Stereoselective Free Radical Reactions in the Preparation of 2-Deoxy-β-D-glucosides

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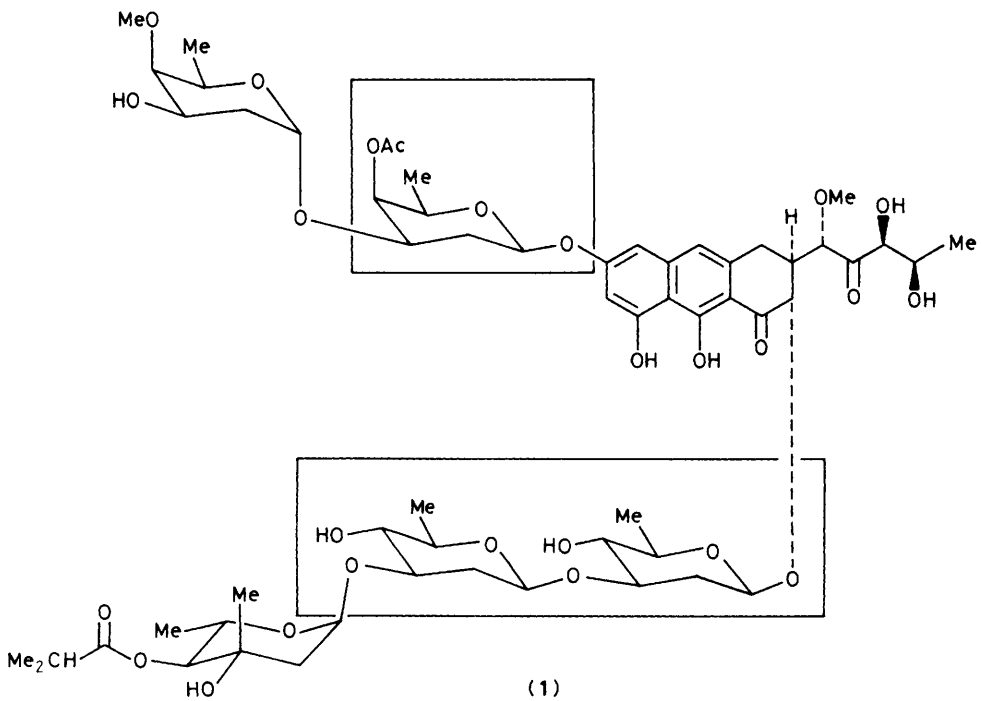
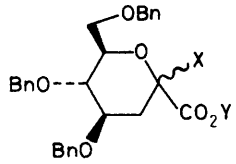
Decarboxylation of the *O*-methyl, *O*-*p*-cresyl and *O*-3β-cholestanyl glycosides of 3-deoxy-4,5,7-tri-*O*-benzyl-D-*arabino*-heptulosonic acid by means of the derived *O*-acyl thiohydroxamates leads stereoselectively to the corresponding 2-deoxy-β-D-glucosides.

The formation of β-glycosidic linkages with 2-deoxy-D-sugars is of some considerable importance owing to their wide occurrence in nature as illustrated[1] by olivomycin A (**1**), a member of the aureolic acid group of antitumour antibiotics.

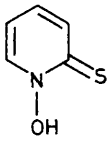


(1)

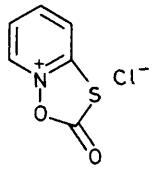


Bn = CH_2Ph

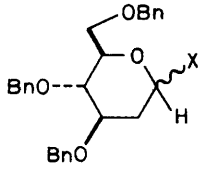
(**2**) X = SPh, Y = Me
(**3**) X = SPh, Y = H
(**4**) X = OMe, Y = Me
(**5**) X = OMe, Y = H
(**6**) X = OC_6H_4-4-Me, Y = Me
(**7**) X = OC_6H_4-4-Me, Y = H
(**8**) X = O-3β-cholestanyl, Y = Me
(**9**) X = O-3β-cholestanyl, Y = H



(**10**)



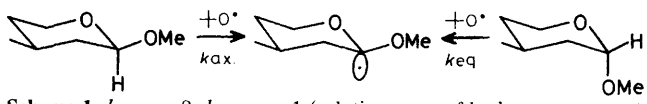
(**11**)



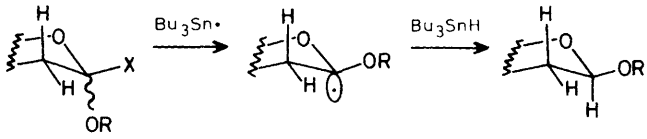
(**12**) X = OMe; β:α = 10:1
(**13**) X = OC_6H_4-4-Me; β only
(**14**) X = O-3β-cholestanyl; β:α = 11:1
(**15**) X = SPh; β:α = 8:1

The application of classical glycosidic coupling reactions to glycosyl donors derived from 2-deoxy-D-sugars leads[2] mainly to the 2-deoxy-α-D-glycosides owing to the lack of stereo-directing anchimeric assistance from the 2-position. Thus in order to form a 2-deoxy-β-D-glycosidic linkage it has been necessary to temporarily introduce a suitable group into the 2-position to direct the coupling reaction. Subsequent reductive removal of this auxiliary provides the 2-deoxy-glycoside as in the work of Thiem[3] and Nicolaou.[4] Here we present some preliminary results which illustrate an entirely new approach to the preparation of 2-deoxy-β-D-glycosidic linkages, which functions in the absence of any anchimeric assistance, and whose key step is a stereoselective free radical reaction.

Recently much progress has been made[5] in the development of free radical chain reactions, based mainly on organotin hydrides,[6] as synthetic methods and in various intramolecular systems (cyclizations) it is possible to predict[7] with confidence the stereochemical outcome. However, in the intermolecular domain, with the exception of some isolated reports,[8] reliable prediction of stereochemistry is at present only possible for reactions involving glycos-1-yl radicals. Thus it is now well appreciated[9] that the radical reactions of acetobromoglucose involve quenching of the glucos-1-yl radical from the α-face; this selectivity has been explained[10] in terms of a preferred boat conformation of the intermediate π-glucos-1-yl radical.

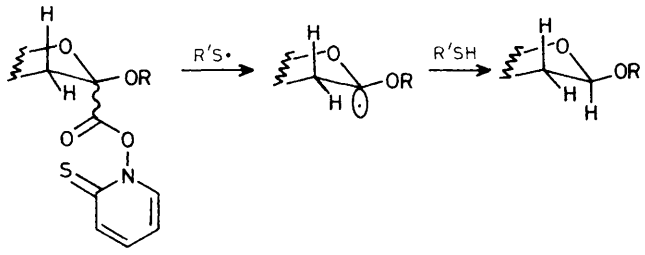


Scheme 1. $k_{axial} = 8$, $k_{equat.} = 1$ (relative rates of hydrogen abstraction by triplet benzophenone at ambient temperature).



X = SPh, SePh, halogen, NO_2

Scheme 2



R′ = $Me(CH_2)_8C(Me)_2$

Scheme 3

The method outlined below is based on stereoselectivity in the quenching of 1-alkoxyglycos-1-yl radicals, a class of reactive intermediate which has hitherto not been employed in organic synthesis.

Reports[11] on the rates of hydrogen abstraction from *cis*- and *trans*-2-methoxy-4-methyltetrahydropyran and on the σ nature of the unique radical formed, in which the single electron occupies the axial position (Scheme 1) led us to propose that tri-n-butylstannane treatment of appropriate mixed orthoesters would furnish 2-deoxy-β-glycosides (Scheme 2).

Synthesis of the required mixed orthoesters however proved to be[12] troublesome and consequently we have modified our approach in such a manner as to generate the required 1-alkoxyglycos-1-yl radicals by radical decarboxylation of ulosonic acid glycosides using the Barton[13] *O*-acyl thiohydroxamate methodology (Scheme 3).

Thus the methyl ulosonate-*O*-methyl glycoside (**4**), prepared from the glycosyl donor (**2**)[14] was saponified to the corresponding acid (**5**) which was coupled with the thiohydroxamic acid (**10**) by means of dicyclohexylcarbodiimide (DCC) to give its bright yellow[13] derived *O*-acyl thiohydroxamate. This latter compound was not isolated but immediately subjected to tungsten photolysis in the presence of excess t-dodecyl mercaptan† to give the 2-deoxy-D-glucoside (**12**)[15] in 36% isolated yield as a 10:1 β:α mixture so vindicating the above hypothesis. A more straightforward procedure involved reaction of the acid (**5**) with salt (**11**)[13]‡ and triethylamine in

† We recommend the use of this inexpensive and relatively odourless thiol in place of t-butyl mercaptan as employed in the original[13] procedure or triethylmethyl mercaptan as in later versions (D. H. R. Barton and D. Crich, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1603; A. J. Bloodworth, D. Crich, and T. Melvin, *J. Chem. Soc., Chem. Commun.*, 1987, 786).

‡ All new compounds gave satisfactory spectroscopic and microanalytical data.

CH_2Cl_2 followed by tungsten photolysis in the presence of the thiol leading to a 40% isolated yield of (**12**), again as a 10:1 β:α mixture. Coupling of *p*-cresol with (**2**) by means of mercuric chloride in CH_2Cl_2 gave the glycoside (**6**) which after saponification to (**7**) was subjected to the decarboxylation procedure yielding the 2-deoxy-D-glucoside (**13**) as a single isomer (β). 3β-Cholestanol was coupled to the glycosyl donor (**2**) with *N*-bromosuccinimide according to Nicolaou[14] to give (**8**), which after saponification to (**9**) was allowed to react with (**11**) and then photolysed in the presence of excess mercaptan to give the 2-deoxyglucoside (**14**) in 51% yield as an 11:1 β:α mixture.

Finally, saponification of (**2**) gave (**3**) which was reacted with (**11**) and then photolysed in the presence of t-dodecyl mercaptan in the standard manner leading to the isolation of the 2-deoxythioglucoside (**15**) in 50% yield as an 8:1 β:α mixture.

In conclusion we have demonstrated that the selective α-facial quenching of glucos-1-yl radicals can be extended to 1-alkoxylglucos-1-yl radicals and have developed this concept into a method for the synthesis of 2-deoxy-β-D-glucosides.

We thank the S.E.R.C. for financial support and the Nuffield Foundation for an equipment grant.

Received, 1st June 1988; Com. 8/02161I

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