"Green" oxidation reactions—application to carbohydrate chemistry

Communication

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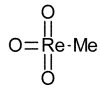
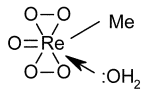
Oxidation of glycals by either methyltrioxorhenium (MTO)–hydrogen peroxide or hydrogen peroxide–acetonitrile in methanol provides direct access to methyl glycosides. The two different reagents proceed with a complementary stereochemical outcome enabling the synthesis of β-D-*gluco*-pyranosides or α-D-*manno*-pyranosides from the same carbohydrate precursor.

Introduction

The development of oxidation processes which are environmentally friendly is currently the focus of much attention.[1] The use of hydrogen peroxide[2,3] in this context is particularly appealing as the inorganic by-product, water, is benign and presents a number of practical advantages (*e.g.* product separation) which may be important especially in an industrial context. The oxidising system comprising of catalytic methyltrioxorhenium (MTO)[4] as the oxygen carrier in conjunction with hydrogen peroxide as re-oxidant is currently one of the most promising in this context. These oxidation reactions, which are thought to proceed *via* the *in situ* generation of the peroxo species **1**, are relatively robust, show good catalytic turnover and are effective in a number of transformations.[5]



MTO



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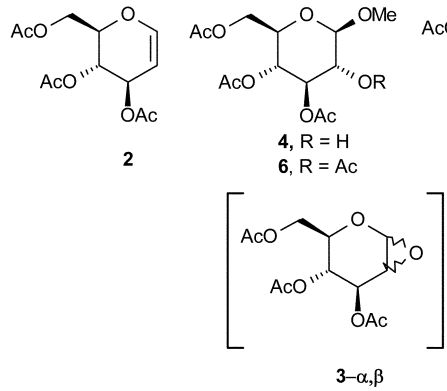
Results and Discussion

In the course of a synthetic project we wished to convert glycal derivatives to their corresponding epoxides and wondered whether the MTO–hydrogen peroxide system would be effective in this transformation.[6] Whilst the oxidation of enol ethers,[7a] silyl enol ethers,[7b] silyl ketene acetals[7c] and furans[7d] has been documented using this reagent combination the analogous functionalisation of more complex substrates such as carbohydrate derivatives has not been described. The recent report by Goti[7e] *et al.* prompts us to publish our results in this area.

We were gratified to find therefore that treatment of 3,4,6-tri-*O*-acetyl-D-glucal **2** with two equivalents of 30% hydrogen peroxide in the presence of a catalytic quantity of MTO in methanol for 2 h at ambient temperature afforded directly the β-D-*gluco*-pyranoside **4**[8a] and the α-D-*manno*-pyranoside **5**[8a] in 78% isolated yield (**4**:**5** = 2:1). We presume that this interconversion proceeds *via* S_N2 opening of the epoxides **3**-α,β by methanol, a reaction which may well be promoted by the presence of the rhenium catalyst which is known to act as a Lewis acid.[4] Direct conversion of the crude product from the oxidation sequence (excess Ac_2O/pyridine, rt, 12 hours; 71%) afforded the acetates **6** and **7** (**6**:**7** = 2:1) whose spectral data were compared directly with authentic samples thereby securing our stereochemical assignment. Encouraged by these initial results we investigated the epoxidation-glycosylation sequence on a variety of glycal derivatives.



Changing acetate to a benzyl protecting group, as in **8**, has little effect on the overall efficiency (76% yield) of the reaction but was more stereoselective affording the β- and α-D-*gluco*-pyranosides **9**[8b] and **10**[8c] as by far the major products (**9**:**10**:**11**[8b] = 11:1:2). The generation of a small quantity of the α-D-*gluco*-pyranoside **10** in this case could arise by equilibration of the β-D-*gluco*-pyranoside **9** or may be due to an erosion of stereospecificity in the ring opening of the α-epoxide **12** as previously observed by Timmers *et al.*[9] Oxidation of the conformationally locked benzylidene acetals **13** and **16**[8d] is selective for the β-D-*gluco*-pyranosides **14** and **17**. In the case of **13**, with a free hydroxyl group at C-3, the glycosides **14**[8e] and **15**[8f] were isolated in 55% yield (**14**:**15** = 2:1) whilst **16**

Green Context

Development of greener methods for carrying out synthetic transformations often is limited to a few simple test reactions, with more complex systems being less thoroughly investigated. Here, novel clean oxidation approaches based on hydrogen peroxide are described which work well for several polyfunctional molecules. High yields and interesting stereochemical outcomes are recorded for a range of protected carbohydrates. ***DJM***

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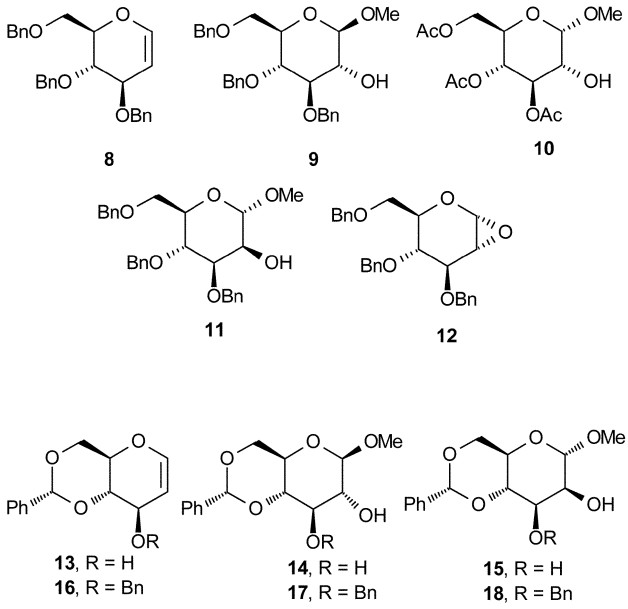

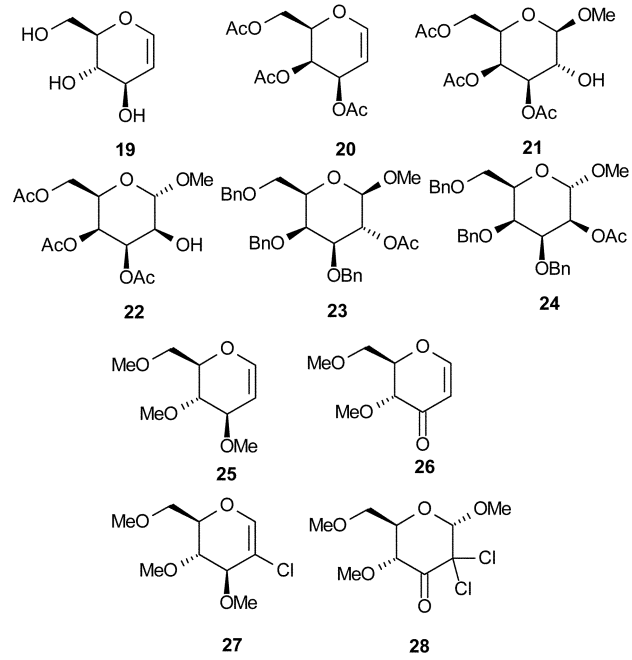

afforded **17**[8g] (61% yield) together with a trace of the alternate diastereoisomer **18**.[8h]

These results indicate that an allylic hydroxyl group has little *syn*-directing ability when the reaction is conducted in methanol, a result which is in keeping with the diastereoselectivity observed in the epoxidation of cyclohex-2-en-1-ol under similar conditions.[10] This effect is mirrored in the case of glucal **19** which on epoxidation, ring opening and peracetylation afforded a 2:1 mixture of the β-D-*gluco*-pyranoside **6** and the α-D-*manno*-pyranoside **7** in 65% overall yield. As to be expected epoxidation of 3,4,6-tri-*O*-acetyl-D-galactal **20** proceeded with a marginally greater selectivity than the corresponding glucal **2**, affording the β-D-*galacto*-pyranoside **21**[8i] and the α-D-*talo*-pyranoside **22**[8j] (**21**:**22** = 3:1) in 73% yield.

The effect of protecting group on the rate of reaction was briefly investigated using a simple competition experiment. Treatment of a 1:1 mixture of **2** and **8** to a catalytic quantity MTO (10 mol%), H_2O_2 (2 eq.) in methanol at ambient temperature for 2 h followed by aqueous work-up and acetylation of the crude reaction mixture afforded the tetracetates **6** and **7** and the monoacetates **23**[6a,8b] and **24**[8b] in 43% and 38% isolated yield respectively. The lack of discrimination observed in this reaction is presumably a reflection of the reactivity[5] of nucleophilic enol ethers towards the electrophilic oxidising agent. Surprisingly oxidation of 3,4,6-tri-*O*-methyl-D-glucal **25**, under our standard conditions, was less clean and afforded a mixture of products including the pyrone **26**[11] (*ca.* 20%) whilst the vinyl chloride **27** afforded the α-D-2,2-dichloro-2-deoxy-*gluco*-pyranoside **28** in 24% isolated yield.[12]

All of the oxidation reactions described above were conducted in homogeneous solution. Recent reports[13] suggest that the urea–hydrogen peroxide inclusion complex (UHP), a stable solid which is commercially available, can also act as a source of hydrogen peroxide in MTO oxidations even though these reactions are heterogeneous when conducted in common organic solvents. We have found that UHP can also act as an alternative to hydrogen peroxide in the oxidation of glycals. For example treatment of **2** with MTO (10 mol%) in methanol in the presence of UHP (2 eq.) at ambient temperature for 2 h afforded, after acylation, the glycosides **6** and **7** (**6**:**7** = 2:1) in 76% isolated yield, a result which is essentially identical to that obtained with hydrogen peroxide itself.

During the course of these investigations the effect of solvent on the efficiency of the epoxidation-ring opening sequence was also briefly investigated. Curiously when acetonitrile was used as solvent in the UHP oxidation of **2** the isolated yield of the methyl glycosides **4** and **5** was diminished considerably (*ca* 10% yield). Blank studies revealed that the problems associated with low turnover lay in the instability of the MTO in acetonitrile containing hydrogen peroxide. In this solvent the MTO decomposed liberating methanol and presumably perrhenate. In addition the stereochemical outcome of the reaction was reversed with the α-D-*manno*-pyranoside **5** now being the major product (**5**:**4** = 3:1). Thinking that in this solvent system at least a different oxidation pathway was operative led us to attempt the oxidation of **8** under Payne-type conditions.[2a] Indeed, exposure of **8** to H_2O_2 (30 % aq.; 5 eq.) and $KHCO_3$ (0.25 eq.) in MeOH containing acetonitrile (5 eq.) at ambient temperature for 48 h followed by a simple aqueous work up afforded the methyl glycosides **9** and **11** in 82% yield,[14] with the α-D-*manno*-pyranoside **11** predominating (*manno*:*gluco* = 3:1). In this case the allylic ether substituent exerts a different effect on the stereochemistry of the epoxidation sequence, possibly *via* the formation of a hydrogen bond between the ether oxygen and reagent, an effect which has been noted by others in the epoxidation of cyclohexene derivatives.[2b]

In conclusion we have demonstrated that either the MTO–hydrogen peroxide or hydrogen peroxide–acetonitrile systems cleanly oxidise a variety of glycals leading directly to methyl glycosides. Although not exhaustive, our preliminary results indicate that the stereochemical outcome of these reactions is complementary: Payne oxidation conditions introducing the epoxide oxygen *syn*- to the allylic oxygen whereas MTO delivers the oxygen *anti*- to the allylic oxygen (Table 1). Given the ease of operation of these reactions they should find applications in carbohydrate chemistry, an area which is currently under investigation.

Table 1 Product distribution from the oxidation of glycals

Substrate	Product	Yield (%)
2	**4** and **5** (**4**:**5** = 2:1)	78[a]
8	**9**, **10** and **11** (**9**:**10**:**11** = 11:1:2)	76[a]
13	**14** and **15** (**14**:**15** = 2:1)	55[a]
16	**17**	61[a]
19	**6** and **7** (**6**:**7** = 2:1)	65[a,b]
20	**21** and **22** (**21**:**22** = 3:1)	73[a]
25	**26**	20[a]
27	**28**	24[a]
2	**6** and **7** (**6**:**7** = 2:1)	76[c,b]
8	**9** and **11** (**9**:**11** = 1:3)	82[d]

[a] Using MTO–H_2O_2. [b] After peracylation. [c] Using MTO-UHP. [d] Using H_2O_2–MeCN.

Experimental

The oxidation of 3,4,6-tri-*O*-acetyl-D-glucal **2** is representative. To a solution of **2** (1.0 g, 3.7 mmol) in methanol (30 mL) was added MTO (9.2 mg, 3.6×10^{-2} mmol) followed by H_2O_2 (0.83 mL of 30% aq. soln., 7.4 mmol). The pale yellow solution was kept at ambient temperature for 2 h after which time water (20 mL) was added. The aqueous phase was extracted (CH_2Cl_2, 3×20 mL), the organic extracts tested for peroxide (starch-iodide paper) dried ($MgSO_4$) and concentrated *in vacuo* affording a mixture of the methyl glycosides **4** and **5** (920 mg 78% yield) in an essentially pure state.

Payne oxidation of 8

To a solution of **8** (0.84 g, 2.0 mmol) in methanol (5.0 mL) was added $KHCO_3$ (50 mg, 0.50 mmol), acetonitrile (0.53 mL, 10 mmol) and H_2O_2 (1.1 mL of 30% aq. soln., 10 mmol) and left to stir at ambient temperature for 48 h. The reaction mixture was extracted (CH_2Cl_2, 3×10 mL), the organic extracts washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to afford a mixture of the methyl glycosides **9** and **11** (770 mg, 82% yield) in an essentially pure state.

Acknowledgements

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