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A CONVENIENT PROCEDURE FOR THE PREPARATION OF FUSED RING CYCLIC ACETALS FROM 2-DEOXY-2-C-(HYDROXYALKYL)-α-D-ALTROPYRANOSIDES AND -ARABINOFURANOSIDES

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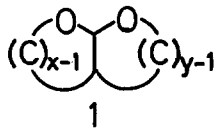
Abstract. Dimethylsulfoxide and acid catalyst promoted cyclizations of methyl 2-deoxy-2-C-(hydroxyalkyl)-α-D-altropyranosides and -arabinofuranosides leading to cis-fused ring cyclic acetals are described.

Bicyclic dioxygenated ring systems of general structure 1, e.g., 2,n-dioxabicyclo[x,y,0]alkanes, with n = 8, 9, 10; x,y = 4,4, 4,3, or 3,3, and their derivatives make up a structural part of many biological active natural products such as azadirachtin, asteltoxin, aflatoxins, and clerodanes.[1] The structural complexity and significant biological activity of these compounds have led to extensive efforts towards the synthesis of these compounds and several strategies for generating diverse cyclic acetal functionalities have been devised. In this communication, we wish to report a convenient procedure for the construction of the ring system 1 by intramolecular acetal exchange reaction which was found during the course of our studies on preparation of macrolide antibiotics from carbohydrates.



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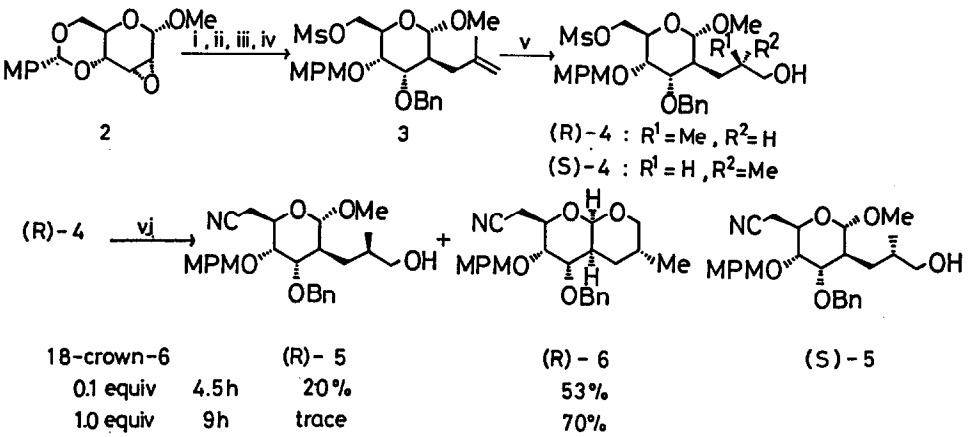
Fully protected 6-O-mesyl-2-deoxy-2-C-(2-methyl-2-propenyl)-α-D-altropyranoside (3) can be readily prepared by the reaction of 2,3-anhydroallopyranoside (2) with 2-methyl-2-propenylmagnesium chloride, followed by benzylation, regioselective acetal bond-cleavage, and subsequent mesylation.[2,3] Hydroboration-oxidation of 3 afforded a mixture of diastereoisomers [(R)-4 and (S)-4] in a ratio of about 1 : 1. In order to introduce carboxyl group at the C-6 of 4, (R)-4 was allowed to react with KCN in the presence of 18-crown-6 (0.1 equiv.) in dimethylsulfoxide (DMSO) at 60 °C for 4.5 h to afford 2,10-dioxabicyclo[4,4,0]decane derivative [(R)-6] in 53% yield along with expected 6-cyano derivative [(R)-5; 20% yield]. On prolonged heating with the use of 1 equiv. of 18-crown-6, (R)-4 gave (R)-6 in 70% yield (Scheme 1).[4]

In view of the availability of starting materials and significance of resulting fused ring cyclic acetals, we turned our attention to the cyclization reaction. In order to search the factors promoting the reaction, 2-deoxy-2-C-(3-hydroxypropyl)-4-O-mesyl-2-α-D-altropyranoside (7a) was treated with KCN

Scheme 1



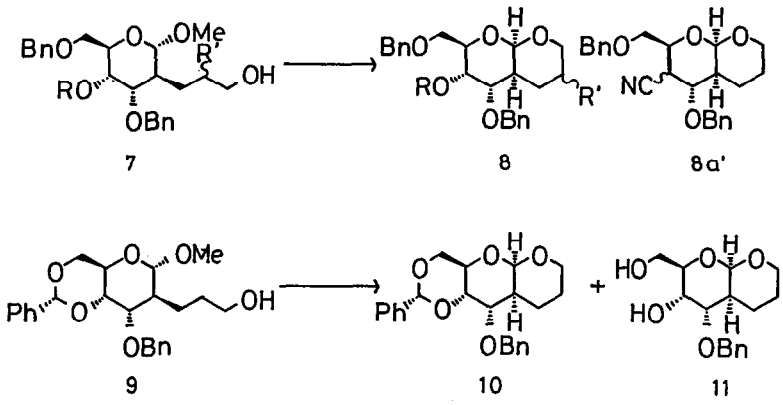
i) $CH_2=C(CH_3)CH_2MgCl$, rt, 16 h (97 %). ii) NaH, BnBr (98 %). iii) DIBAH, CH_2Cl_2, 0 °C, 2 h (70 %) or $LiEt_3BH$, $TiCl_4$, -78 °C, 0.25 h (70 %). iv) MsCl, Et_3N, 0 °C, 2 h (quant.). v) BH_3-SMe_2, THF, 0 °C, 3 h, then H_2O_2, NaOHaq, 0 °C, 1 h [99 %; (R)-4:(S)-4=48:51]. vi) KCN, 18-crown-6, DMSO. MP = 4-$MeOC_6H_4$-; MPM = 4-$MeOC_6H_4CH_2$-

in the presence of 18-crown-6 in DMSO at 60 °C for 20 h, in which a complex mixture of products was formed without any detectable formation of cyclized products (8a and/or 8a'). However, when 7a was heated in DMSO at 75 °C for 4 h in the absence of KCN and crown ethers, cyclization took place smoothly to give 8a in 77% yield. Similarly, 7b and 7e afforded 8b and 8e in good yields (Scheme 2; Table 1; entries 1, 6, 10).[5] No reaction took place when 7a was heated at 80 °C in dioxane, benzene, or tetrachloroethylene (Table 1; entries 3, 4, 5). These results indicate that DMSO facilitates intramolecular acetal exchange reaction leading to cis-fused ring cyclic acetals. Recently, Kametani and coworkers have reported that various acetals are converted into the parent carbonyl compounds in DMSO-H_2O system.[6] The results described above are consistent with their findings.

Contrary to the case of (R)-4, (S)-4 reacted with KCN under practically identical conditions used for (R)-4 giving (S)-5 in 42% yield without detectable formation of cyclized product. Dibenzyl derivative 7e used in the above reaction consists of diastereomeric mixtures in the ratio of 1 : 1.5 (HPLC), while the ratio changed to 3.5 : 1 in the recovered 7e (17%) (Table 1; entry 10). The product 8e consists of a pair of diastereomers in a ratio of 1 : 2 (HPLC).[7] These results suggest that DMSO-promoted cyclization is affected by the structure of the side chain in substrates.

Intramolecular acetal exchange reaction was effectively carried out under acidic conditions. Thus treatment of 7a in $CHCl_3$ in the presence of camphorsulfonic acid (CSA) at room temperature at 4 h and then 60 °C for 2 h afforded 8a in 83% yield (Table 1; entry 2). Similarly, 7c and 7d afforded the corresponding bicyclic derivatives (8c and 8b) in good yields (Table 1; entries 7, 8). Boron trifluoride etherate could also be utilized as effective catalyst (Table 1; entry 9). However, 4,6-O-benzylidenealtropyranoside 9 was cyclized in the presence of boron trifluoride etherate with concomitant removal of the benzylidene group to give 10 and 11 in a ratio of 1 : 2 (Table 1; entry 12).

Scheme 2



7,8	R	R'
a	Ms	H
b	H	H
c	t-BuPh$_2$Si	H
d	MPM	H
e	Ms	Me

Table 1. Cyclization of 7, 9, 12, and 14 under various conditions

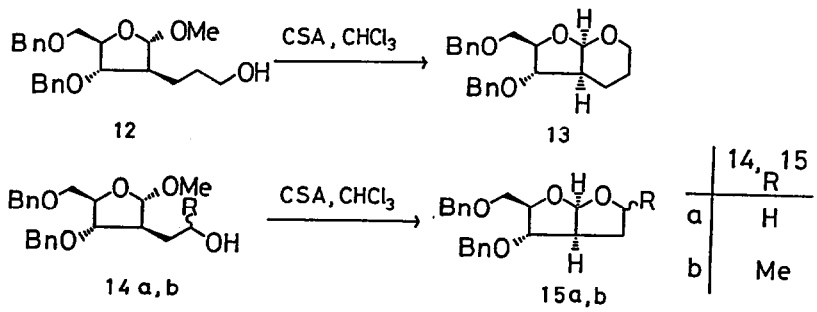
Entry	Substrate and Conditions[a]	Product (Yield/%)[b]	$J_{1,2}$/Hz
1	7a DMSO, 75 °C, 4h	8a (77)	2.44[c]
2	$CHCl_3$, CSA, rt, 4h→60 °C, 2 h	8a (83)	
3	Dioxane, 80 °C, 5 h	- (Recovery; 98%)	
4	Benzene, 80 °C, 6 h	- (Recovery; 100%)	
5	Tetrachloroethylene, 80 °C, 6h	- (Recovery; 97%)	
6	7b DMSO, 75 °C, 5.5 h	8b (88)	2.30
7	7c $CHCl_3$, CSA, rt, 5 h	8c (96)	2.97
8	7d $CHCl_3$, CSA, rt, 5 h	8b (83)	
9	$CHCl_3$, BF_3 OEt_2, 0 °C, 2 h	8b (75)	
10	7e DMSO, 70 °C, 5 h	8e (83)	1.17, 2.44
11	9 $CHCl_3$, CSA, rt, 5 h	10 (26)	2.31[c]
12	$CHCl_3$, BF_3 OEt_2, 0 °C, 2h	10 (23), 11 (44)	2.31[d]
13	12 $CHCl_3$, CSA, rt, 4 h→50 °C, 1 h	13 (88)	3.36
14	14a $CHCl_3$, CSA, rt, 3 h	15a (83)	5.49
15	14b $CHCl_3$, CSA, rt, 18 h	15b (78)	5.49

a) rt = Room temperature. b) Isolated yield. c) NOE was observed between H-1 and H-5. d) For 11.

The reaction of 2-deoxy-2-C-(hydroxyalkyl)-α-D-arabinofuranosides was next attempted. As expected, 12, 14a, and 14b were successfully converted into the corresponding bicyclic compounds (13, 15a, and 15b) respectively as shown in Scheme 3 (Table 1 entries 13, 14, 15).[8]

The work described in this paper demonstrates that various cis-fused 2,n-dioxabicyclo[x,y,0]alkanes, with n = 8, 9, or 10; x,y = 4,4, 4,3, or 3,3, can be prepared from 2-deoxy-2-C-(hydroxyalkyl)-α-D-pyranosides and -furanosides.

Scheme 3



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2) T. Asano, S. Yokota, and O. Mitsunobu, Chem. Lett., 1983, 343.

3) T. Mikami, H. Asano, and O. Mitsunobu, Chem. Lett., 1987, 2033.

4) The structure of (R)-6 was determined by NMR including NOE experiment. The structures of (R)-4 and (S)-4 were assigned based on that of (R)-6.

5) For the preparation of perhydrofuro[2,3b]furan skeleton by intramolecular acetal exchange reaction, see for example, ref 1) and K. Tadano, H. Yamada, Y. Idogaki, S. Ogawa, and T. Suami, Tetrahedron Lett., 29, 655 (1988).

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7) The absolute configurations of 7e and 8e have not yet been determined.

8) Compound 12 and 14b were prepared respectively by hydroboration-oxidation and oxymercuration-demercuration of methyl 3,5-di-O-benzyl-2-deoxy-2-C-(2-propenyl)-α-D-arabinofuranoside. The latter reaction gave rise to a mixture of diastereomeric isomers in a ratio of 43 : 57. The mixture was used in the cyclization reaction.

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