Selective Deprotection of Acetals with Me_3SiCH_2MgCl. Peterson-Type Olefination of Acetals†

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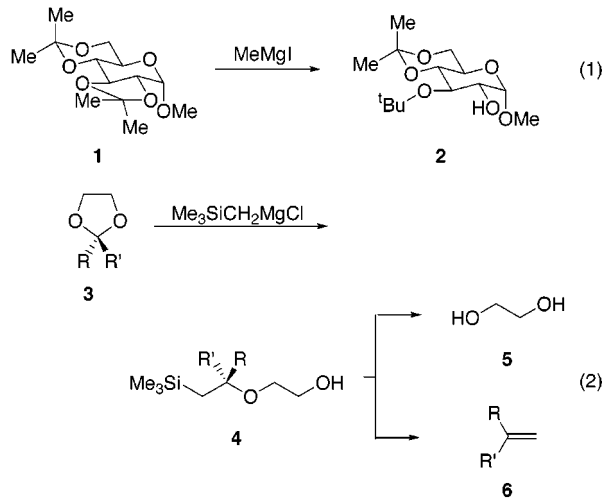
By employing the chelation strategy, treatment of an acetal of a contiguous diol with Me_3SiCH_2MgCl liberates the corresponding diol regioselectively. In addition, acetals of different structural variety are transformed upon treatment with Me_3SiCH_2MgCl and ZnI_2 into the corresponding olefination products in good yield.

The acetal functionality can be considered as a protected carbonyl group.[1] For a cyclic acetal, it can also be viewed as a protected contiguous diol. It is well documented that Grignard reagents can react with cyclic acetals in aromatic hydrocarbon solvent. This kind of transformation serves as a useful entry for the synthesis of a variety of alkoxyalcohols regio- and/or stereoselectively (eq 1)[2−4] and provides a powerful arsenal to selectively differentiate the hydroxy groups of a contiguous diol. It is noteworthy that chelation plays a pivotal role to direct the regioselectivity of the ring-opening process of cyclic acetals.[3,4] The reaction has been extensively applied for the synthesis of a variety of partially protected carbohydrates, inositols, and other polyols.[2−4] A β-silylethyl group is commonly used to protect the hydroxy functionality and can readily be removed by treatment with BF_3.[5] It is envisaged that treatment of an acetal of a contiguous diol **3** with R_3SiCH_2MgCl would lead to the corresponding β-silyl-substituted alkoxy alcohol **4**, which could be converted to the corresponding diol **5** (eq 2). This procedure would serve as an alternative method to regenerate the diols from the corresponding acetals. On the other hand, it is known that a β-silyl-substituted alcohol can readily be transformed into an alkene upon treatment with an acid.[6] Consequently, elimination of the alkoxy moiety and the silyl group from **4** may produce the corresponding olefination product **6** (eq 2). In other words, it is conceivable to convert an acetal directly into the corresponding alkene with a silylmethyl Grignard reagent. In this paper, we report the details on the use of the above strategies to transform the acetal functionality into the corresponding diol upon treatment with Me_3SiCH_2MgCl. In addition, a direct conversion of an acetal group into the corresponding terminal alkene will also be disclosed.[7]



Results and Discussion

Prototype. In the beginning of this investigation, the bisacetal of threitol **7** was allowed to react with excess Me_3SiCH_2MgCl in refluxing benzene for 20 h to give diol **8** in 67% yield (eq 3). In a similar manner, the bisacetal of mannitol derivative **9** was converted into the corresponding diol **10** in 61% yield (eq 4). It is noteworthy that only one of the acetal moieties in **7** and **9** was cleaved under these conditions. The reaction may proceed via the corresponding silyl-substituted alkoxy alcohol intermediates **11** or **12**. Indeed, treatment of acetal **13** or **14** with 1 equiv of Me_3SiCH_2MgCl in refluxing benzene yielded **15** or **16**, respectively. The remaining C−O bond in **16** can be cleaved to give **17** in 62% yield, when excess Me_3SiCH_2MgCl was employed (eq 5).

† Dedicated to Professor K.-T. Wang on the occasion of his 70th birthday.

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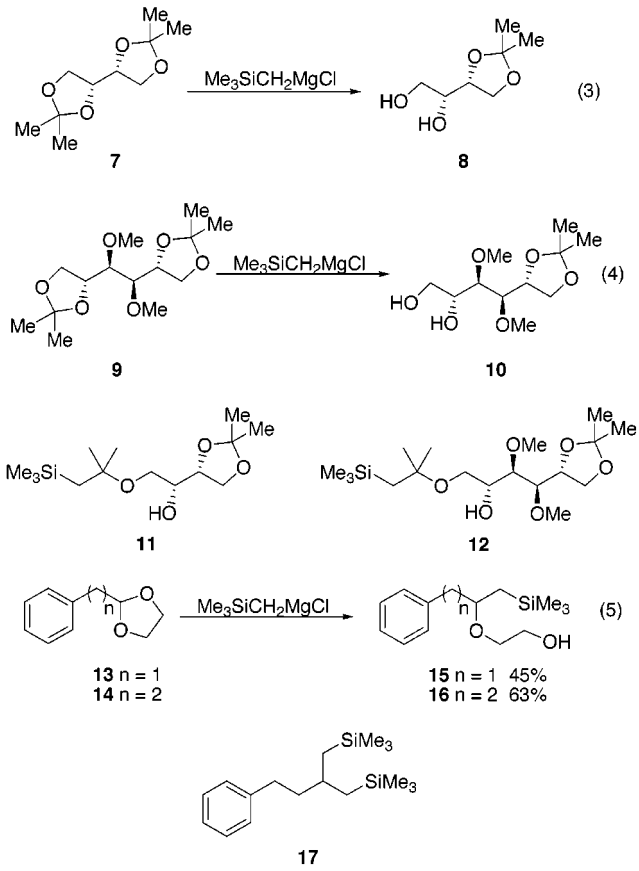
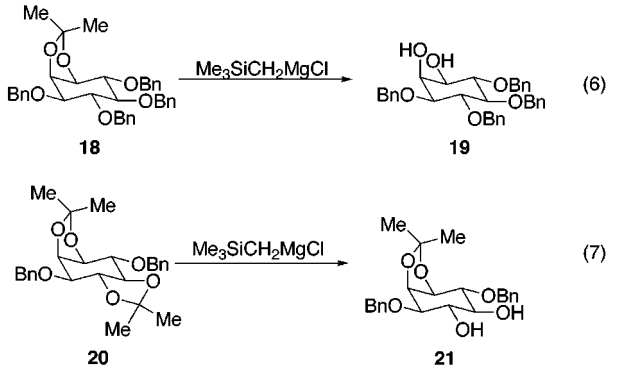
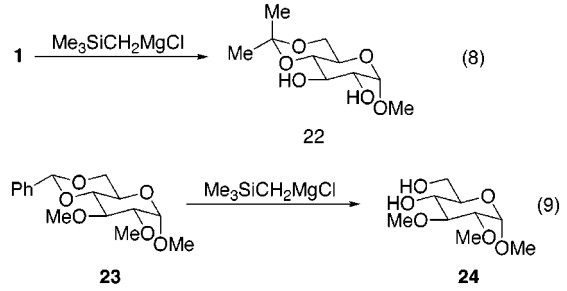


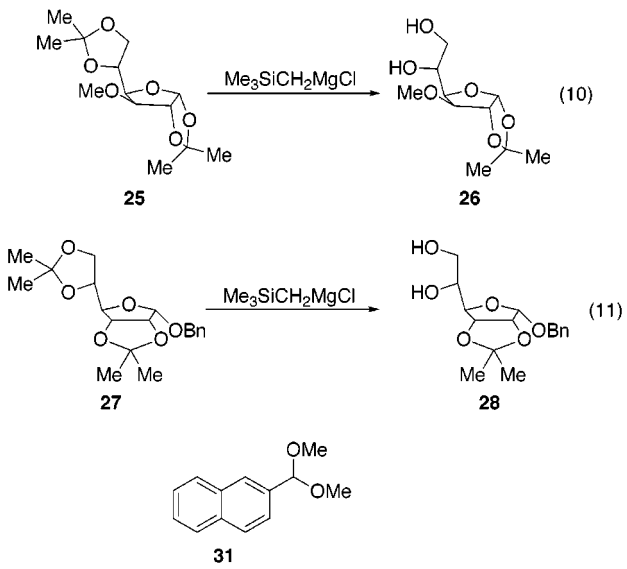
Acetals derived from cyclic diols can also be deprotected under these conditions. Thus, the reaction of *myo*-inositol derivative **18** with excess Me_3SiCH_2MgCl gave diol **19** in 67% yield (eq 6). The more strained trans-fused dioxolane reacted faster that the cis-fused analogue. Diol **21** was obtained exclusively in 79% yield from the reaction of bis-acetal **20** with excess Me_3SiCH_2MgCl (eq 7).



Regioselectivity. In the presence of a neighboring heteroatom, the alkylative ring-opening process of cyclic acetals occurs regioselectively.[2−4] It is believed that the chelation has played a key role to direct the selectivity of this ring-opening reaction. This procedure has been extensively used in the synthesis of various monosaccharide derivatives and related compounds having only one free hydroxy group at the specific position.[4] By employing this strategy, it was felt that acetonides can be deprotected regioselectively. Glucopyranoside bisacetonide **1** was treated with 2 equiv of Me_3SiCH_2MgCl in benzene under reflux for 48 h followed by the usual workup to give the corresponding 2,3-diol **22** in 68% yield (eq 8). Presumably, the anomeric ether moiety may play a key role to direct the selectivity of this reaction. The 4,6-diol of glucopyranoside **24** was obtained in 76% yield from the reaction of **23** under similar conditions (eq 9).



The treatments of acetals of furanosides **25** and **27** with Me_3SiCH_2MgCl in refluxing benzene yielded 5,6-diols **26** (57%) and **28** (72%), respectively (eqs 10 and 11). It appears that the oxygen atom of the furanoside heterocycle in **25** and **27** directs the regioselective deprotection of the acetonide moiety.



Olefination. Olefination of a carbonyl equivalent has been shown to be one of the most useful transformations for the carbon−carbon double-bond formation. Wittig reaction[8] and Peterson olefination[9] are prominent methodologies for this purpose. It is known that dithioacetals can undergo cross-coupling elimination processes upon treatment with the Grignard reagent in the presence of a nickel catalyst leading to the corresponding alkenation products.[10] However, similar olefination reactions with acetals have not been known. As shown in eq 5, the intermediates **14** and **16** were isolated from the reactions of **13** and **15** with Me_3SiCH_2MgCl and further reaction of **16** gave the geminal bis-silylmethylation product **17**. This finding indicates that the C−O bond in **14** and **16** can be labile under the reaction conditions. It was felt that the Lewis acidity of the magnesium species may not be strong enough to promote the Peterson-type olefination. Among a series of Lewis acids (BF_3, Et_2AlCl,

(8) For a recent review, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
(9) For a recent review, see: Ager, D. J. *Org. React.* **1990**, *38*, 1.
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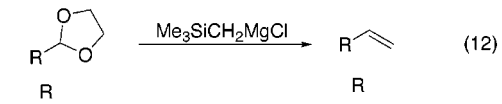
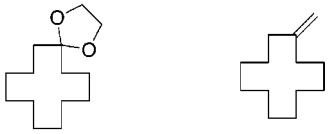
$(Me_3SiCH_2)_3Al$, LiF, KF, $ZnBr_2$, and ZnI_2) we have tested, only ZnI_2 was found to be a suitable promoter for the olefination reactions. It is noteworthy that the acetal did not react with ZnI_2 in benzene in the absence of the Grignard reagent, starting materials being recovered in 80−90% yield. This result ruled out the possibility of the hydrolysis of the acetal followed by Peterson olefination under the reaction conditions.

In a typical procedure, 3 equiv of Me_3SiCH_2MgCl was treated with 1 equiv of ZnI_2 in ether for 3−4 h. Solvent was removed in vacuo, and a benzene solution of 1 equiv of acetal was added. The mixture was heated under reflux for 8 h. After the usual workup procedure, the olefination product was obtained. Thus, 2-(2-naphthyl)dioxolane **29** gave the corresponding styrene **30** in 92% yield. Acyclic acetal **31** also afforded **30** in 90% yield.The acetal derived from α,β-unsaturated aldehyde **32** behaved similarly, and phenylbutadiene **33** was obtained in 82% yield. Aliphatic acetals under the same conditions can also be converted into the corresponding alkenes in good yields. For example, 4-phenyl-1-butene **35** was isolated in 79% yield when **34** was treated with Me_3SiCH_2MgCl and ZnI_2 under the same conditions. In a similar manner, **36** was converted into **37** in 78% yield (eq 12).



29	2-Naphthyl	**30**	2-Naphthyl
32	β-styryl	**33**	β-styryl
34	2-phenylethyl	**35**	2-phenylethyl
36	1-phenyl-2-propyl	**37**	1-phenyl-2-propyl

An acetal derived from a ketone can also be transformed into the corresponding olefination product. For example, the reaction of **38** with Me_3SiCH_2MgCl and ZnI_2 in the presence of HMPA under similar conditions afforded **39** in 66% yield. It is interesting to note that HMPA was essential to promote olefination of ketals cleanly.



38 **39**

In summary, we have depicted a useful regioselective deprotection procedure of the acetal functionality of a contiguous diol under "basic" conditions. By employing the chelation strategy, the diol can be obtained regioselectively. In addition, we have demonstrated for the first time that acetals of different structural variety can be transformed upon treatment with Me_3SiCH_2MgCl and ZnI_2 into the corresponding alkenes in good yield. Further applications of this methodology in synthesis is in progress in our laboratory.

Experimental Section

General procedure A for the Reaction of Acetal with Me_3SiCH_2MgCl. An ether solution of Me_3SiCH_2MgCl (1.0 M, 3 equiv) was evacuated. A solution of acetonide (1 equiv) in benzene (20 mL) was added, and the mixture was heated under reflux for 20−48 h. After being cooled to room temperature, the mixture was quenched with EtOH. Silica gel was added, and the solvent was removed in vacuo. The residue was chromatographed on silica gel to afford the product.

Reaction of 7 with Me_3SiCH_2MgCl. According to the general procedure A, **7** (404 mg, 2.0 mmol) in benzene (10 mL) was allowed to react with Me_3SiCH_2MgCl (10 mL, 1.0 M in Et_2O, 10 mmol) under reflux for 20 h. After workup, the residue was chromatographed on silica gel (gradient solvent system: EtOAc/hexane = 4:1 to 1:0 to EtOAc/EtOH = 3:1) to afford **8** (217 mg, 67%): $[\alpha]^{20}$ +2.1 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz) δ 1.35 (s, 3 H), 1.41 (s, 3 H), 2.26 (bs, 1 H), 2.60 (bs, 1 H), 3.62−3.67 (m, 3 H), 3.84 (dd, *J* = 6.4, 8.2 Hz, 1 H), 4.03 (dd, *J* = 6.4, 8.2 Hz, 1 H), 4.15 (m, 1 H); ^{13}C NMR (100 MHz) δ 25.3, 26.4, 64.3, 65.9, 71.4, 76.6, 109.6; HRMS calcd for $C_7H_{15}O_4$ (M + 1) 163.0970, found 163.0972. Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.57; H, 9.04.

Reaction of 14 with Me_3SiCH_2MgCl. According to the general procedure A, a mixture of **14** (0.89 g, 5.0 mmol) and Me_3SiCH_2MgCl (5 mL of a 1.0 M solution in ether, 5 mmol) in benzene (50 mL) was refluxed for 24 h and worked up as usual to give **16** as an oil (0.87 g, 65%): IR (NaCl) ν 3443 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9 H), 0.83 (dd, *J* = 7.6, 14.5 Hz, 1 H), 1.01 (dd, *J* = 6.3, 14.5 Hz, 1 H), 1.55−1.75 (br s, 1 H), 1.73−1.86 (m, 2 H), 2.55−2.73 (m, 2 H), 3.43−3.52 (m, 3 H), 3.70 (t, *J* = 4.7 Hz, 2 H), 7.10−7.32 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.7, 22.5, 31.5, 38.0, 62.2, 68.8, 77.2, 125.7, 128.3, 142.2; IR (neat) ν 3443; HRMS calcd for $C_{15}H_{26}SiO_2$ 266.1702, found 266.1718.

According to the general procedure A, the reaction of **16** (266 mg, 1.0 mmol) with Me_3SiCH_2MgCl (5 mL of a 1.0 M solution in ether, 5 mmol) in benzene (5 mL) yielded **17** as an oil (181 mg, 62%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 18 H), 0.61 (dd, *J* = 6.0, 14.7 Hz, 2 H), 0.74 (dd, *J* = 6.8, 14.7 Hz, 2 H), 1.50−1.64 (m, 2 H), 1.69−1.81 (m, 1 H), 2.60 (t, *J* = 8.0 Hz, 2 H), 7.14−7.33 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −0.3, 25.5, 30.7, 33.1, 41.7, 125.5, 128.3, 128.4, 143.1; HRMS calcd for $C_{17}H_{32}Si_2$ 292.2042, found 292.2044.

Reaction of 20 with Me_3SiCH_2MgCl. According to the general procedure A, **20** (220 mg, 0.5 mmol) in benzene (15.0 mL) reacts with Me_3SiCH_2MgCl (2.0 mL, 1.0 M in Et_2O, 2.0 mmol) under reflux for 20 h. After workup, the residue was chromatographed on silica gel (EtOAc/hexane = 4:1 to 1:1 to EtOAc/EtOH = 1:1) to afford **21** (150 mg, 79%): mp 158−161 °C (lit.[11] mp 161−163 °C).

Reaction of 1 with Me_3SiCH_2MgCl. According to the general procedure A, **1** (0.548 mg, 2.0 mmol) in benzene (20.0 mL) reacts with Me_3SiCH_2MgCl (6.0 mL, 1.0 M in Et_2O, 6.0 mmol) under 60 °C for 48 h. After workup, the residue was chromatographed on silica gel (EtOAc/hexane = 4:1 to 1:1) to afford **22** (320 mg, 68%): mp 83−85 °C; $[\alpha]^{20}_D$ +112.5 (*c* 1.7, $CHCl_3$) (lit.[12] mp 84−86 °C; $[\alpha]^{18}_D$ +105.5 (*c* 5.0, H_2O)).

General Procedure B for the Olefination of Acetal with Me_3SiCH_2MgCl. A mixture of Me_3SiCH_2MgCl in ether (0.6 M, 5 mL, 3 mmol) and ZnI_2 (0.32 g, 1.0 mmol) was refluxed for 6 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. Benzene (5 mL) was then introduced, followed by the addition of acetal (1.0 mmol) in benzene (5 mL). The mixture was refluxed for 8 h, cooled to room temperature, quenched with NaOH (10%), and diluted with ether (10 mL). The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated in vacuo. The residue was chromatographed on silica gel (hexane) to yield the corresponding olefination product.

2-Vinylnaphthalene (30). According to the general procedure B, the reaction of **29** (0.20 g, 1.0 mmol) with Me_3SiCH_2MgCl in ether (0.6 M, 5 mL, 3.0 mmol) and ZnI_2 (0.32 g 1.0 mmol) afforded **30** (142 mg, 92%), which exhibited spectroscopic properties identical to those of the authentic sample.[13]

In a similar manner, the reaction of **31** (202 mg, 1.0 mmol) with Me_3SiCH_2MgCl in ether (0.6M, 5 mL, 3 mmol) and ZnI_2 (319 mg, 1.0 mmol) gave **30** (139 mg, 90%).

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Methylenecyclododecane (39). According to the general procedure B, **34** (226 mg, 1.0 mmol) was allowed to react with Me_3SiCH_2MgCl in ether (0.6 M, 5 mL, 3 mmol), ZnI_2 (319 mg, 1.0 mmol) in the presence of HMPA (0.1 mL) to yield **39** (118 mg, 66%) as a colorless liquid (100 °C, 0.05 mmHg, Kugerohr). The spectral data proved identical to those of the authentic sample.[14]

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Supporting Information Available: Experimental details for the reactions of **9**, **13**, **18**, **23**, **25**, and **27** and preparation of **33**, **35**, and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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