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DIASTEREOSELECTIVE RADICAL REACTIONS : β–FACE SELECTIVE QUENCHING OF THE 1,2-*O*-ISOPROPYLIDENE-3,4,6-TRI-*O*-BENZYL-D-GLUCOPYRANOS-1-YL RADICAL

David Crich*, [a, b] and Linda B. L. Lim[a]

a: Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK

and

b: Department of Chemistry, University of Illinois at Chicago (M/C 111), Box 4348, Chicago, Il 60680, USA

Summary : Pyrolysis of 3,4,6-tri-*O*-benzyl-1-carbomethoxy-1,2-dideoxy-1-phenylsulfonyl-D-glucopyranose provides the corresponding 1-carbomethoxyglucal which reacts with osmium tetroxide to form a *gluco*-diol.This diol is converted to an acetonide which is saponified and subjected to the Barton reductive decarboxylation procedure with exclusive quenching of the intermediate radical from the β-face representing the first example of a reaction in which a glucopyranosyl radical is selectively quenched from this direction.An improved procedure for the preparation of 3,4,6-tri-*O*-benzyl-D-glucopyranose is presented.

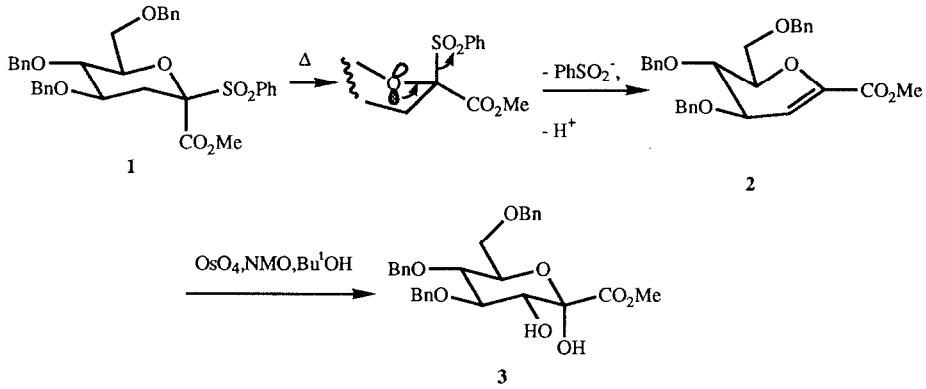
Diastereoselectivity in free radical reactions is an area of considerable current interest[1] with remarkable progress having been made recently in the acyclic stereoselection field by the Curran,[2] Giese[3] and Porter[4] groups. One area of particular interest is that of face selectivity in the quenching of glycos-1-yl (or anomeric) radicals.Thus, the 2,3,4,6-tetraacetates of both the glucopyranos-1-yl and the mannopyranos-1-yl radicals are quenched with high selectivity from the α-face by standard radical traps.[5] This selectivity has been interpreted, on the basis of electron paramagnetic resonance studies, in terms of the intermediate radicals adopting conformations in which the p-orbital occupied by the single electron is periplanar with the β-C-O bond (twisted $B_{2,5}$ and $^4C_1$ conformations for the glucosyl and mannosyl radicals respectively).[6] Good face selectivity is also obtained under certain conditions with anomeric furanosyl radicals.[7] In this laboratory we have been interested in the development of new methodology for the preparation of 2-deoxy-β-glycopyranosidic linkages by the face selective quenching of 1-alkoxy-2-deoxyglycosyl radicals.[8,9] An extension of our methodology has enabled the preparation of the corresponding 2-deoxy-β-*C*-glucosides by thiol quenching of the appropriate anomeric radical.[10] In this letter we report on the further extension of our reductive decarboxylation based methodology to the highly α-facial selective quenching of a 1-alkoxyglucosyl radical and the impressive reversal of this selectivity when the intermediate radical is constrained by the presence of 1,2-*O*-isopropylidene group.

Synthesis of the appropriate radical precursor began with the readily available, crystalline ulosonate ester (1).[8] Attempted eliminations of the sulfinic acid moiety from 1 under a variety of acidic and basic conditions, including the use of magnesium bromide as advocated[11] by Ley for related compounds, were completely fruitless owing probably to the equatorial disposition of the sulfonyl group. This being the case we reasoned that inversion of the conformation of 1 to a boat or alternative chair conformation

* Address correspondence to this author at his Chicago address

would place the leaving group in an axial position antiperiplanar to a ring oxygen lone pair and so greatly facilitate elimination. In the event, heating of **1** under vacuum to 200 ^{0}C in a kugelrohr apparatus gave, after a simple extractive work-up and crystallisation, the 1-carbomethoxyglucal (**2**) in 88% yield on a gram scale (Scheme 1).

Functionalisation at C-2 was achieved by means of an osmium tetroxide catalysed dihydroxlation using *N*-methylmorpoline-*N*-oxide as reoxidant according to the general procedure of Van Rheenan[12] giving a 92% isolated yield of a single crystalline diol (**3**)[13] that was subsequently assigned the *gluco*-configuration by correlation with known compounds (*vide infra*).Stoichiometric osmium tetroxide dihydroxylation of simple D-glucal and its triacetate is known to proceed with high selectivity for the formation of glucose rather than mannose derivatives.[14] Similarly oxyamination of D-glucal with osmium tetroxide and chloramine T provides a mixture of regioisomeric products but which all have the *gluco*-configuration.[15] These observations are at variance with the empirical rule of Kishi[16] in which allylic alcohols and ethers are predicted to react with osmium tetroxide in such a manner that the relative stereochemistry of the preexisting hydroxy, or alkoxy, group and the adjacent newly introduced hydroxy group is *erythro*.We speculate that the predominating stereodirecting factor in the dihydroxylation of glycals is the pseudoaxial lone pair on the ring oxygen and that attack takes place from the antiperiplanar direction.

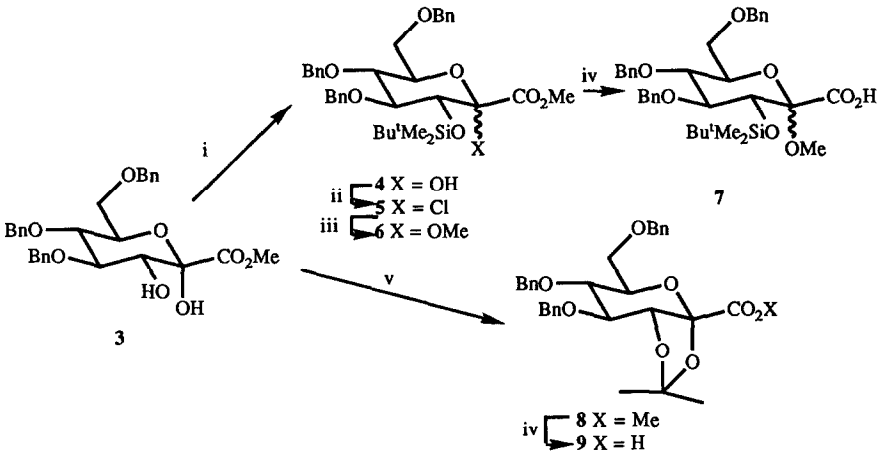


Scheme 1

Reaction of the diol (**3**) with *t*-butyldimethylsilyl triflate in dichloromethane in the presence of pyridine at 0 ^{0}C gave the monosilyl derivative (**4**) in 96% isolated yield. Brief treatment of this product with thionyl chloride in benzene at reflux gave an unassigned mixture of the glycosyl chlorides (**5**) in 97% yield which, on heating to reflux in methanol with magnesium bromide etherate, gave the methyl glycosides (**6**) in 63% yield. Finally saponification of **6** afforded the radical precursor (**7**) essentially quantitively. Reaction of diol (**3**) with 2,2-dimethoxypropane and hydrogen chloride gas gave 76% of the acetonide (**8**) which on saponification gave the corresponding acid (**9**) (Scheme 2).

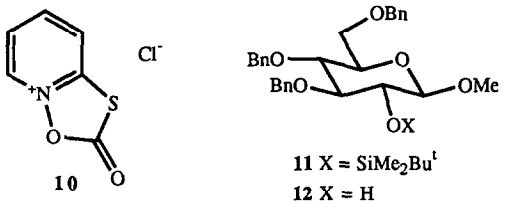
Reductive decarboxylation of the acid (**7**) was achieved by means of the Barton *O*-acyl thiohydroxamate methodology[17] which has served us well in our earlier work.[8,10] Thus reaction of the triethylammonium salt of **7** with the heterocyclic reagent (**10**)[17] in dichloromethane at 0 ^{0}C under a nitrogen atmosphere gave the corresponding bright yellow *O*-acyl thiohydroxamate which was treated *in situ* with commercial *t*-dodecyl mercaptan and then photolysed with a 500 W tungsten lamp to give, after silica gel chromatography, the glucoside (**11**) in 65% yield. The identity of **11** , and hence the *gluco*-configuration of the diol (**3**), was established spectroscopically and also, on desilylation with tetrabutylammonium fluoride, by correlation with the literature compound (**12**).[18] The diastereoselectivity of the reductive decarboxylation reaction was very high (> 95:5 β:α) as estimated by ^{1}H-nmr at 400 MHz on the crude reaction mixture before chromatography. This selectivity is worthy of comment in so far as it is significantly greater than that seen in the corresponding 2-deoxy series and is possiblily indicative of the adoption of a $B_{2,5}$ like conformation, as

suggested by Giese and Sustmann for related glucosyl radicals,[6] by the present radical. A similar increase in selectivity was also observed by Kahne in his related system in going from the 2-deoxyglucosyl series to the glucosyl series.[9]



i) $Bu^tMe_2SiOSO_2CF_3$; ii) $SOCl_2$; iii) MeOH,$MgBr_2$; iv) a,KOH,b,H_3^+O ; v) $MeC(OMe)_2Me$,HCl.

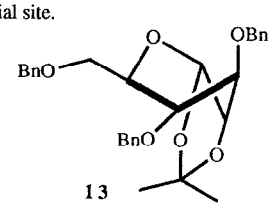
Scheme 2



The identical reductive decarboxylation procedure was then applied to the acid (**9**) resulting in the formation of a single isolated diastereoisomer (**13**) in 67% yield. The acetonide (**13**) was eventually assigned the *cis*-fused configuration with the pyranose ring in the $^OS_2$ twist boat conformation as illutrated on the basis of the ^{1}H-nmr spectrum.[19] Initially some confusion arose when the mp and spectral data for **13** did not correlate with those in the literature for the same substance prepared by an alternative route.[20] Thus it was necessary to prepare an authentic sample of **13** by a further alternative route. This was achieved by reaction of the glucal (**14**)[21] with a catalytic quantity of osmium tetroxide in the presence of *N*-methylmorpholine-*N*-oxide providng the known diol (**15**)[22] in essentially quantitative yield as a mixture of anomers. Reaction of this diol with acetone and a trace of camphor-10-sulfonic acid in benzene at reflux in a Dean Stark apparatus for three days gave 45% of **13** identical in all respects to the sample isolated above. We note in passing that the present preparation of diol (**15**) is a considerable improvement over the literature method and is worthy of adoption as standard practice.

To our knowledge the highly selective formation of the *cis*-fused acetonide on decarboxylation represents the first example of a glucopyranosyl radical reaction in which the normal preferance for α–facial quenching is reversed. It is well known in carbohydrate chemistry that whenever possible under equilibrating conditions 5-membered acetonide rings prefer to fuse *cis* rather than *trans* to 6-membered rings[23] and that kinetic conditions have to be adopted in order to obtain the *trans*-fused isomers.[24] This preference is also seen in the cyclitols[25] and even in simple cyclohexane-1,2-diols.[26] Evidently this propensity for *cis*-acetonide formation overules the usual preference of glucosyl radicals for α-facial quenching. We venture to suggest that as in other radicals substituted with two ether

groups the radical intermediate between **9** and **13** is an sp^3 hybridised σ radical[8] and that in this particular case the single electron occupies the equatorial site.



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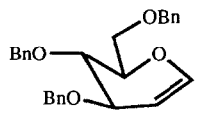

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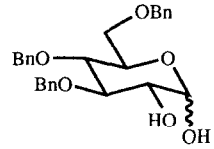

15

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