf})_2$ and $\text{Sc}(\text{OTf})_3$ provided a complex mixture, while $\text{Zn}(\text{OAc})_2$ 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 $\text{Zn}(\text{OAc})_2$ in DMF at 100°C furnished the desired 2,8-dioxabicyclo[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. $\text{Zn}(\text{OAc})_2$ -Mediated Rearrangement of **7**^a

Run	Solvent	Temp.($^\circ\text{C}$)	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	-	-

^a4.0 Equiv. of $\text{Zn}(\text{OAc})_2$ 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 $\text{Zn}(\text{OAc})_2$ -mediated rearrangement reaction.

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8. All new compounds were fully characterized by IR, NMR, and high-resolution mass spectra.
9. **8**: $[\alpha]_D^{24} +3.3^\circ$ (c 0.40, CHCl₃), ¹H (400 MHz, CDCl₃) 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); ¹³C (100MHz, CDCl₃) 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 C₂₃H₂₉O₄ (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.

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