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Mild Oxidative One-Pot Allyl Group Cleavage

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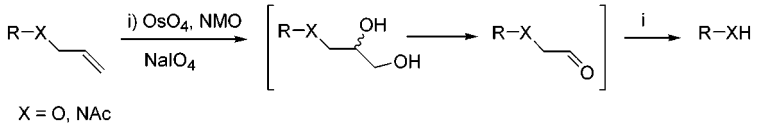
ABSTRACT

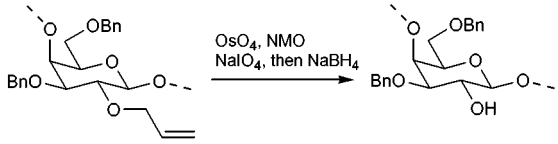


A new one-pot method is described for the removal of *O*- and *N*-allyl protecting groups under oxidative conditions at near neutral pH. The allyl group undergoes hydroxylation and subsequent periodate scission of the vicinal diol, followed by repetition of this reaction sequence on the enolic form of the aldehyde intermediate.

The allyl ether is a common protecting group that permits orthogonal protection strategies with a wide range of protecting groups and is widely employed in multistep synthetic schemes. Common allyl deprotection methods are two-step procedures that include isomerization to the more labile 1-propenyl group with a variety of agents. The most frequently employed conditions are treatment of allyl ether with *t*-BuOK,[1] Wilkinson catalyst,[2] Pd/C,[3] $PdCl_2$,[4] ruthenium(II),[5] and iridium(I)[6] complexes followed usually by acid hydrolysis or oxidation of the resulting enol ether. Also reported are methods including oxidative conditions such as DDQ,[7] SeO_2,[8] and NBS-*hν*.[9] On the other hand, transformation of the allylic double bond may be used to provide a convenient attachment point in various conjugation strategies.[10]

In the course of our investigation into the synthesis of glycoconjugate inhibitors of bacterial AB_5 toxin binding to target cell membranes,[11] we performed a sequence of reactions intended to convert a hexopyranoside 2-*O*-allyl ether into a 2-hydroxyethyl linker (Scheme 1). When all

Scheme 1. Side Product Formed during Attempts To Convert an Allyl Group to a 2-Hydroxyethyl Substituent[11]



steps, including oxidation of the double bond by OsO_4 and 4-methylmorpholine *N*-oxide followed by periodate oxidation of the resulting diol and final reduction of the aldehyde with $NaBH_4$, were conducted in one pot, a significant quantity of side product was observed.

The identification of this unknown as the product of allyl ether cleavage provided an opportunity to develop a new method for allyl group deprotection.

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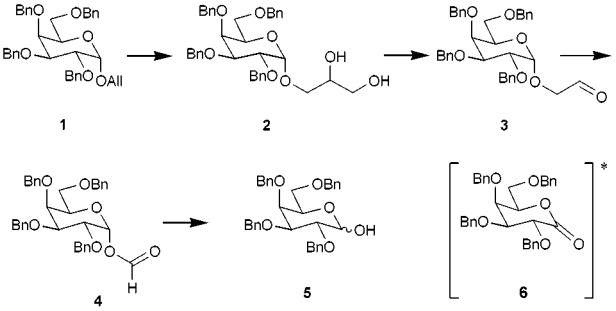
Two specific oxidizing reagents were employed for the reaction: osmium tetroxide with 4-methylmorpholine *N*-oxide as a co-oxidant that specifically oxidizes double bonds and a periodate salt that cleaves vicinal diols.

The reaction conditions for deprotection were optimized on the allyl galactoside **1**[12] as an example (Scheme 2).

Scheme 2. One-Pot, Allyl Group Cleavage of Allyl Galactoside **1** and the Sequential Products Observed during Conversion of **1** to **5**[a]



[a] Asterisk indicates side product observed under homogeneous conditions.

Heterogeneous conditions in which an aqueous solution of 3 equiv of sodium or potassium periodate was added to a dioxane solution of **1**, containing 3 equiv of 4-methylmorpholine *N*-oxide and a catalytic amount of OsO_4, were found to give the best yield. At room temperature, the reaction gives a good yield (73%) of pure product in 4−5 days. Increasing the temperature to 50−60 °C reduces the reaction time to 5−16 h but the yield of **5** is lower (60%).

Over the course of the reaction, the allyl group gradually oxidizes to an *O*-formate derivative which undergoes slow hydrolysis. Intermediates accumulate in the reaction mixture and can be isolated at certain stages of the reaction. Thus, diol **2** (as an epimeric mixture), aldehyde **3**, and formate **4** were each isolated and characterized.

Homogeneous conditions that employed tetrabutylammonium periodate were also explored, but no noticeable acceleration of the reaction was observed. Presumably, the rate-limiting step is the double bond dihydroxylation, whereas diol cleavage occurs rapidly.

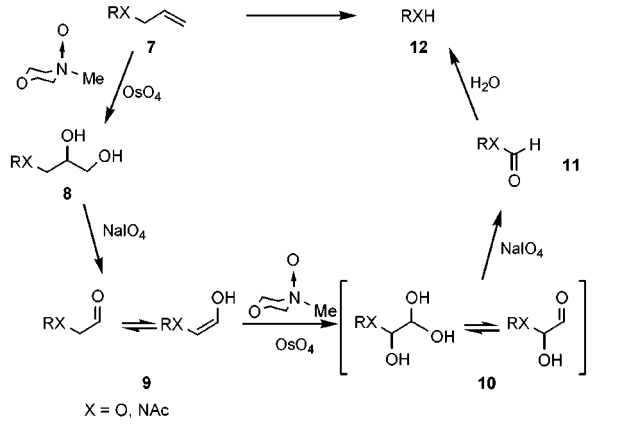
Water is an important constituent of the reaction mixture even in the homogeneous reaction format. Water is required to complete the catalytic cycle and regenerate OsO_4,[13] and its quantity may change the course of the reaction. When water was used as co-solvent (dioxane−water = 3:2), the composition of the reaction mixture resembled that under heterogeneous conditions. However, when just ∼10 equiv of water was used, only trace amounts of the target hydroxyl derivative **5**[14] were observed after 24 h at 60 °C and the reaction mixture consisted mainly of diol **2** and, surprisingly, some product of overoxidation, galactonolactone **6** (Scheme 2).

Under the heterogeneous conditions, the intermediate aldehyde **3** accumulates in the reaction mixture immediately after $NaIO_4$ is added and can be isolated. Evidently, the presence of both oxidizing agents, 4-methylmorpholine *N*-oxide with catalytic OsO_4 and $NaIO_4$, is necessary for the conversion of the aldehyde **3** into the free hydroxyl derivative **5**: stirring of a solution of **2** at 60 °C and in the presence of any one of the oxidizing agents separately led only to unidentified decomposition products, whereas the reaction with a mixture of both agents gave the target alcohol in 67% yield.

Some decomposition of periodate under the reaction conditions is possible. Therefore, addition of extra amounts of an $NaIO_4$ solution during the advanced stages of the process (if TLC indicates accumulation of the diol intermediate) may improve yields by 10−20%.

On the basis of these observations, a mechanism for the oxidative removal of the allyl functionality is proposed in Scheme 3. It includes an initial osmium tetroxide-catalyzed

Scheme 3. Proposed Mechanism of Allyl Group Oxidative Cleavage



dihydroxylation of the double bond in **7**, followed by periodate oxidation of the resulting glycerol derivative **8** to provide the glycolaldehyde ether **9**. The enol tautomeric form of the aldehyde **9** undergoes further OsO_4-promoted oxidation to give hemiacetal **10**, which may either undergo hydrolysis directly to free hydroxy compound **12** or be subjected to one more oxidative cleavage by peroxide to generate the hydrolysis prone formate derivative **11**.

During the review of this manuscript, one referee suggested that formation of an enamine intermediate should promote allyl group cleavage by shifting the aldehyde−enol tautomeric equilibrium. Indeed, when reaction with **1** was conducted in the presence of 1 equiv of a secondary amine, piperidine, complete conversion into **5** was achieved in 3 h (see Table 1, entry 3).

Further examples of oxidative cleavage of allyl groups in different chemical environments are presented in Scheme 4.

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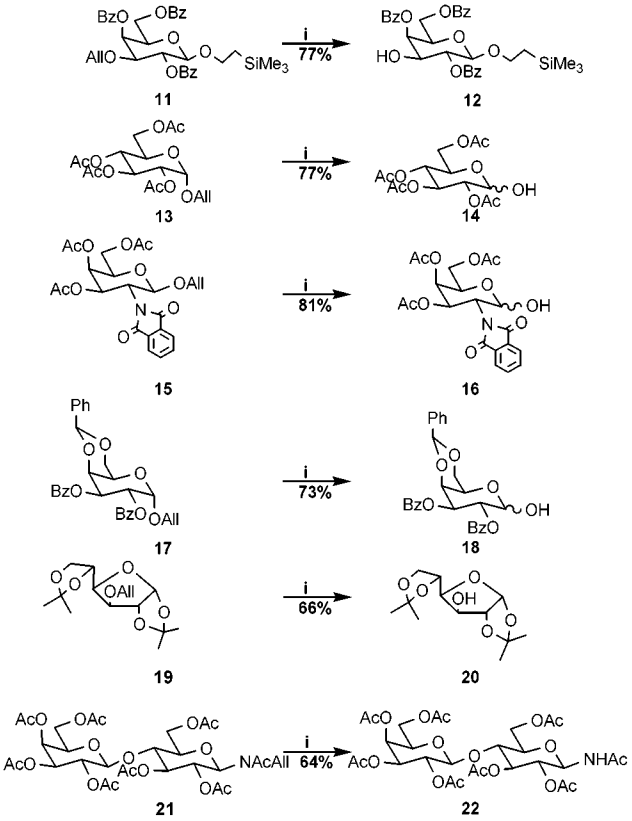
Table 1. Optimization of Reaction Conditions and Test Reactions

entry	substrate	reaction conditions	products
1	**1**	NMO (3 equiv), OsO_4, dioxane−water (10:1), aqueous $NaIO_4$ (2 equiv), 60 °C, 18 h	**5** (60%), **4** (8%)
2	**1**	NMO (3 equiv), OsO_4, dioxane−water (10:1), aqueous $NaIO_4$ (2 equiv), 20 °C, 5 days	**5** (73%), **4** (10%)
3	**1**	1. NMO (3 equiv), OsO_4, dioxane−water (10:1), 60 °C 1 h 2. piperidine (1 equiv), aqueous $NaIO_4$ (2 equiv), 60 °C, 3 h	**5** (75%), **4** (4%)
4	**1**	1. NMO (3 equiv), OsO_4, dioxane−water (10:1), 20 °C, 5 h 2. aqueous $NaIO_4$ (2 equiv), 20 °C, 30 min	**3** (77%)
5	**3**	NMO (3 equiv), OsO_4, dioxane−water (10:1), 60 °C, 16 h	partial decomposition[a]
6	**3**	aqueous $NaIO_4$ (2 equiv), dioxane−water (10:1), 60 °C, 16 h	partial decomposition[a]
7	**1**	NMO (3 equiv), OsO_4, dioxane, water (10 equiv), Bu_4NIO_4 (2 equiv), 50 °C, 5 days	**2** (40%), **5** (16%), **6** (22%)
8	**1**	NMO (3 equiv), OsO_4, dioxane−water (3:1), Bu_4NIO_4 (2 equiv), 20 °C, 5 days	**2** (13%), **5** (55%)

[a] TLC detection.

They include selective removal of *O*-allyl ethers from secondary alcohol and anomeric positions, in the presence of base-labile ester protecting groups as well as acid-labile cyclic ketal and acetals of diol. The last entry demonstrates the possibility of *N*-allyl deprotection. Typical deprotection procedures with and without the inclusion of a secondary amine to accelerate the reaction are described.[26]

Scheme 4. Representative Examples of Allyl Group Cleavage[a]



[a] (i) 4-Methylmorpholine *N*-oxide, OsO_4, $NaIO_4$, dioxane−water (2:1), 60 °C 18 h.

Allyl derivatives **11**,[15] **13**,[16] **15**,[17] **17**,[18] **19**,[19] and **21**[20] were prepared according to known procedures. The products of deallylation **12**,[21] **14**,[22] **16**,[23] **20**[24] and **22**[25] were previously described. The new compound **18** was characterized by proton NMR and mass spectra (see Supporting Information).

The oxidative cleavage of allyl groups is compatible with a wide range of common *O*- and *N*-protective groups and generally proceeds without oxidation of the liberated hydroxyl group. The stable intermediates may be observed by TLC as the reaction proceeds to completion. Benzyl ethers

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(26) **Typical Procedures for Allyl Deprotection. i.** To a solution of allyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside **1** (585 mg, 1.007 mmol) in dioxane (5 mL) and water (0.5 mL) was added a mixture of 4-methylmorpholine *N*-oxide (3 equiv, 354 mg) and OsO_4 (0.2 mL, 100 mg/mL solution in *t*-BuOH) followed by addition of a suspension of $NaIO_4$ (3 equiv, 646 mg) in water (2 mL). The mixture was stirred at 60 °C for 18 h and then diluted with brine and extracted with DCM. Chromatography on silica gel with hexanes−ethyl acetate (8:2−6:4) gave formate **4** (46 mg, 8%) and the target 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose **5** (335 mg, 60%). **ii.** To a solution of allyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside **1** (390 mg, 0.671 mmol) in dioxane (10 mL) and water (1 mL) were added 4-methylmorpholine *N*-oxide (3 equiv, 236 mg) and OsO_4 (0.3 mL, 100 mg/mL solution in *t*-BuOH). The mixture was stirred at 60 °C for 2 h followed by addition of piperidine (1 equiv, 57 mg) and suspension of $NaIO_4$ (3 equiv, 431 mg) in water (5 mL). The mixture was stirred at 60 °C for 3 h and then diluted with brine and extracted with DCM. Chromatography on silica gel with hexanes−ethyl acetate (8:2−6:4) gave formate **4** (18 mg, 4.6%) and 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose **5** (275 mg, 75%).

are unaffected by the reaction conditions. The reaction is relatively independent of pH. Reaction conditions are slightly basic due to the presence of morpholine, but slight acidification with acetic acid does not affect the reaction course and enables the reaction to proceed without migration of ester groups.

Functional groups susceptible to oxidation are obviously incompatible with this method of allyl deprotection and include thioethers, thioglycosides, vicinal diols, and alkenes. Deprotection may be achieved with a relatively extended reaction time of 10−20 h at 60 °C. However, addition of secondary amine, which presumably accelerates the rate-limiting step by formation of an enamine intermediate, dramatically shortens reaction time to 5 h at 60 °C.

The new method is well suited to selective deprotection of a wide variety of orthogonally protected polyhydroxy derivatives, and its application permits novel manipulation of more complex allyl protecting groups either in solution or on solid-phase supports. The later will be the topic of future communications.

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Supporting Information Available: Spectral data for previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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