Regioselective Mono-oxidation of Non-protected Carbohydrates by Brominolysis of the Tin Intermediates[1,2]

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Most of the glycosides examined were smoothly oxidized by the bis-tributyltin oxide–bromine method without protection of the other hydroxyl groups to the mono-oxo derivatives in high yield and with high regioselectivity. The regioselectivity (position of oxidation) can be predicted from two independent rules: anomeric control (the oxidation takes place at C-3 for the glycosides which have an equatorial glycosidic linkage and at C-4 for those which have an axial glycosidic linkage) and axial oxidation for *cis*-1,2 glycols.

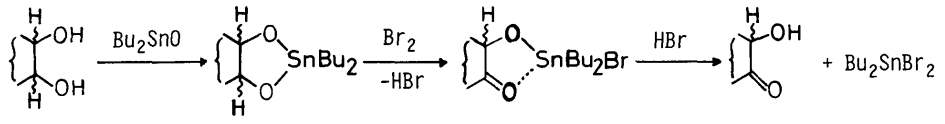
Keywords carbohydrate; glycoside; oxidation; regioselective oxidation; bis-tributyltin oxide–bromine; dibutyltin oxide–bromine; brominolysis; oxo-glycoside; ^{13}C-NMR

It is well known that the O–Sn linkage formed from hydroxyl groups by the action of bis-tributyltin oxide or dibutyltin oxide is very sensitive to brominolysis and yields a carbonyl compound at the speed of titration. Thus, this reaction provides a method of mild oxidation of a hydroxyl group to the corresponding carbonyl compound, as shown in Chart 1.[4,5]

Of the two reactions in Chart 1, the dibutyltin oxide method seems to be promising for selective oxidation of diols. Thus, David and Thieffry[6] succeeded in mono-oxidation of partially protected carbohydrate diols (such as **1**) on treatment with Bu_2SnO followed by brominolysis, where oxidation occurred in good yield at the secondary hydroxyl group in primary-secondary 1,3-glycols. The reaction was skillfully utilized by Hanessian and Roy[7] in their total synthesis of (+)-spectinomycin; they oxidized the triol **3** to the keto diol **4** in high yield, where Bu_2SnO activated the secondary hydroxyl group in the secondary-tertiary 1,2-glycol by forming a cyclic stannylene derivative.

However, the method had never been applied to a compound having more than three contiguous hydroxyl groups, such as non-protected carbohydrate, until we

A : brominolysis of a dibutylstannylene derivative



B : brominolysis of a tributylstannane derivative

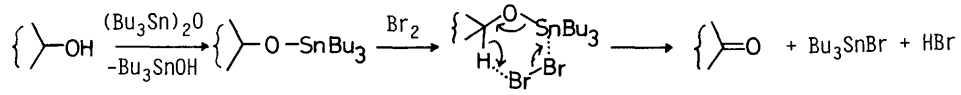


Chart 1. Oxidation of a Hydroxyl Group *via* Tin Intermediates

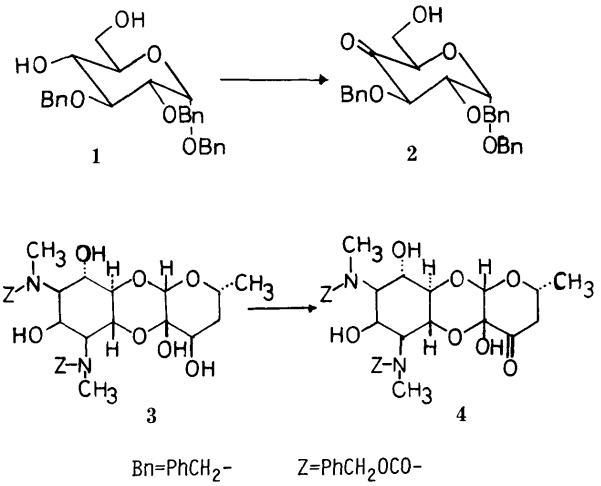


Chart 2. Examples of Mono-oxidation by the Bu_2SnO–Br_2 Method

reported[2a] the oxidation of Me β-L-Ara[8] to the corresponding 4-oxo derivative in an appreciable yield.

Our success in regioselective acylation,[9] alkylation,[10] and thioacylation[11] of various non-protected glycosides through a tin intermediate suggested to us that a particular hydroxyl group in a carbohydrate may be selectively activated by bis-tributyltin oxide or dibutyltin oxide, even if more than three hydroxyl groups are present contiguously. If this hypothesis is correct, the procedure, when combined with brominolysis, may permit the regioselective oxidation of a carbohydrate hydroxyl group without the use of a protection–deprotection procedure.

In this paper, we describe in detail our results on the mono-oxidation of non-protected glycosides, comparing the Bu_2SnO–Br_2 method and the $(Bu_3Sn)_2O$–Br_2 method. To our surprise, the latter method was sometimes superior to the former in both yield and regioselectivity.

Results and Discussion

Oxidation *via* the Stannylation with Dibutyltin Oxide[2a] Firstly, we chose Me β-L-Ara **5** as the substrate of oxidation, since the cyclic stannylene ring is most easily formed with the *cis* 1,2-glycol system among the three contiguous hydroxyls in this compound. Stannylation of **5** in methanol as described in the previous paper[9] followed by brominolysis of the product in $CHCl_3$ afforded a syrupy oxidation product in 72% yield. Although the product in the reaction mixture showed only one spot on thin-layer chromatography (TLC), two spots were seen after chromatography on silica gel. The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum exhibited three OMe peaks at δ 3.30, 3.34 and 3.41, revealing that the product is a mixture of at least three compounds. However, this mixture gave a single oxime **7**, mp 138—139 °C, when treated with hydroxylamine. Corresponding to the ^{1}H-NMR evidence, the gas-liquid chromatography (GLC) of the trimethylsilyl (TMS) derivative showed three peaks (Fig. 1). The gas chromatography–mass spectrum (GC-MS) revealed that the peak at t_R 2.1 min is a monomer and the other two are dimeric forms, because they showed M^+ at *m/z* 306 and 612, respectively. $NaBH_4$ reduction of the above mixture gave Me β-L-Ara **5** and Me α-D-Xyl **22** in a ratio of 6:4 as confirmed by TLC on an HBO_3 impregnated plate and by GLC of the TMS derivative, no other product being found in the reaction mixture. Therefore we concluded that the oxidation product is methyl β-L-*threo*-4-pentulopyranoside **6** and it rapidly dimerized to **8** and/or **9**, all of which behaved as a monomer **6** on hydride reduction and oximation. The monomer/dimer ratio changed depending on the amount subjected to chromatography, or on keeping the mixture at room temperature (see also below).

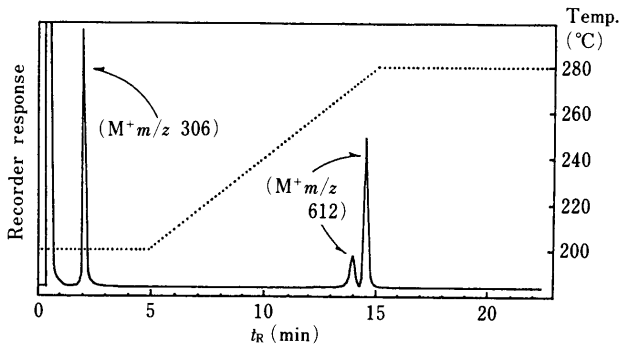


Fig. 1. Gas Chromatogram of Methyl β-L-*threo*-Pentopyranos-4-uloside as the TMS Derivative

The reason why only the axial hydroxyl was oxidized regioselectively may be explained by considering the cyclic mechanism (see **10**) shown in Chart 3, where the equatorial hydrogen can be eliminated by bromine which is coordinated to the tin atom. This is in remarkable contrast to acylation[9] and alkylation,[10] in which the equatorial hydroxyl group in a *cis*-1,2-glycol is always acylated or alkylated.

Application of this oxidation method to Me α-D-Glc, however, gave an unsatisfactory result. The yield of oxidation was low and the product was a mixture, though the reaction conditions were not optimized. The stannylated product, when used as a suspension, regenerated a considerable amount of the starting glycoside on brominolysis. As already suggested by David and Thieffry,[6] it is necessary to avoid acid hydrolysis of the O–Sn linkage by hydrogen bromide generated during brominolysis in this oxidation. The recommended proton scavenger[6] such as Bu_3SnOMe and molecular sieves were not so effective as expected. Therefore, we sought a more effective method.

Oxidation *via* Stannylation with Bis-tributyltin Oxide[2b] There is another interesting report on the oxidation of diols. Ueno *et al.*[12] treated the 1,2- or 1,3-glycols of primary and secondary hydroxyls by simultaneous addition of $(Bu_3Sn)_2O$ and Br_2 in dichloromethane, where the secondary hydroxyl group was oxidized usually in 66—86% yield. Of course their conditions are not applicable to the oxidation of non-protected carbohydrates, since the substrates are not soluble in dichloromethane. Actually oxidation of Me α-D-Glc by their procedure resulted in complete recovery of the starting material. This indicates that the stannylation process is crucial in this oxidation.

After several fruitless attempts, we found that the following modification is suitable for oxidation of non-protected glycosides: that is, stannylation of the glycosides in refluxing chloroform with an excess of $(Bu_3Sn)_2O$ in the presence of molecular sieves 3A until the glycosides dissolved completely, followed by *in situ* brominolysis of the cooled mixture, then chromatography on silica gel without an extraction procedure (see Experimental).

By this modified method, most of the glycosides examined were smoothly oxidized, giving rise to a single monooxidation product in 70—96% yield. It was also found that at least 2 mol eq of $(Bu_3Sn)_2O$ was necessary to complete the reaction.

The product from Me β-D-Glc **11**, mp 130—134 °C,

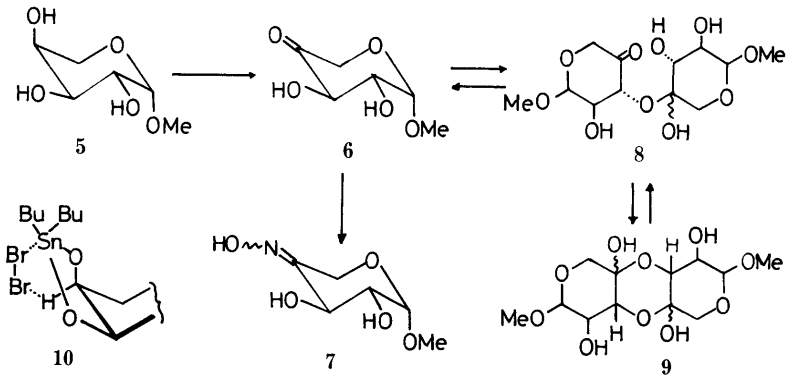


Chart 3

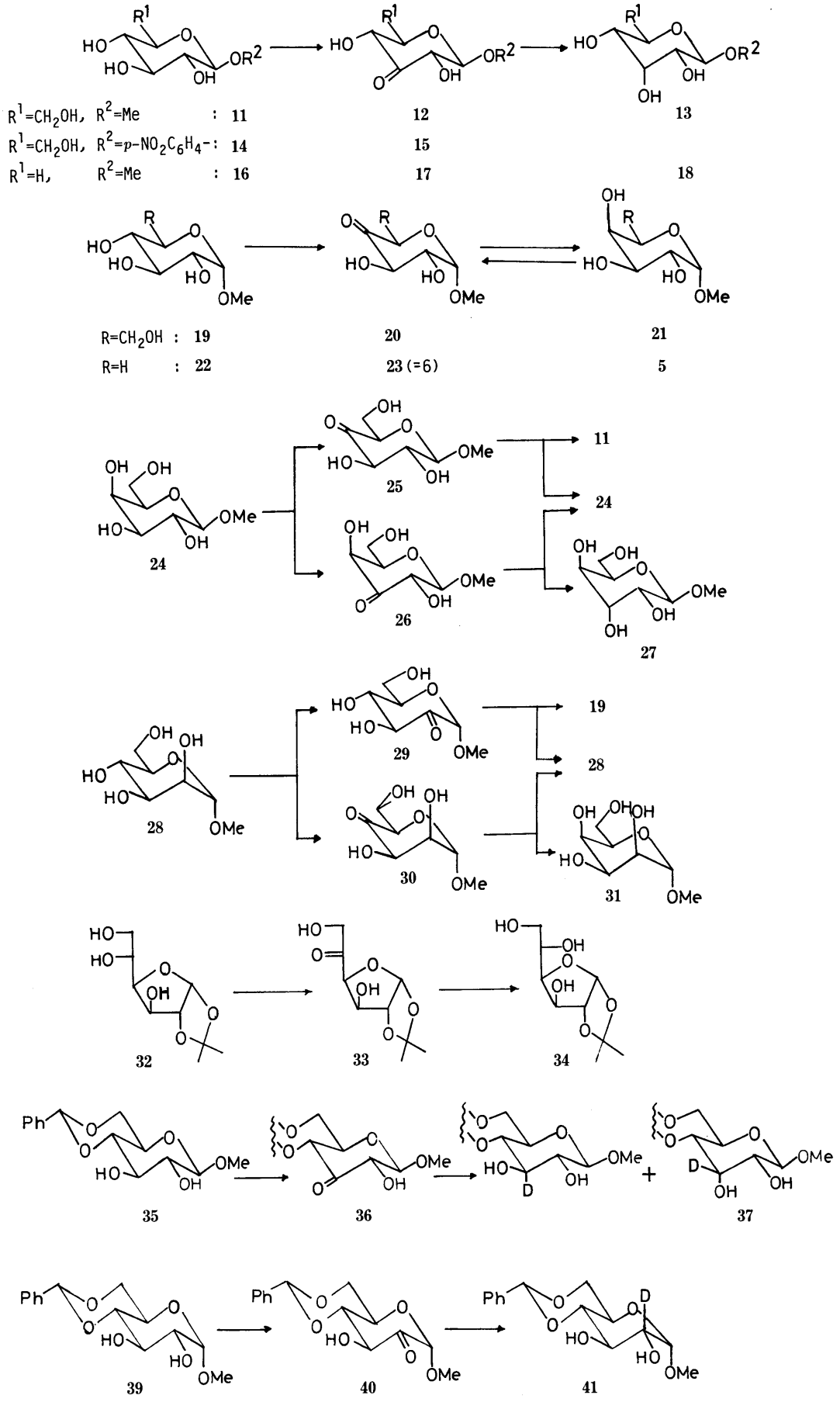


Chart 4

TABLE I. ^{13}C-NMR Spectra of Oxo-glycosides (in Pyridine-d_5)

Compd.	C-1	C-2	C-3	C-4	C-5	C-6
12[a]	106.4 (+0.9)	78.2 (+2.7)	207.4	73.5 (+2.1)	78.0 (−0.3)	62.0 (−0.6)
15[b]	102.4	77.7 (+2.2)	206.4	73.5 (+2.1)	79.0 (+0.7)	61.9 (−0.7)
17[c]	107.5 (+1.4)	78.2 (+3.5)	206.9	73.2 (+2.2)	66.9 (0)	
20[d]	101.0 (−0.3)	74.6 (+0.9)	77.4 (+2.1)	205.8	76.1 (+2.1)	60.5 (−2.3)
29[e]	101.5 (−0.2)	201.6	78.8 (+3.5)	74.7 (+2.7)	75.6 (+1.6)	61.9 (−0.9)
30[f]	104.2 (+1.9)	71.7 (−0.1)	76.4 (+3.6)	208.2	77.7 (+3.0)	62.5 (−0.3)
33[g]	105.8 (+0.9)	85.3 (0)	76.4 (+0.4)	84.5 (+4.9)	209.2	68.1 (+4.4)
36[h]	107.7 (+1.6)	78.4 (+2.8)	199.5	82.2 (−0.1)	67.2 (+0.2)	69.5 (+0.3)
40[i]	100.8 (+0.8)	198.8	74.7 (+3.4)	83.9 (+2.9)	62.8 (+0.4)	68.6 (−0.3)

Parenthetical values indicate the differences of chemical shifts: *a*) Δ(**12**−**11**), *b*) Δ(**15**−**11**), *c*) Δ(**17**−**16**), *d*) Δ(**20**−**19**), *e*) Δ(**29**−**19**), *f*) Δ(**30**−**28**), *g*) Δ(**33**−**32**), *h*) Δ(**36**−**35**), and *i*) Δ(**40**−**39**).

exhibited a single OMe peak at δ3.62 in the ^{1}H-NMR spectrum and showed a single peak in GLC of its TMS derivative. The ^{13}C-NMR spectrum (Table I) clearly indicated that the compound is the 3-oxo derivative **12** because the signal of C-3 appeared at δ207.4, and C-2 and C-4 showed downfield shifts.[13] In agreement with this assignment, $NaBH_4$ reduction of **12** in methanol gave Me β-D-Glc **11** almost quantitatively, while hydrogenation in AcOH over PtO_2 gave Me β-D-All **13** together with a small amount of Me β-D-Glc **11** as confirmed by GLC of the TMS derivative.

Lindberg and Theander[14] obtained Me β-D-*ribo*-3-hexulopyranoside **12** by dichromate oxidation of **11** in the presence of oxalic acid and gave the melting point as 127—128 °C. However, their isolation procedure is tedious and the yield was extremely low (less than 1%).[15]

The *p*-nitrophenyl derivative **14** was also smoothly oxidized in over 80% yield to the corresponding 3-oxo derivative **15**, although 4 mol eq of $(Bu_3Sn)_2O$ was necessary to complete the reaction in this case. The structure of the oxidation product was determined from the ^{13}C-NMR spectrum as above (Table I).

Me β-D-Xyl **16** similarly gave the 3-oxo derivative **17** in more than 90% yield. The product, on reduction with $NaBH_4$, regenerated **16**, while on catalytic hydrogenation over PtO_2 in AcOH it gave Me β-D-Rib **18**[16] and Me β-D-Xyl **16** in a ratio of 9:1 as confirmed by TLC and GLC of the TMS derivative. The same 3-oxo derivative **17** was obtained by Lindberg and Slessor[17] by dimethyl sulfoxide–acetic anhydride oxidation of the Me β-D-Xyl phenylboronate derivative followed by methanolysis of the protecting group. Clearly our new method is superior to the reported procedure in both simplicity and yield.

In contrast to the β-D-glycosides, Me α-D-Glc **19** was oxidized to the 4-oxo derivative **20**. The product gave an OMe peak in the ^{1}H-NMR spectrum at δ3.52 accompanied with small peaks, whose intensity ratio suggested that the major product amounts for more than 75%.[18] The ^{13}C-NMR spectrum confirmed the position of the carbonyl group (see Table I). $NaBH_4$ reduction of this product in methanol gave Me α-D-Glc **19** and Me α-D-Gal **21** in a ratio of *ca.* 7:3.

Me α-D-Gal **21** gave the same 4-oxo derivative **20** in *ca.* 70% yield. The identity was confirmed by TLC and GLC of the TMS derivative, and by the ^{1}H- and ^{13}C-NMR spectra.

Me α-D-Xyl **22** and Me β-L-Ara **5** gave the same product **23** in over 80% yield. This was found to be identical with the product obtained from Me β-L-Ara **5** by the use of dibutyltin oxide and bromine oxidation (see above). The GLC of this product, as the TMS derivative, again indicated that it is a mixture of monomer and dimers but in a different ratio from the mixture obtained above. The structure of the product was definitively confirmed by converting it into the oxime **7**, which was identical with the sample obtained above.

From the above results, we can conclude that the oxidation takes place at C-3 for the glycosides which have an equatorial glycosidic linkage (usually β-glycosides) and at C-4 for those which have an axial glycosidic linkage (usually α-glycosides), although we can not explain why at present. However, it should be noted that the position of oxidation is different from that of acylation (or alkylation) through activation with bis-tributyltin oxide in those glycosides, the latter reaction occurs at O-6 for Me β-D-Glc **11**, Me α-D-Glc **19**, and Me α-D-Gal **21**, O-4 for Me β-D-Xyl **16**, O-2 for Me α-D-Xyl **22**, and O-3 for Me β-L-Ara **5** and Me β-D-Gal **24**.[9]

Next, what would be expected for a *cis*-1,2 glycol system in this oxidation method? The oxidation of Me β-D-Gal **24** and Me α-D-Man **28** was examined, since the results for Me α-D-Gal **21** and Me β-L-Ara **5** suggested oxidation of an axial hydroxyl group. If the oxidation follows two different rules, these compounds should each give two products. Actually their oxidation was proved to be less regioselective. In the case of **24**, the oxidation product obtained in 70% yield showed a broad single spot on TLC, but had complex OMe signals at *ca.* δ3.6, suggesting that the product is a mixture. Oximation of this product with hydroxylamine confirmed this. The product was an inseparable mixture of two compounds as shown by the ^{13}C-NMR. $NaBH_4$ reduction of the oxidation product gave Me β-D-Glc **11**, Me β-D-Gal **24** and Me β-D-Gul **27** in a ratio of 1:2:1 (GLC of the TMS derivatives), while catalytic hydrogenation in AcOH over PtO_2 gave Me β-D-Gal **24** and Me β-D-Gul **27** in a ratio of 5:2. The formation of **27** in these reactions was confirmed by an alternative synthesis.[19] Thus, the oxidation product was concluded to be a mixture of two regioisomeric oxo derivatives, the 4-oxo and the 3-oxo derivatives, **25** and **26**, in a ratio of *ca.* 5:2. This conclusion was supported by detailed analysis of the ^{13}C-NMR spectra.

The oxidation product from Me α-D-Man **28** (50%; net yield 76%) showed two spots on TLC. Chromatography allowed separation of these compounds. The major product

showed signals of OMe at δ 3.34 and of CO at δ 208.2 in the ^{1}H- and ^{13}C-NMR spectra. $NaBH_4$ reduction of this gave Me α-D-Man **28** and Me α-D-Glc **19** in a ratio of *ca.* 1 : 1 (GLC of the TMS derivatives), indicating that it is the 2-oxo derivative **29**. Similarly, $NaBH_4$ treatment of the minor product gave a mixture of two compounds in a ratio of 2 : 1 (GLC of the TMS derivatives). The larger peak was identical with that of Me α-D-Man **28** and the other was concluded to be due to Me α-D-Tal **31** because the latter peak was not identical with those of Me α-D-Alt[20] and Me α-D-Glc **19**. Those considerations suggested that the minor product in the oxidation is the 4-oxo derivative **30**. Thus, the oxidation of **28** gave a mixture of two regioisomeric oxo derivatives, the 2-oxo derivative **29** and the 4-oxo derivative **30**, with preference for the former.

From the above results we can conclude that, in the present oxidation, two different rules are operating independently: these are, anomeric control for pyranosides and axial oxidation for *cis*-1,2-glycols. The oxidation following the latter rule always occurs preferentially when the two groups are present in the same molecule.

Oxidation of a compound containing a primary-secondary 1,2-glycol system was also highly regioselective, as expected. Thus, 1,2-*O*-isopropylidene-α-D-glucofuranose **32** gave the 5-oxo derivative **33** in 92% yield as crystals. Previously the same compound was obtained by Theander[21] as an amorphous solid in only 0.1% yield by a usual chromate oxidation of **32**. Reduction of **33** with tetra-*n*-butylammonium borohydride in dichloromethane gave a 3 : 1 mixture of 1,2-*O*-isopropylidene-β-L-idofuranose **34**[22] and the original compound **32**. This transformation not only established the position of oxidation but provided an efficacious method of preparation of L-idose.

This oxidation is also highly regioselective for a di-equatorially disposed *trans*-1,2-glycol system. For example, methyl 4,6-*O*-benzylidene-β-D-glucopyranoside **35** and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **39** were oxidized to the 3-oxo and 2-oxo derivatives, **36** and **40**, in more than 90% yield,[23] respectively. Since the ^{13}C-NMR of these products did not give confirmatory evidence on the position of the carbonyl group and **40** was prone to dimerize rapidly (the stereochemistry of the dimers will be discussed in a forthcoming publication), the structures of the native oxidation products, **36** and **40**, were determined as follows. The product **36** from the β-glucoside, on reduction with $NaBH_4$, gave methyl 4,6-*O*-benzylidene-β-D-alloside **37** (H instead of D) and the original glucoside **35** in a ratio of 2 : 1. A similar reduction of **36** with $NaBD_4$ gave a mixture of the alloside **37** and the glucoside **38**, in the both of which C-3 was completely deuterated as confirmed by the ^{1}H- and ^{13}C-NMR spectra. No deuterium was found at the other positions. This evidence established that the oxidation had taken place at C-3. Similarly, the native oxidation product **40** (as well as the dimers) quantitatively regenerated **39** on $NaBH_4$ reduction. The α-glucoside **41** obtained by $NaBD_4$ reduction was proved to be fully deuterated only at C-2 by the ^{1}H- and ^{13}C-NMR spectra, thus confirming that the oxidation had taken place at C-2.

Most of the oxo-glycosides readily formed dimers to various extents, as suggested above. Details of this monomer–dimer equilibration and the stereochemistry of the dimers will be discussed in a separate paper.

Conclusion

In conclusion, most glycosides are smoothly oxidized by the bis-tributyltin oxide–bromine method to yield mono-oxo derivatives without protection of the other hydroxyl groups, in high yield and with high regioselectivity, where a secondary hydroxyl group was always oxidized. The regioselectivity (position of oxidation) can be predicted from two rules: the configuration of the anomeric center (anomeric control) and the nature of the glycol system (axial oxidation of a *cis*-1,2-glycol).

Although we can not explain at present why such anomeric control occurs in this oxidation, the method proposed here should have great synthetic value. The ulosides, thus prepared, are useful intermediates not only to rare sugars, selectively deuterated sugars, branched sugars, and amino sugars, but also to chiral synthesis of complex molecules.

In addition to the examples indicated above, further examples will be presented in forthcoming publications.

Experimental

Melting points were determined on a Yanaco micro hot stage melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jasco IRA-2 spectrometer and the data are given in cm^{-1}. ^{1}H-NMR (100 MHz) and ^{13}C-NMR (25 MHz) spectra were recorded with a JEOL FX100 FT NMR spectrometer in pyridine-d_5 solution with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values. GLC analyses were carried out with a Shimadzu GC4CM-PF gas chromatograph with an FID detector, using N_2 (50—80 ml/min) as a carrier gas. The TMS derivatives were prepared by the method of Sweeley *et al.*[24] A sample (1—2 mg) in dry pyridine (2 drops) was shaken vigorously with hexamethyldisilazane (2 drops) and trimethylsilyl chloride (1 drop). After 10 min at room temperature, the mixture was centrifuged and the supernatant (1—2 μl) was directly injected into a glass column (2 m × 3 mm i.d.) packed with 1.5% OV-1 on Shimalite W (80—100 mesh). The relative retention times (Rt_R) of the reference compounds are as follows. Series A (hexoses): Me β-D-Glc 1.00, Me α-D-Glc 0.91, Me β-D-Gal 0.82, Me α-D-Gal 0.71, Me α-D-Man 0.60, Me β-D-All 0.89, Me α-D-Alt 0.47, Me β-D-Gul 0.51, and Me α-D-Gul 0.46. Series B (pentoses): Me β-D-Xyl 1.00, Me α-D-Xyl 0.89, Me β-L-Ara 0.54, Me α-L-Ara 0.56, and Me β-D-Rib 0.63. MS and GC-MS were taken with a Hitachi M-80 machine. Column chromatography was performed on Wakogel C-200. For TLC, Kieselgel $60F_{254}$ precoated plates were used and spots were developed by spraying 1% $Ce(SO_4)_2$ in 10% H_2SO_4 and heating the plates at 100 °C until coloration took place.

Oxidation of Me β-L-Ara 5 by the Bu_2SnO–Br_2 Method Me β-L-Ara **5** (200 mg) and Bu_2SnO (0.91 g, 3 eq) in methanol (30 ml) were heated under reflux for 3 h, then the solvent was evaporated off. The dried residue was dissolved in chloroform (10 ml) (slightly turbid), crushed molecular sieves 4A (0.7 g) was added, then bromine (0.23 g, 1.2 eq) in chloroform (4 ml) was added dropwise to the solution at room temperature. The color of bromine disappeared immediately. The resulting solution (TLC, one spot of **6** together with a small amount of **5**) was directly poured onto the silica gel column and the column was washed thoroughly with chloroform, then with chloroform–ethyl acetate (1 : 1) to remove tin compounds. Elution of the column with ethyl acetate then gave the 4-oxo derivative **6** as a gum (143 mg, 72%), which showed two spots on TLC corresponding to the monomer **6** and the dimers (**8** and/or **9**). IR ($CHCl_3$): 3400 (OH), 1735 (CO). ^{1}H-NMR (60 MHz): 3.41, 3.34, 3.30 (OMe). GC-MS (TMS-derivative): see Fig. 1. Peak 1 (2.1 min, M^+ *m/z* 306), peak 2 (14.0 min, M^+ *m/z* 612), and peak 3 (14.5 min, M^+ *m/z* 612). On standing for a week, the product gave only peak 2 and peak 3.

Hydride Reduction of the 4-Oxo Derivative 6 The above mixture (180 mg) in methanol (10 ml) was reduced with sodium borohydride (200 mg) for 1 h at room temperature, then the mixture was weakly acidified with a few drops of HCl and concentrated. The residue was treated with boiling methanol several times to remove borate complexes, then analyzed by TLC and GLC. TLC on a boric acid-impregnated plate showed two spots corresponding to Me β-L-Ara **5** and Me α-D-Xyl **22**. GLC of the TMS derivative showed two peaks corresponding to **5** and **22** (peak ratio, 6 : 4).

Oxidation of the 4-Oxo Derivative 6 The oxidation product (130 mg),

hydroxylamine hydrochloride (200 mg), and sodium carbonate (250 mg) in methanol (10 ml) were refluxed for 2 h. The precipitate was removed by filtration and the filtrate was concentrated to dryness. The residue was chromatographed in ethyl acetate to yield the oxime **7** (70 mg), which crystallized from ethyl acetate as colorless needles, mp 138—139 °C. IR: 3300, 1640 (C=N). ^{1}H-NMR: 5.79 (OH), 5.31 (1H, d, J=14.5 Hz, C_{5eq}-H), 5.22 (1H, d, J=2.8 Hz, C_1-H), 5.14 (1H, d, J=8.2 Hz, C_3-H), 4.66 (1H, d, J=14.5 Hz, C_{5ax}-H), 4.36 (1H, dd, J=2.8, 8.2 Hz, C_2-H), 3.49 (3H, s, OMe). ^{13}C-NMR: 55.7 (OMe), 55.9 (C_5), 71.0 (C_2), 74.6 (C_3), 101.3 (C_1), 155.0 (C_4). *Anal.* Calcd for $C_6H_{11}NO_5$: C, 40.68; H, 6.26; N, 7.91. Found: C, 40.52; H, 6.22; N, 7.78.

Oxidation of Glycosides by the $(Bu_3Sn)_2O$–Br_2 Method (General Procedure) A dried glycoside (0.5—1 g), (n-$Bu_3Sn)_2O$ (*ca.* 2 eq), and an excess of molecular sieves 3A in chloroform (20—40 ml) were heated under reflux until the glycoside dissolved completely (2—3 h required), then cooled. To this mixture, bromine (*ca.* 2 eq required) was added at 0 °C with stirring until the solution was faintly colored (5—8 min), then the mixture was rapidly poured onto a column of silica gel. The column was washed thoroughly with chloroform to remove tin compound(s), then eluted with ethyl acetate (with monitoring by TLC) to yield the oxo derivative (70—96%) which was sufficiently pure as judged by ^{13}C-NMR (in most cases) and could be used without further purification. Further elution of the column with methanol gave the starting material (if present).

Oxidation of Me β-D-Glc 11 The oxidation was done as described in the general procedure to yield the 3-oxo derivative **12** (97%) as colorless prisms from ethyl acetate–methanol, mp 130—132 °C (lit. mp 127—128 °C).[14] IR (KBr): 1730. ^{1}H-NMR: 3.62 (OMe). MS *m/z*: 193 (M^++1, 1%), 103 (100%). *Anal.* Calcd for $C_7H_{12}O_6$: C, 43.75; H, 6.29. Found: C, 43.72; H, 6.39.

Compound **12** (25 mg) in methanol (15 ml) was treated with $NaBH_4$ (30 mg) and worked up as described for the reduction of **6**. TLC and GLC (TMS derivative) showed the presence of only one product **11**. Acetylation of this with acetic anhydride and pyridine gave Me β-D-Glc tetraacetate.

Hydrogenation of **12** as described for the hydrogenation of **17** (see below) gave Me β-D-All **13** and Me β-D-Glc **11** in a ratio of *ca.* 9 : 1 (GLC of the TMS derivative).

Oxidation of *p*-Nitrophenyl β-D-Glc 14 Stannylation of **14** (0.2 g) was done with 1.6 g (4 eq) of $(Bu_3Sn)_2O$ and the resulting product was treated with bromine (*ca.* 4 eq) as described in the general procedure to yield the 3-oxo derivative **15** (117 mg, 59%), mp 189—193 °C, as prisms from ethyl acetate–methanol. The starting material (36 mg, 18%) and a mixture of **14** and **15** (80 mg) were recovered. IR (KBr): 1730. *Anal.* Calcd for $C_{12}H_{13}NO_8$: C, 48.16; H, 4.38; N, 4.68. Found: C, 48.01; H, 4.42; N, 4.65.

Oxidation of Me β-D-Xyl 16 The oxidation was done as described in the general procedure to give the 3-oxo derivative **17** (93%) as a gum. IR (film): 1732. ^{1}H-NMR: 3.60 (OMe). MS *m/z*: 130 (M^+ − MeOH, 9%).

Reduction of **17** with $NaBH_4$ as described above gave a single compound, **16** (TLC and GLC of TMS derivative).

Compound **17** (620 mg) in AcOH (20 ml) was hydrogenated over PtO_2 (0.6 g) under an H_2 pressure of 4 kg/cm^2 for 10 h at room temperature. Removal of the catalyst and solvent gave a gummy residue which was lyophilized after addition of a small amount of water. The TMS derivative of the product showed two peaks in GLC corresponding to Me β-D-Xyl **16** and Me β-D-Rib **18** in a ratio of 1 : 9.

Oxidation of Me α-D-Glc 19 The reaction was done as described in the general procedure to give the 4-oxo derivative **20** (65%), a gum, with recovery of **19** (29%). IR (film): 1731. ^{1}H-NMR: 3.52, 3.45 w (OMe). MS *m/z*: 161 (M^+ − OMe, 10%). This was identical with the compound described below.

Oxidation of Me α-D-Gal 21 The reaction was done as described in the general procedure to yield **20** (70%) with recovery of **21** (22%).

Reduction of **20** with $NaBH_4$ in methanol and work-up as described above gave two products, Me α-D-Glc **19** and Me α-D-Gal **21**, in a ratio of *ca.* 7 : 3 (GLC of TMS derivative).

Oxidation of Me α-D-Xyl 22 The reaction was done as described in the general procedure to yield **23** (92%), as a gum. ^{1}H-NMR: 3.48, 3.40, 3.37 (OMe). This was identical with the product obtained by Bu_2SnO–Br_2 oxidation of **5**, but with different compositions of **6** and **8** and/or **9**.

Reduction of this mixture with $NaBH_4$ in methanol gave Me α-D-Xyl **22** and Me β-L-Ara **5** in a ratio of *ca.* 2 : 1 (GLC of TMS derivative).

The mixture was treated with hydroxylamine as described for **6** to give the oxime **7**, mp 128—132 °C, in 65% yield. The identity was confirmed by mixed melting point determination, and TLC and spectral comparisons.

Oxidation of Me β-L-Ara 5 The oxidation was done as described in the general procedure to yield the product in 93% yield. This was identical with the compound obtained above and formed the same oxime **7** on reaction with hydroxylamine.

Oxidation of Me β-D-Gal 24 The oxidation of **24** (1.0 g) was done as described in the general procedure to yield a mixture of **25** and **26** (665 mg, 67%), which showed a single spot on TLC and a single peak on GLC (TMS derivative).

Reduction of this mixture with $NaBH_4$ and work-up as described above gave the product as a syrup; GLC (TMS derivative) showed three peaks corresponding to Me β-D-Glc **11**, Me β-D-Gal **24**, and Me β-D-Gul **27**, in a ratio of 1 : 2 : 1.

Hydrogenation of the above mixture in AcOH over PtO_2 gave a syrupy product which showed two peaks corresponding to **24** and **27** in a ratio of 5 : 2 in GLC (TMS derivative). The acetate prepared by treatment with acetic anhydride and pyridine also showed two peaks in GLC corresponding to Me β-D-Gal tetraacetate and Me β-D-Gul tetraacetate in a ratio of 5 : 2.

Me α- and β-D-Gul D-Gulose was prepared from D-gulono-γ-lactone according to Isbell.[19] This was methylated by using methanol and concentrated hydrochloric acid to give a 1 : 2 mixture of Me α- and β-D-Gul. The ratio was determined by GLC of the TMS derivatives. ^{1}H-NMR: 3.59 (OMe). The acetate was prepared by acetylation.

Oxidation of Me α-D-Man 28 The oxidation was done as described in the general procedure. The product showed two spots on TLC in addition to **28**. They were separated by chromatography to give a mixture of **29** and **30** (370 mg) and **29** (600 mg), and the mixture was again chromatographed to yield **30** (113 mg) and **29** (contaminated with **30**) (250 mg). These compounds were unstable in pyridine-d_5 and changed into a complex mixture (possibly due to dimerization) during ^{13}C-NMR measurements. ^{1}H-NMR: 3.42 (OMe for **29**), 3.34 (OMe for **30**).

Compounds **29** (crude) and **30** were reduced with $NaBH_4$ in methanol and the products, after work-up as above, were analyzed by high performance liquid chromatography and GLC (TMS derivatives), respectively. The GLC of the product from **29** showed two peaks corresponding to Me α-D-Man **28** and Me α-D-Glc **19** in a ratio of *ca.* 1 : 1. The GLC of the product from **30** showed three peaks at Rt_R 0.60, 0.72, and 0.91 in a ratio of 2 : 1 : trace. The peaks were assigned as those of Me α-D-Man **28**, Me α-D-Tal **31**, and Me α-D-Glc **19** (this was derived from the contaminating **29**).

Oxidation of 1,2-*O*-Isopropylidene-α-D-glucofuranose 32 1,2-*O*-Isopropylidene-α-D-glucofuranose **32** (1 g) was oxidized as described in the general procedure. The 5-oxo derivative **33** (910 mg, 92%) obtained on work-up was crystallized as colorless needles from ether, mp 108—110 °C. IR (KBr): 1718. ^{1}H-NMR: 1.33, 1.48 (each 3H, s, $O_2C(CH_3)_2$), 4.51 (2H, s, H_2-6), 4.54 (1H, d, J=3.3 Hz, H-2), 4.58 (1H, d, J=3.2 Hz, H-4), 4.76 (1H, d, J=3.2 Hz, H-3), 6.06 (1H, d, J=3.3 Hz, H-1). ^{13}C-NMR: 112.6 (O–C–O), 26.3, 27.0 (Me), see Table I for the others. MS *m/z*: 203 (M^+ − CH_3). *Anal.* Calcd for $C_9H_{14}O_6 \cdot 1/2\,H_2O$: C, 47.58; H, 6.61. Found: C, 47.55; H, 6.53.

Bu_4NBH_4 Reduction of the 5-Oxo Derivative 33 The 5-oxo derivative **33** (200 mg) in CH_2Cl_2 (20 ml) was reduced with Bu_4NBH_4 (120 mg) at 0 °C for 30 min by addition of the reagent in portions. After decomposition of excess reagent with 2 drops of AcOH, the mixture was concentrated to dryness, and the residue in $CHCl_3$–MeOH (9 : 1) was chromatographed to give a mixture of D-gluco and L-ido isomers. This was acetylated with Ac_2O–pyridine and the product (gluco/ido ratio 1/3 by GLC) was separated by MPLC on a Lobar Si 60 column (solvent, benzene : ethyl acetate = 4 : 1) to give the triacetate of **32** (66 mg, 21%) and **34** (170 mg, 54%). The latter formed colorless prisms, mp 83—84 °C, from ether–hexane. IR (KBr): 1742, 1728. MS *m/z*: 347 (M^++1), 331 (M^+ − CH_3), 169 (100%). *Anal.* Calcd for $C_{15}H_{22}O_9$: C, 52.02; H, 6.40. Found: C, 51.94; H, 6.60.

Methanolysis of this (147 mg) with 3% NH_3–MeOH gave 1,2-*O*-isopropylidene-β-L-idofuranose **34**, mp 113—116 °C (lit. mp 112—113 °C),[22] as colorless prisms from methanol–ether (91 mg, 98%). MS *m/z*: 221 (M^++1).

Oxidation of Methyl 4,6-*O*-Benzylidene-β-D-glucopyranoside 35 Me 4,6-*O*-Benzylidene-β-D-Glc **35** (1 g) was oxidized and chromatographed as described in the general procedure. After removal of tin compound(s), the subsequent eluate with chloroform gave the 3-oxo derivative **36** (670 mg, 68%), and the ethyl acetate eluate gave its hydrate (324 mg) slightly contaminated with the starting material. The 3-oxo derivative **36** crystallized from ethyl acetate–hexane as colorless needles, mp 187—190 °C. IR (KBr): 1740. ^{1}H-NMR ($CDCl_3$): 3.65 (3H, s, OMe), 3.87 (1H, m, H-5), 4.05 (1H, t, J=9.6 Hz, H-6), 4.60 (1H, dd, J=4.4, 9.6 Hz, H-6), 4.72 (1H, d, J=8.1 Hz, H-1), 4.75—4.90 (2H, H-4, H-2), 5.83 (1H, s, H-7), 7.34—7.79 (5H,

Ar-H). ^{13}C-NMR: 101.7 (O–C–O), 57.3 (OMe), see Table I for the others. MS *m/z*: 281 ($M^+ + 1$), 107 (100%). *Anal.* Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 59.65; H, 5.78.

The hydrate (contaminated with **35**) yielded the following data. IR (KBr): no CO absorption. ^{13}C-NMR: 105.5 (C-1), 77.5 (C-2), 94.5 (C-3), 84.2 (C-4), 66.8 (C-5), 68.8 (C-6), 102.1 (C-7), 56.5 (OMe). On heating of this *in vacuo* over P_2O_5, it gave **36** (TLC and ^{13}C-NMR).

The 3-oxo derivative **36**, on $NaBH_4$ reduction in methanol, gave a mixture of Me 4,6-*O*-benzylidene-β-D-Glc **35** and Me 4,6-*O*-benzylidene-β-D-All **37** (H instead of D) in a ratio of 1 : 2 (GLC of the TMS derivatives).

Methyl 4,6-*O*-Benzylidene-3-deuterio-β-D-allopyranoside 37 and Methyl 4,6-*O*-Benzylidene-3-deuterio-β-D-glucopyranoside 38 The 3-oxo derivative **36** was reduced with $NaBD_4$ as described above to yield the deuterated mixture of the alloside **37** and the glucoside **38** in a ratio of 2 : 1. **37**: ^{13}C-NMR: 103.8 (C-1), 72.2 (C-2), 80.3 (C-4), 63.6 (C-5), 69.8 (C-6), 101.9 (C-7), 56.9 (OMe). **38**: ^{13}C-NMR: 106.1 (C-1), 75.6 (C-2), 82.3 (C-4), 67.0 (C-5), 69.2 (C-6), 102.0 (C-7), 57.0 (OMe).

Oxidation of Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside 39 Me 4,6-*O*-benzylidene-α-D-Glc **39** (0.5 g) was oxidized and worked up as described in the general procedure to yield the 2-oxo derivative **40** (463 mg, 93%) as a gum. IR ($CHCl_3$): 1745. ^{1}H-NMR ($CDCl_3$): 3.48 (3H, s, OMe), 3.53—3.88 (1H, H-5), 3.77 (1H, t, J = 10.1 Hz, H-4), 4.04—4.50 (2H, H_2-6), 4.68 (1H, d, J = 10.1 Hz, H-3), 4.83 (1H, s, H-1), 5.53 (1H, s, H-7), 7.31—7.38 (5H, Ar-H). ^{13}C-NMR: 101.6 (O–C–O), 55.8 (OMe), see Table I for other data. This compound rapidly changed into two dimers (mp 248—252 °C and mp 159—164 °C, IR: no CO absorptions) on standing in a solvent.

Freshly prepared 2-oxo derivative (30 mg) in methanol was reduced with $NaBH_4$ for 2 h to give **39** as a sole product (TLC and GLC of TMS derivative).

Methyl 4,6-*O*-Benzylidene-2-deuterio-α-D-glucopyranoside 41 Freshly prepared 2-oxo derivative **40** (50 mg) was reduced with $NaBD_4$ as described above to give Me 4,6-*O*-benzylidene-2-deuterio-α-D-Glc **41** in a quantitative yield. ^{13}C-NMR: 99.9 (C-1), 71.2 (C-3), 81.0 (C-4), 62.4 (C-5), 68.9 (C-6), 101.8 (C-7), 55.4 (OMe).

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