

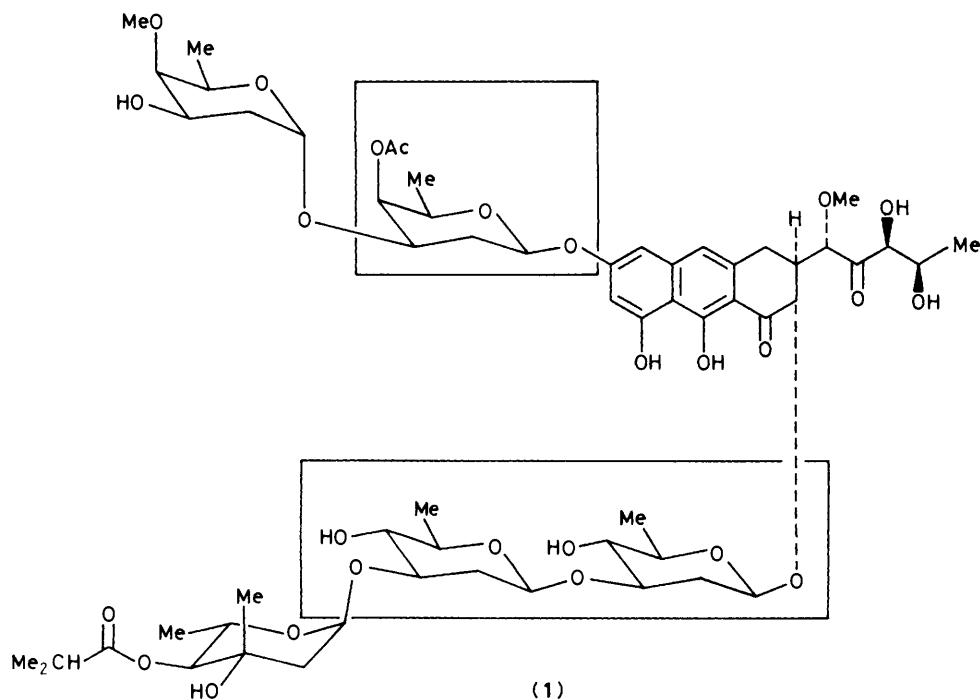
Stereoselective Free Radical Reactions in the Preparation of 2-Deoxy- β -D-glucosides

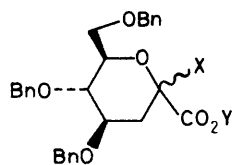
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Decarboxylation of the *O*-methyl, *O*-*p*-cresyl and *O*-3 β -cholestanyl glycosides of 3-deoxy-4,5,7-tri-*O*-benzyl-D-*arabino*-heptulosonic acid by means of the derived *O*-acyl thiohydroxamates leads stereoselectively to the corresponding 2-deoxy-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

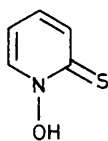
The formation of β -glycosidic linkages with 2-deoxy-D-sugars is of some considerable importance owing to their wide occurrence in nature as illustrated¹ by olivomycin A (**1**), a member of the aureolic acid group of antitumour antibiotics.



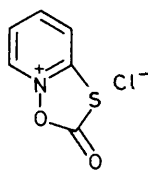


Bn = CH₂Ph

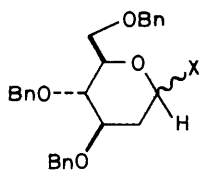
- (2) X = SPh, Y = Me
 (3) X = SPh, Y = H
 (4) X = OMe, Y = Me
 (5) X = OMe, Y = H
 (6) X = OC₆H₄-4-Me, Y = Me
 (7) X = OC₆H₄-4-Me, Y = H
 (8) X = O-3β-cholestanyl, Y = Me
 (9) X = O-3β-cholestanyl, Y = H



(10)



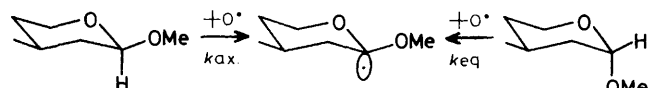
(11)



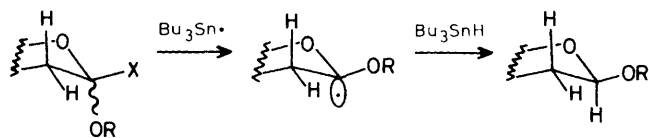
- (12) X = OMe; β:α = 10:1
 (13) X = OC₆H₄-4-Me; β only
 (14) X = O-3β-cholestanyl; β:α = 11:1
 (15) X = SPh; β:α = 8:1

The application of classical glycosidic coupling reactions to glycosyl donors derived from 2-deoxy-D-sugars leads² 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 Thiem³ 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 made⁵ 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 predict⁷ 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 appreciated⁹ that the radical reactions of acetobromoglucose involve quenching of the glucos-1-yl radical from the α-face; this selectivity has been explained¹⁰ in terms of a preferred boat conformation of the intermediate π-glucos-1-yl radical.

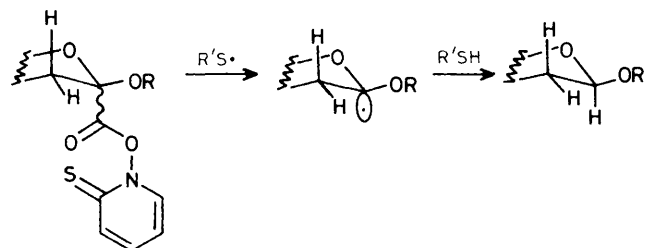


Scheme 1. $k_{\text{axial}} = 8$, $k_{\text{equat.}} = 1$ (relative rates of hydrogen abstraction by triplet benzophenone at ambient temperature).



X = SPh, SePh, halogen, NO₂

Scheme 2



R' = Me(CH₂)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.

Reports¹¹ 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 be¹² 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 Barton¹³ *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 yellow¹³ 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 original¹³ procedure or triethylmethyl mercaptan as in later versions (D. H. R. Barton and D. Crick, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1603; A. J. Bloodworth, D. Crick, and T. Melvin, *J. Chem. Soc., Chem. Commun.*, 1987, 786).

‡ All new compounds gave satisfactory spectroscopic and microanalytical data.

CH₂Cl₂ 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 CH₂Cl₂ 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 Nicolaou¹⁴ 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-alkoxyglucos-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. 8/021611

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