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ON THE STEREOCHEMISTRY OF OSMIUM TETRAOXIDE OXIDATIONS OF ALLYLIC SYSTEMS USED IN THE SYNTHESIS OF HIGHER-CARBON SUGARS*†

JOHN S. BRIMACOMBE** AND ABUL K. M. S. KABIR
Chemistry Department, Dundee University, Dundee DD1 4HN (Great Britain)
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ABSTRACT

The stereochemistry of the major osmylation products of carbohydrate-based allylic alcohols can usually be predicted by application of Kishi's empirical rule. In particular, the addition of OsO_4 can be formulated as taking place in the more abundant conformation on the surface *anti* to a pyranose or furanose ring-oxygen atom located at a stereocentre adjacent to the olefinic linkage. Exceptions to Kishi's empirical rule for osmylation are sometimes encountered with conjugated carbonyl compounds.

INTRODUCTION

In recent years, the control of stereochemistry in acyclic systems has attracted increasing attention from both synthetic and theoretical viewpoints[2]. In connection with developing new approaches to the synthesis of higher-carbon sugars, we have been interested in applying Kishi's empirical rule[3] to predict the stereoselectivity of OsO_4 oxidations of acyclic allylic alcohols based on carbohydrates. For allylic alcohols bearing hydroxyl or alkoxyl groups at a neighbouring stereocentre, Kishi's empirical rule[3] predicts that the relative stereochemistry between the pre-existing hydroxyl or alkoxyl group and the adjacent newly introduced hydroxyl group of the major product is *erythro*. Based on the known preference of such systems to adopt an eclipsed conformation[4], and assuming that this conformational preference is reflected in the transition state, the stereochemical outcome of the osmylation process may be formulated as arising from preferential attack of OsO_4 on the face of the olefinic linkage opposite to that of the pre-existing hydroxyl or alkoxyl group when the molecule adopts the sterically least compressed conformation **1**. In other words, the osmylation may be regarded as being *anti* stereoselective with respect to the hydroxyl or alkoxyl group at the adjacent stereocentre in conformation **1**.

*Dedicated to Professor Bengt Lindberg.
†Higher-carbon Sugars, Part 11. For Part 10, see ref. 1.
**To whom enquiries should be addressed.

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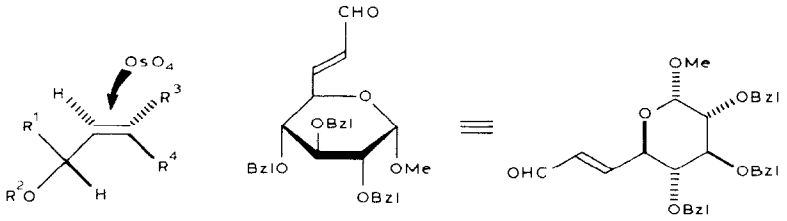
Support for this mode of attack comes from the fact that the stereoselectivity observed for the osmylation of (*Z*)-allylic alcohols and their derivatives, for which conformation **1** (R^3 = H, $R^4 \neq$ H) would be expected to be more abundant than either of the other two eclipsed conformations, is normally higher than that of the corresponding (*E*)-allylic alcohols and their derivatives **1** ($R^3 \neq$ H, R^4 = H)[3]. Explanations based on stereoelectronic considerations have also been advanced[5] to rationalise the stereochemical outcome of such osmylations, and it has also been noted[6] that the osmylation process is difficult to characterise, in part because the reaction pathway is not well understood. In the absence of firm knowledge of the geometry of the transition state, the picture presented by Kishi[3] is conveniently simple at this stage in the development of our understanding, and agrees extremely well with other examples to be found in the literature. It must always be borne in mind that OsO_4 is a large electrophile, so that bulky R^1 groups might hamper the approach of the electrophile to the upper surface of the conformation **1**.



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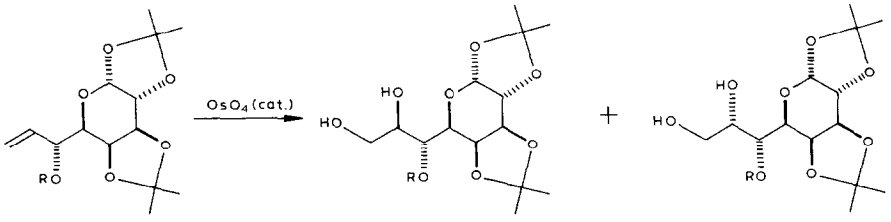
RESULTS AND DISCUSSION

Over the past three years, we have subjected numerous carbohydrate-based allylic systems to OsO_4 oxidation under catalytic conditions[7]*, and it seems timely to gather together these and some new results for comment, particularly as they underscore many of the points made by Kishi[3]. Where interesting new points or examples have emerged, reference is made occasionally to work other than our own.

The acyclic allylic systems studied have been classified into four groups. The first three classifications are based on whether the osmylation is directed by an exocyclic hydroxyl or alkoxyl group (group A) or a pyranose or furanose ring-oxygen atom (groups B and C, respectively) at a stereocentre at one end of the olefinic linkage. The fourth group (D) contains conjugated carbonyl compounds, for which Kishi's empirical rule[3] must be applied more circumspectly since several exceptions have been found among these systems. The synthesis of most of the compounds within each of these groups has been described[5,8–18], and usually

*The catalytic procedure tends to be a little less stereoselective than the stoichiometric procedure[3], but the cost of the stoichiometric procedure becomes prohibitive for large-scale work.

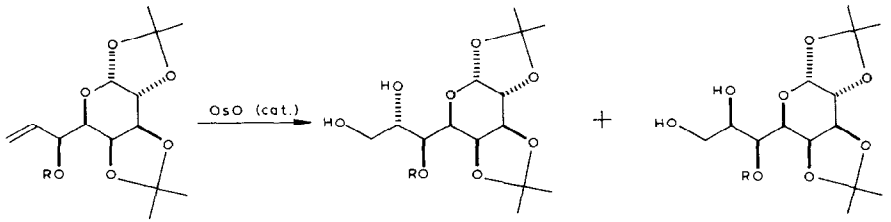
A Acyclic non-conjugated systems



3a[8] R = H
3b[12] R = Bzl
3c[12] R = CH_2OMe

4a R = H ratio >20 : 1
4b R = Bzl ratio 5 : 1
4c R = CH_2OMe ratio 4 : 1

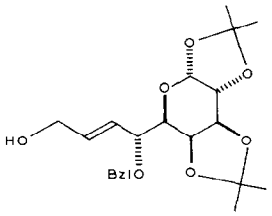
5a R = H
5b R = Bzl
5c R = CH_2OMe



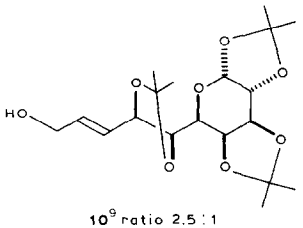
6a[1,12] R = H
6b[1] R = Bzl

7a R = H ratio 3 : 1
7b R = Bzl ratio 4 : 1

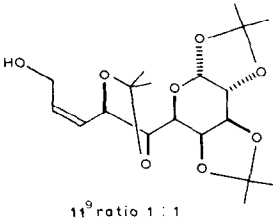
8a R = H
8b R = Bzl



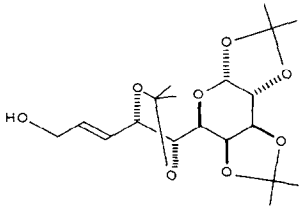
9[12] ratio 8.5 : 1



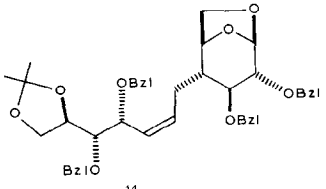
10[9] ratio 2.5 : 1



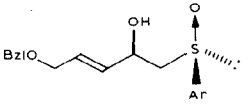
11[9] ratio 1 : 1



12[9] ratio 1.5 : 1



13[14] ratio 6 : 1



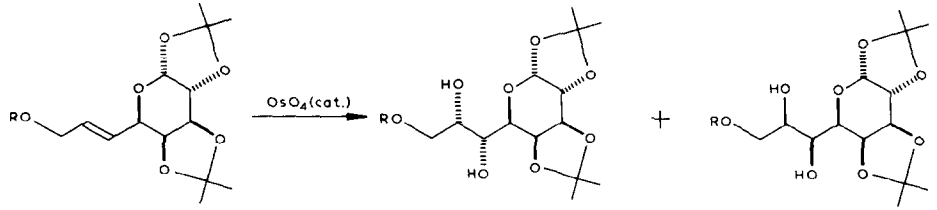
14[15] ratio 1 : 0

involves Wittig olefination of appropriate aldehydes and, if required, subsequent functional-group manipulation. By way of example, the synthesis of methyl (*E*)-2,3,4-tri-*O*-benzyl-6,7-dideoxy-α-D-*gluco*-oct-6-enopyranoside (**25a**) *via* the unsaturated dialdose derivative **2** is described in the Experimental. After catalytic osmylation, the ratios of the two products could usually be determined by integration over the signals for the anomeric protons or, where appropriate, the methoxyl protons (*e.g.*, for **25a** and **26**) in the 360-MHz ^{1}H-n.m.r. spectra. With few exceptions, the stereochemistry of the major osmylation products has been established by their conversion into known compounds, by independent synthesis or chemical correlations, and, occasionally, by physical methods (usually by X-ray crystallographic analysis of a suitable derivative)[5,8–18]. One or two examples showing the formation of both osmylation products are included for each group, with the stereoisomer predicted by Kishi's empirical formulation appearing first. In other examples, the ratio indicated for each compound represents the ratio of the major and minor stereoisomers produced on osmylation, with the proportion of the stereoisomer predicted by Kishi's empirical formulation[3] given first.

The results obtained with the acyclic non-conjugated compounds in group A require little comment, since they generally conform to Kishi's empirical rule by undergoing osmylation in an *anti* fashion with respect to the hydroxyl or alkoxyl group at an adjacent stereocentre. One notable exception, however, is the complete lack of stereoselectivity displayed by the (*Z*)-decenopyranose **11**, whereas the corresponding (*E*)-isomer **10** exhibits a modest stereoselectivity in favour of the predicted product. This result runs counter to the general trend in which the stereoselectivity for the osmylation of (*Z*)-allylic alcohols is higher than that for the corresponding (*E*)-isomer[3].

The examples assembled in group B demonstrate the ability of the pyranose ring-oxygen atom to direct the stereoselectivity of catalytic osmylations. With one exception (see **27**), the major stereoisomer can be formulated as arising from *anti* addition of OsO_4 with respect to the pyranose ring-oxygen atom in the sterically least compressed conformation akin to **1**. This formulation applies to the D-*galacto* compounds **15, 18, 21, 22,** and **23**, and (±)-**24**, as well as to the D-*gluco* and D-*manno* compounds **25** and **26**, respectively. The behaviour of the *C*-silylated D-*gluco* compound **27** towards osmylation is anomalous, whereas the related D-*galacto* compound **23** yields the predicted product with exceptionally high stereoselectivity[16]. From an examination of molecular models, it appears that the sheer bulk of the *tert*-butyldimethylsilyloxy group in an equatorial orientation impedes the attack of OsO_4 from the direction *anti* with respect to the pyranose ring-oxygen atom in the preferred conformation. Note, however, that the presence of the sterically less-demanding benzoyloxy or benzyloxy group at C-4 of the (*E*)-octenopyranosides **24, 25**, and **26** does not result in anomalous behaviour. A point of practical significance is that the stereoselectivity of the osmylation process improves markedly when the primary hydroxyl group of **25a** is esterified with a bulky acid residue, as in **25b**.

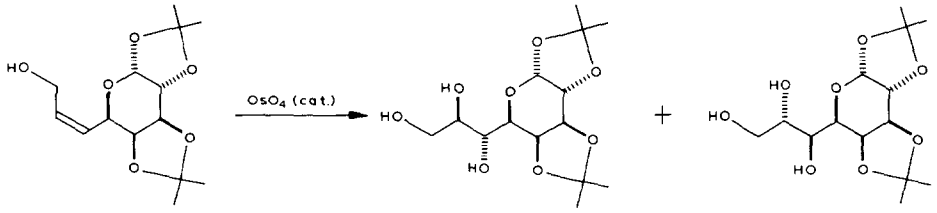
B 6-Enopyranose systems



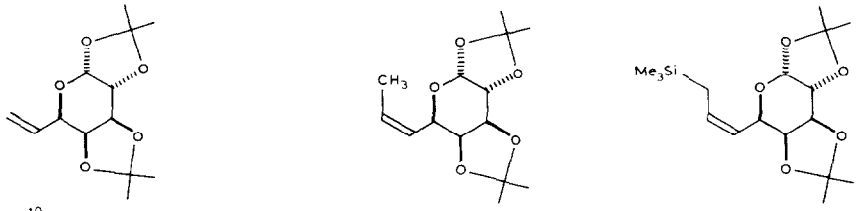
15a[6] R = H
15b[8] R = Bzl

16a R = H ratio 7 : 1
16b R = Bzl ratio 3 : 1

17a R = H
17b R = Bzl



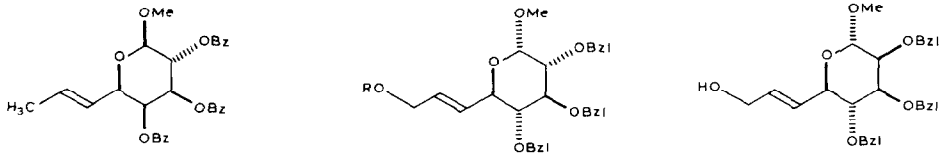
18[8] **19** ratio 7 : 1 **20**



21[10] ratio 2.5 : 1

22[6] ratio 1 : 0

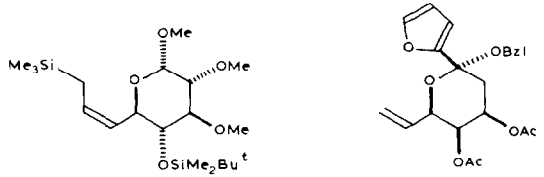
23[16] ratio 20 : 1



(±)-**24**[5] ratio 1 : 0

25a[13] R = H, ratio 3 : 1
25b[3] R = $COCMe_3$, ratio 8 : 1

26[13] ratio 4 : 1

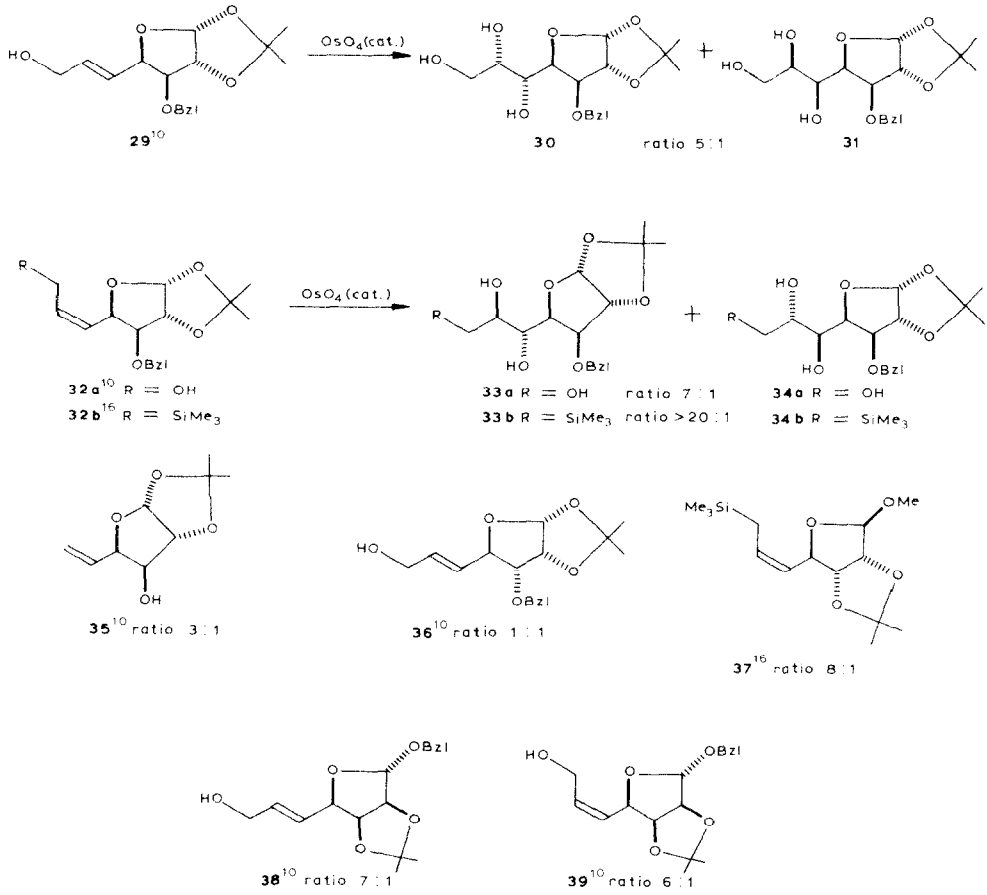


27[16] ratio 1 : 2

(±)-**28**[17] ratio 1 : 0

For the compounds in group C, the addition of OsO_4 may be formulated as being *anti* stereoselective with respect to the furanose ring-oxygen atom. Most members of this group exhibit a reasonable degree of stereoselectivity towards osmylation. The complete lack of stereoselectivity displayed by (*E*)-3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hept-5-enofuranose (**36**) is, once again, probably steric in origin, since the behaviour of its C-3 epimer **29** conforms with the empirical formulation. It seems likely that the benzyl group at O-3 of **36** hampers the approach of the incoming electrophile to the face *anti* to the furanose ring-oxygen atom. However, the *C*-silylated D-*ribo* compound **37**, which has O-3 incorporated into a dioxolane ring forming part of a rigid bicyclic system, behaves in the predicted manner[16]. Thus, where poor stereoselectivity results from injudicious protection of the hydroxyl groups on the furanose ring, a change in the mode of protection or removal of the offending group altogether might lead to a better result*.

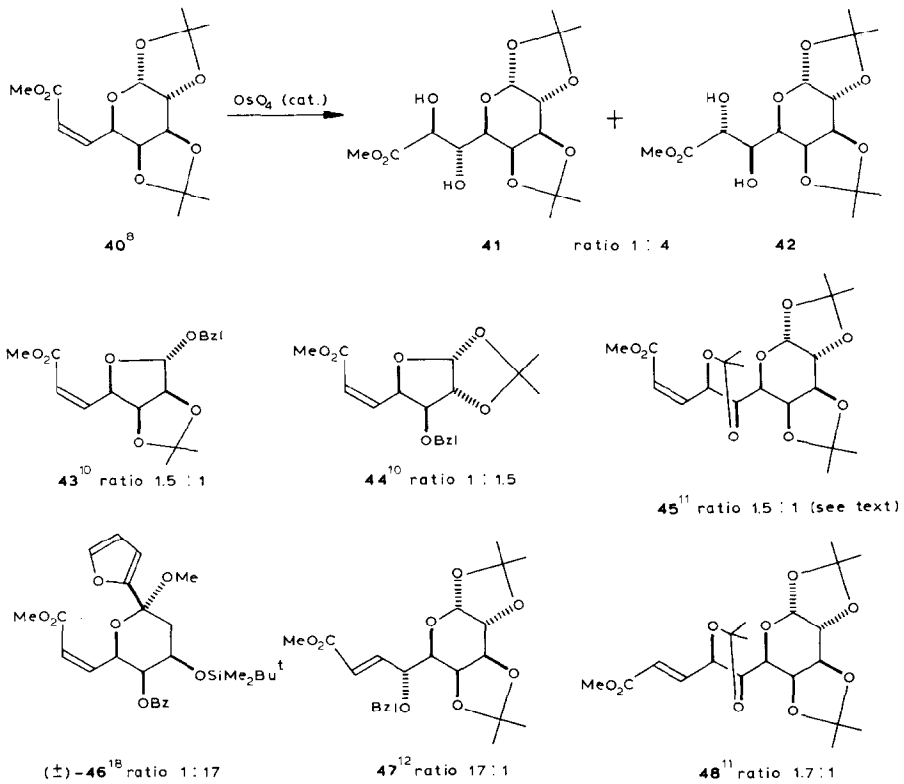
C 5-Enofuranose systems



*While this may prove to be so, our experience also indicates that isolation of the osmylation products becomes more difficult as more hydroxyl groups are left unprotected.

It is among the osmylations of conjugate carbonyl compounds (shown in group D) that exceptions to Kishi's empirical rule[3] are most likely to be encountered or where the stereoselectivity diminishes noticeably. In contrast to those of their hydroxymethyl analogues **18** and **32a**, the osmylations of the (*Z*)-conjugate esters **40** and **44** breach Kishi's formulation to a greater or lesser degree. This situation might be attributed to differences in the preferred conformation between the $\alpha\beta$-unsaturated esters and isolated olefinic systems[3]. Based on the yields of the products isolated, the osmylation of the racemic (*Z*)-conjugate ester **46** also infringes Kishi's formulation to an exceptional degree[18]. For the (*Z*)-conjugate ester **43**, the stereoselectivity favours the predicted stereoisomer, but only marginally. The stereoselectivity for the osmylation of the (*Z*)-conjugate ester **45** is equally low, but, since the products were not identified, a decision as to their compliance with Kishi's formulation cannot be made. It may be significant that all the known exceptions (see also ref. 3) to Kishi's empirical rule among this class of compound possess the (*Z*)-geometry, whereas the catalytic osmylation of all the (*E*)-conjugate esters so far examined resulted in the predicted major stereoisomer, albeit with varying degrees of stereoselectivity that sometimes can be gratifyingly high (*e.g.*, with **47**[12]).

D Conjugated systems



40[8] **41** ratio 1 : 4 **42**

43[10] ratio 1.5 : 1 **44**[10] ratio 1 : 1.5 **45**[11] ratio 1.5 : 1 (see text)

(±)-**46**[18] ratio 1 : 17 **47**[12] ratio 17 : 1 **48**[11] ratio 1.7 : 1

It is hoped that the foregoing examples and comments will provide useful guidelines for those engaged in or contemplating the synthesis of higher-carbon sugars. One additional point noted by Kishi[3] is worth mentioning in view of the current trend to synthesise higher-carbon sugars containing ten or more carbon atoms by convergent, rather than linear, processes. Where hydroxyl or alkoxyl groups are attached to stereocentres at both ends of the olefinic linkage, their effects on the osmylation process seem to be additive (*i.e.*, they may complement or counteract each other). By and large, the osmylation route offers a number of advantages over traditional approaches[19] to the synthesis of seven-[10], eight-[8], and nine-carbon sugars[12], but, because of low stereoselectivities (*e.g.*, with **10** and **12**), is less satisfactory for the synthesis of ten-carbon sugars by an iterative, linear approach[9]. Potentially new and improved syntheses of such compounds as **3a** and **6a**, *via* propargylic alcohols[20,21], and other innovations[22] should also greatly increase the overall efficiency of the routes to higher-carbon sugars in these and similar cases. In our experience, the osmylation procedure can be scaled up without difficulty. It has been used successfully on a multigram scale for the synthesis (from **38**) of partially protected derivatives of L-*glycero*-D-*manno*-heptose, which were subsequently incorporated into oligosaccharides duplicating sections of the basal core region of bacterial lipopolysaccharides[23].

EXPERIMENTAL

General methods. — The general methods used are described in ref. 1. With the exception of those of compounds **2, 25a**, and **26**, syntheses of all the other compounds have already been described in either full or abbreviated form and are referenced accordingly.

Methyl (E)-*2,3,4-tri*-O-*benzyl-6,7-dideoxy*-α-D-gluco-*oct-6-enodialdo-1,5-pyranoside* (**2**). — A solution of methyl 2,3,4-tri-*O*-benzyl-α-D-*gluco*-hexodialdo-1,5-pyranoside (~4.5 g, 9.7 mmol; prepared by Swern oxidation[24] of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside) and formylmethylenetriphenylphosphorane[25] (3.3 g, 10.8 mmol) in anhydrous benzene (70 mL) was boiled under reflux for 90 min, cooled, and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution with 50:1 dichloromethane–acetone) gave **2** (3.57 g, 75%), m.p. 60–60.5° (from ether–hexane), $[\alpha]_D$ +90.5° (*c* 0.9, chloroform) (Found: C, 73.55; H, 6.75. $C_{30}H_{32}O_6$ calc.: C, 73.75; H, 6.6%). ^{1}H-N.m.r. data: δ 9.34 (d, 1 H, $J_{7,8}$ 8 Hz, CHO), 7.38–7.24 (3 m, 15 H, 3 Ph), 6.66 (dd, 1 H, $J_{5,6}$ 4.2, $J_{6,7}$ 15.8 Hz, H-6), 6.28 (ddd, 1 H, $J_{5,7}$ 1.7 Hz, H-7), 4.92 (ABq, 2 H, J_{AB} 11 Hz, PhCH_2), 4.73 (ABq, 2 H, J_{AB} 12 Hz, PhCH_2), 4.71 (ABq, 2 H, J_{AB} 11 Hz, PhCH_2), 4.62 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), and 3.35 (s, 3 H, OMe).

Methyl (E)-*2,3,4-tri*-O-*benzyl-6,7-dideoxy*-α-D-gluco-*oct-6-enopyranoside* (**25a**). — To a stirred and cooled (0°) solution of **2** (1.9 g, 3.9 mmol) in anhydrous dichloromethane (10 mL) under nitrogen was gradually added a M solution of di-isobutylaluminium hydride (6 mL, 6 mmol), while the internal temperature was kept

below 5°. The mixture was stirred for 2 h at 0°, the excess of the reagent was then destroyed with saturated, aqueous ammonium chloride, and dichloromethane (100 mL) was added. Insoluble material was filtered off through glass wool, and the filtrate was washed with a little water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution with 10:1 dichloromethane–acetone) gave **25a** (1.6 g, 84%) as a syrup that slowly crystallised. Trituration with hexane and filtration gave **25a** having m.p. 63.5–64.5°, $[\alpha]_D$ +25° (*c* 1.1, chloroform) (Found: C, 73.1; H, 6.8. $C_{30}H_{34}O_6$ calc.: C, 73.4; H, 7.0%). ^{1}H-N.m.r. data: δ 7.38–7.25 (3 m, 15 H, 3 Ph), 5.95 and 5.65 (2 m, 2 H, $J_{6,7}$ 15.5 Hz, H-6 and H-7), 4.90, 4.74, and 4.69 (3 ABq, 6 H, J_{AB} ~11 Hz, 3 PhCH_2), 4.58 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), and 3.37 (s, 3 H, OMe).

Methyl (E)-*2,3,4-tri*-O-*benzyl-6,7-dideoxy*-α-D-manno-*oct-6-enopyranoside* (**26**). — Compound **26**, $[\alpha]_D$ +45.5° (*c* 0.95, chloroform), was obtained from methyl 2,3,4-tri-*O*-benzyl-α-D-*manno*-hexodialdo-1,5-pyranoside in a similar fashion to **25a** (Found: C, 73.3; H, 7.0%). ^{1}H-N.m.r. data: δ 7.40–7.25 (3 m, 15 H, 3 Ph), 6.02 and 5.81 (2 m, 2 H, $J_{6,7}$ 15.5 Hz, H-6 and H-7), 4.74 (ABq, 2 H, J_{AB} 11 Hz, PhCH_2), 4.76 (ABq, 2 H, J_{AB} 12.5 Hz, PhCH_2), 4.70 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 4.65 (ABq, 2 H, J_{AB} 11.9 Hz, PhCH_2), and 3.31 (s, 3 H, OMe).

General procedure for catalytic osmylation[7]. — A solution of the olefinic sugar (1 equiv.), *N*-methylmorpholine *N*-oxide monohydrate (2 equiv.), and osmium tetraoxide (~0.05–0.1 equiv.) in acetone–water (8:1, 5 mL/mmol of substrate) was stirred at room temperature until t.l.c. indicated that the reaction was complete. The mixture was then diluted with chloroform (50 mL/mmol of substrate), washed with 5M hydrochloric acid (2 mL/mmol of substrate), and shaken vigorously for several minutes with aqueous 45% sodium metabisulphite (3 mL/mmol of substrate). After drying ($MgSO_4$) and concentration under reduced pressure, a solution of the residue in an appropriate solvent was passed down a column of silica gel to remove inorganic impurities, without effecting a separation of the osmylation products. After concentration, the ratio of the products was determined by integration over the resonances for the anomeric protons (or for methyl glycopyranosides over the resonances for the methoxyl protons) in the 360-MHz ^{1}H-n.m.r. spectrum.

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