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Regioselective C–O bond cleavage reactions of acetals

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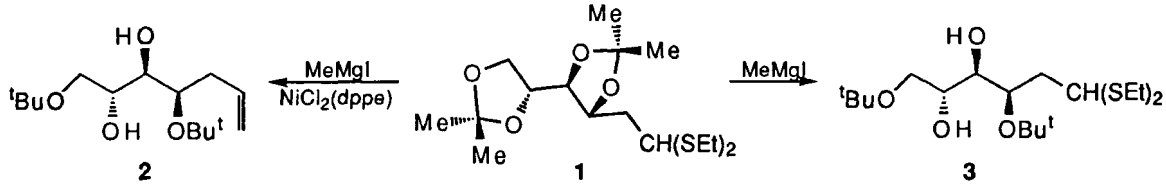
Abstract

Reactions of acetonide derivatives of monosaccharides with the Grignard reagent in benzene afford the corresponding monosaccharide derivatives having only one free hydroxy group. 1,4-di-alkoxy-(2*S*,3*S*)-2,3-butanediols are obtained from the reactions of 2*S*,3*S*-threitol bisketals with Grignard reagents or with $LiAlH_4/AlCl_3$. The reactions of benzylic acetals prepared from 1,4-dialkoxy-(2*S*,3*S*)-2,3-butanediols and aromatic aldehydes, with aryl or secondary or sterically hindered Grignard reagents give the corresponding ring-opening products in high diastereoselectivity. Other synthetic applications of such tunable chiral diols are briefly described.

Differentiation of a contiguous diol by a selective protection procedure is important in organic synthesis. Acetal functionality is one of the most useful protective groups for these diols.[1] Selective transformation of an acetal with an organometallic reagent into a hydroxyalkyl ether demonstrates a powerful arsenal for this purpose.[2] With the aid of $TiCl_4$ or aluminum reagents or the like, high stereoselectivity can be obtained from the reactions of methyl or a straight chain aliphatic nucleophile with acetals.[3] Regioselective reduction of 1,2-*O*-benzylidene derivatives of certain carbohydrates with DIBAL-H and alkylative ring-opening reactions of acetals having a neighboring hydroxy group (but not an alkoxy group) with Me_3Al have been investigated.[4,5] Presumably, a chelation model would explain the selectivity of these reactions. Although chelation assistance in the regioselective activation of a C-H bond is well documented, the application of this concept to direct the reaction of C-X bonds has been rare.[4-9] We recently uncovered the activation of the aliphatic C-S bonds by means of chelation under the nickel-catalyzed cross coupling reaction conditions.[6] During the course of this investigation, we found that the acetonide protective groups in **1** also undergo the regioselective ring-opening giving diol **2** under the reaction conditions. The dithioacetal group is activated because of the chelation of the sulfur moiety with the nickel catalyst. In the absence of the nickel catalyst, only acetonide moieties undergo the ring-opening reaction to give **3** while the dithioacetal group remains intact. In this regard, coordination of the magnesium with the oxygen atoms may occur leading to the selective cleavage of the C-O bonds. In this report, we address the generality of the regioselective ring-opening reactions of various acetals with Grignard reagents and with hydride nucleophiles.

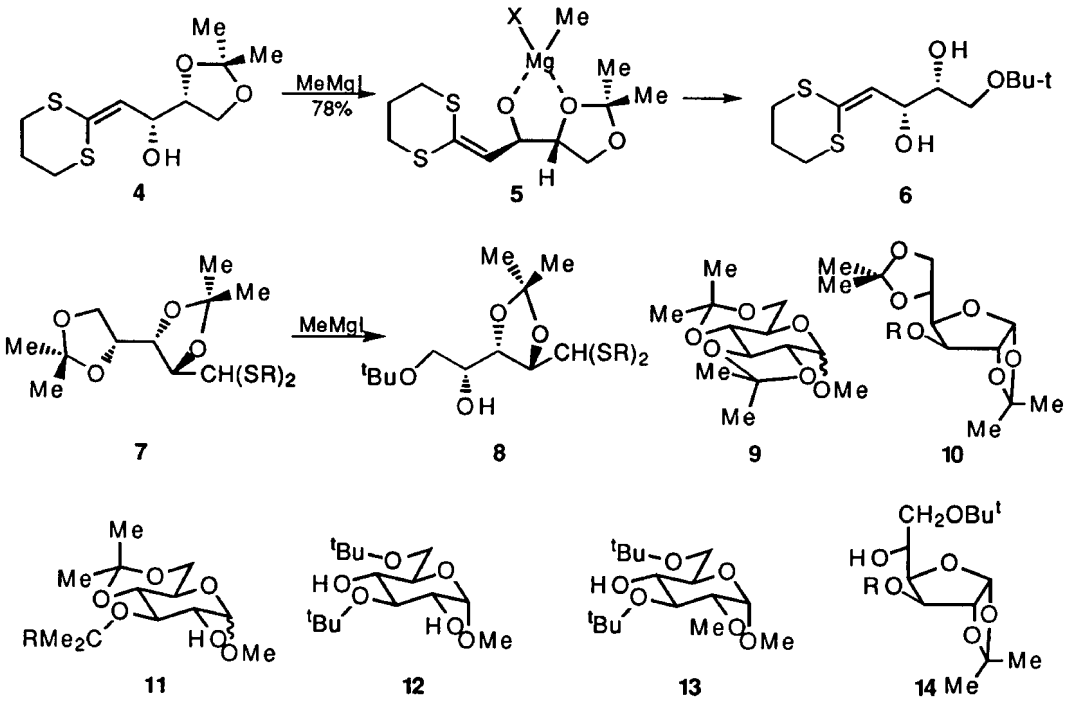


2 **1** **3**

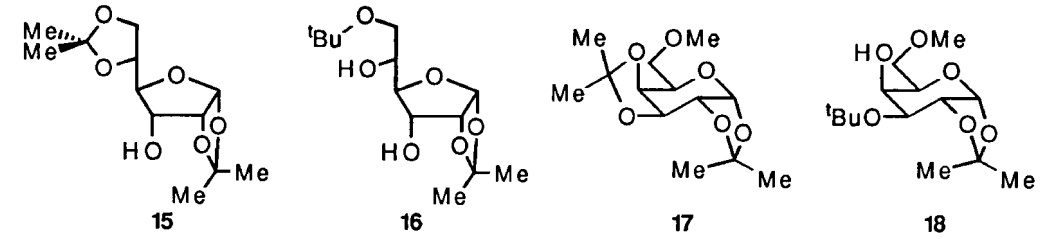
MONOSACCHARIDE DERIVATIVES HAVING ONE FREE HYDROXY GROUP

The hydroxy functions in carbohydrates are conveniently protected by acetal groups. Selective deprotection of these acetals would be particularly valuable in the derivatization of carbohydrates. Reaction of **4** with MeMgI affords the corresponding diol **6** in 78% yield. It seems likely that the chelation with magnesium leading to intermediate **5** may play a key role in controlling such selectivity. At 60 °C, bisacetonide **7** is transformed to monohydroxy derivative **8**. The two glucose acetonides are readily accessible by literature procedures. Treatment of **9** with the Grignard reagent in benzene-ether yields **11** exclusively. Interestingly, both anomeric α- and β-methoxy groups in **9** give the same cleavage pattern, liberating the 2-hydroxy derivatives **11**. The chelation of OMe group and the neighboring oxygen

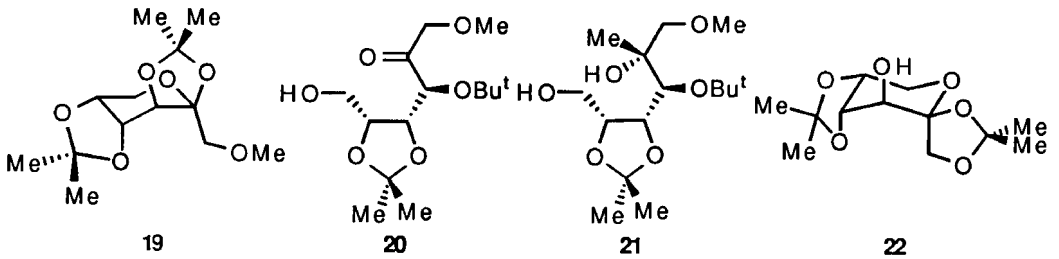
function at C_2 with magnesium may account for the results. When **9** (α-OMe) is treated with MeMgI under refluxing toluene conditions for 36 h, diol **12** is isolated in 71% yield.[7]

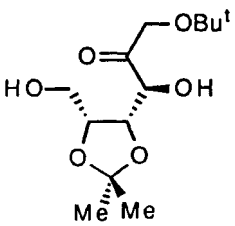


Methylation of **11** (R = Me) with MeI/NaH followed by treatment with MeMgI gives the corresponding 4-OH derivative **13** in 58% yield. The reaction of **10** (R = H) under the same conditions yields **14** having hydroxy groups at C_3 and C_5 positions. In a similar manner, treatment of **10** (R = Me) with MeMgI gives **14** (R = Me) exclusively in 68% yield. The presence of a β-hydroxy or β-methoxy group at C_3 in **10** appears not to be essential for the selectivity of this ring-opening process. Thus, the reaction of allose derivative **15** also affords 54% yield of the corresponding 5-OH product **16**. These results indicate that the chelation with the oxygen atom on the five-membered heterocycle may determine the selectivity in these reactions. The reaction with galactose derivative **17** furnishes the 4-hydroxy derivative **18** in 52% yield. Presumably, the chelation with the methoxy group at C_6 controls the regioselectivity.[8]



The transformations involving fructose derivatives are interesting. Thus, treatment of **19** with MeMgI under usual conditions gives selectively **21** in 75% yield. Apparently, the methoxy group at C_1 would assist the cleavage reaction to occur at C_2 giving a ketone intermediate **20** which further reacts with MeMgI stereoselectively to yield **21**. In a similar manner, the hydroxy group at C_3 also aids the regioselective ring-opening of the acetonide at C_2 in the reaction of **22** to afford **24** via **23**.[8]





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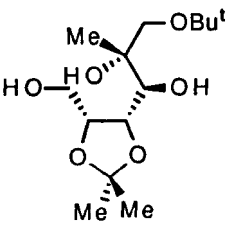

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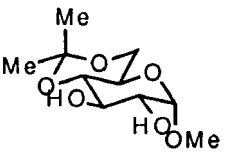

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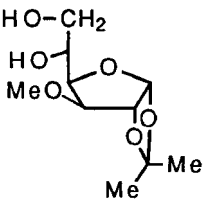

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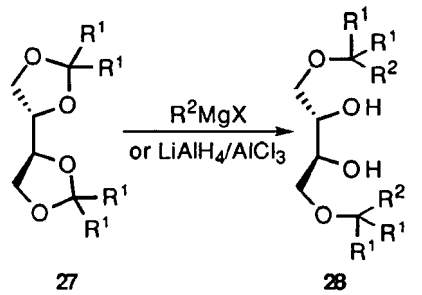
SELECTIVE DEPROTECTION OF ACETONIDES TO LIBERATE DIOLS

Trimethylsilylethyl group is a useful protective group for alcohols and can readily be removed by treatment with BF_3.[1] Upon treatment with Me_3SiCH_2MgCl, **11** yields the corresponding diol **25** selectively. Similarly, diol **26** is isolated from the reaction of **10** with Me_3SiCH_2MgCl. Presumably, intermediate **11** (R = Me_3SiCH_2) is involved; indeed, when $PhMe_2SiCH_2MgCl$ is employed, the corresponding silylethyl ether **11** (R = $PhMe_2SiCH_2$) has been isolated. This transformation provides an unprecedented procedure for the regioselective deprotection of a ketal group under basic conditions.

SYNTHESIS OF TUNABLE C_2-CHIRAL 1,2-DIOLS

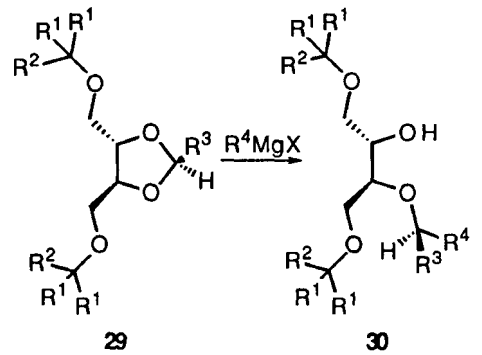
As described in the previous section, the reactions of a neighboring bis-acetonide with MeMgI afford the corresponding diols regioselectively. This strategy can be used for the synthesis of various tunable C_2-chiral diols. Thus, 1,4-di-*tert*-alkoxy-(2*S*,3*S*)-2,3-butanediols **28** (R^2 = alkyl) can be easily accessible from the corresponding L-tartaric acid-based bisketals **27**.[6] Reduction of the bisketals **27** with $LiAlH_4$-$AlCl_3$ yields the corresponding 1,4-di-*sec*-alkoxy-(2*S*,3*S*)-2,3-butanediols **28** (R^2 = H).[10,11]



27 **28**

	R^2MgX			$LiAlH_4/AlCl_3$	
R^1	R^2	%Yield	R^1	R^2	%Yield
Me	Me	89	Me	H	58
Me	Et	77	Et	H	77
Me	i-Pr	64	R^1R^1 c-C_5H_8	H	64
Me	$PhCH_2$	60			
Et	Me	85	R^1R^1 c-C_6H_{10}	H	60
R^1R^1 c-C_5H_8	Me	70			
R^1R^1 c-C_6H_{10}	Me	70			

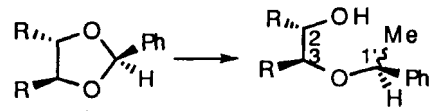
Diols **28** might demonstrate certain unique properties to serve as an auxiliary in asymmetric synthesis. First, the size of the alkoxy substituents can be tuned. Second, the oxygen atom in the alkoxy substituent can act as an additional ligand for complexation with the metallic species which would result in the enhancement of the stereoselectivity of the reaction. This advantage has been made use of in the diastereoselective ring-opening reactions of chiral acetals **29** with Grignard reagents. Treatment of (4*S*,5*S*)-**29** with cyclic secondary, aryl or sterically hindered Grignard reagents in refluxing benzene solution affords diastereoselectively the corresponding ring-opening products **30** in good yield.[10]



29 **30**

R^1	R^2	R^3	R^4	%Yield	de %
Me	Me	Ph	c-C_5H_9	83	96
Me	Me	p-PhC_6H_4	c-C_5H_9	84	95
Me	i-Pr	p-PhC_6H_4	c-C_5H_9	78	96
Me	Me	p-BrC_6H_4	c-C_5H_9	77	95
Me	Me	m-$MeOC_6H_4$	c-C_6H_{11}	80	98
Me	Me	Ph	c-C_6H_{11}	84	98
Me	Me	m-$MeOC_6H_4$	Ph	73	98
Me	Me	m-$MeOC_6H_4$	Me_3CCH_2	81	94

Several interesting features about the ring-opening reactions with the Grignard reagent are worthy of comment. These results provide the first example on the highly diastereoselective ring-opening of chiral acetals using sterically hindered or secondary cyclic Grignard reagents. Interestingly, the diastereoselectivities for the reactions of **29** with MeMgI in the presence and in the absence of $TiCl_2(OPr^i)_2$ are opposite. Presumably, the titanium reagent competes with the Grignard reagent for complexation resulting in the discrepancy in selectivity.[10] It is noteworthy that the selectivity of such titanium-promoted reaction parallels to those in the other substrates using similar conditions.[3]

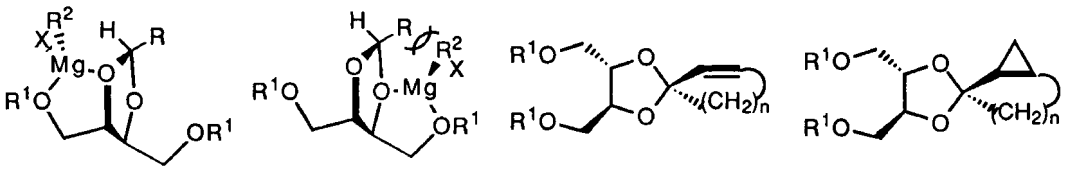


29 R = ^{t}BuOCH$_2$
31 R = Me

30
32

R	Reagent	%Yield	R/S
Me	MeMgI	82	1.8
^{t}BuOCH$_2$	MeMgI	83	0.6
^{t}BuOCH$_2$	MeMgI, $TiCl_2(OPr^i)_2$	71	2.3

As mentioned earlier, the oxygen atom in the alkoxy substituent can act as an additional ligand for complexation with the metallic species. Accordingly, complexation between the substrate **29** and the Grignard reagent may occur; and with bulky Grignard reagent, intermediate **33** would be more stable than its stereoisomer **34**. Although the actual mode of the ring-opening reaction of acetals is not yet clear, retentive displacement of the C-O bond by an alkyl group from intermediate **33** is speculated.



33 **34** **35** **36**

In order to clarify the validity of this conjecture, the reaction of (4*S*,5*S*)-**31**, which does not have the oxygen atom on the side chain for chelation, with MeMgI under similar conditions gives **32** in 82% yield with 30%de in favor of (2*S*,3*S*,1'*R*)-**32**. The selectivity is just opposite to that observed for the reactions of **29**. This discrepancy suggests that the chelation intermediate **33** may be involved in the reaction of **29** with Grignard reagents leading to the displacement of a C-O bond by a C-C bond.[10]

Other synthetic usage of the tunable chiral diols has been executed. For example, excellent diastereoselectivity (up to 98%de) has been observed in the Simmons-Smith cyclopropanation of the cyclic enone-ketals **35** to give **36**.[12] Further applications on the asymmetric synthesis using such tunable chiral auxiliary are in progress in our laboratory.

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