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SEQUENTIAL DIASTEREOSELECTIVE FREE RADICAL REACTIONS: SYNTHESIS OF AN ADVANCED OLIVOMYCIN A C-D DISACCHARIDE

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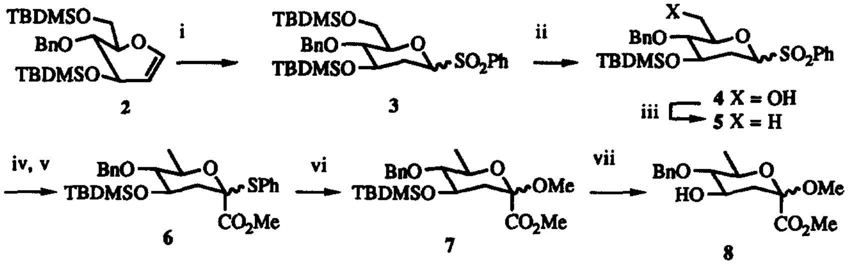
Summary: The synthesis of an advanced olivomycin A C-D disaccharide is described in which the anomeric configuration of both 2-deoxy-β-glycosidic linkages is determined by a sequential diastereoselective radical reaction at the end of the synthesis.

The prediction and control of diastereoselectivity in free radical reactions is a subject of extensive current interest. Considerable progress has been made in particular in the area of acyclic radical diastereoselection.[1] Our own efforts in the field of radical diastereoselectivity have centered on the generation and trapping of 1-alkoxyglycosyl radicals and their use in the preparation of 2-deoxy-β-glycosidic linkages,[2,3] one of the more difficult types glycosidic bond to access by conventional means.[4,5,6] In this letter we describe a convergent approach to the synthesis of an advanced olivomycin A C-D disaccharide (1) in which the stereochemistry at both anomeric positions is determined in a novel sequential diastereoselective radical reaction based on our earlier studies.[2]

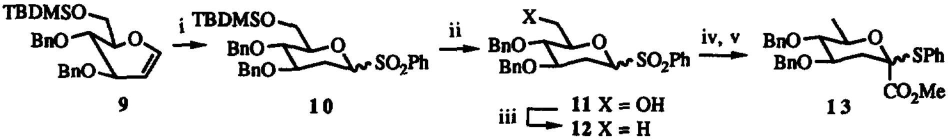
The sequential diastereoselective radical strategy adopted for the formation of 1 required the preparation of a disaccharide 14 comprised of two ulosonic acids linked 2-4 and coupled at the reducing end to methanol. This in turn required the preparation, in the D-series, of two ulosonate esters, one in the form of the glycosyl acceptor 8 with its free 4-OH group, and the other as the glycosyl donor 13.

Our initial attempts at the preparation of 8 from D-glucal by minor modifications of our general synthetic approach to heptulosonic acids[2] were hindered by problems with the regioselective introduction of appropriate protecting groups.[7] Eventually this problem was solved by use of the readily available, regioselectively protected D-glucal 2[8] introduced by Schmidt. The synthesis of 8 from 2 was largely uneventful and is described in Scheme 1. The most noteworthy features of the synthesis were the use of the ammonium fluoride in methanol[9] for the selective removal of the primary silyl group in the conversion of 3→4 and the timing of the tin hydride mediated removal of the 6-OH group which was chosen so as to facilitate removal of stannane derived byproducts. A closely related procedure, starting from an alternatively protected glucal 9,[10] was used for the preparation of the eventual D-unit (13) of the target molecule (Scheme 2).



i: a) HCl; b) PhSH, ^{i}Pr$_2$EtN; c) Mg monoperoxyphthalate (MMPP),70%; ii: NH$_4$F, MeOH, 77%; iii: a)TsCl, py; b) NaI, EtCOMe, Δ; c) Bu$_3$SnH, 85%; iv: a) LiN^{i}Pr$_2$, -78°C; b) MeOCOOMe, 79%; v: a) Li naphthalenide (LN); b) PhSSPh, 68%; vi: HgCl$_2$, MeOH, 93%; vii: camphor-10-sulfonic acid, MeOH, 62%

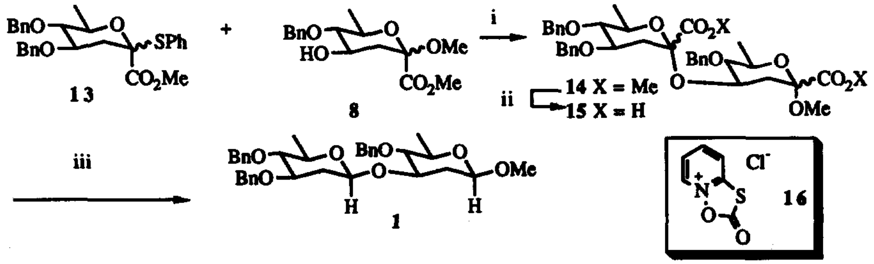
Scheme 1



i: a) HCl; b) PhSH, ^{i}Pr$_2$EtN; c) MMPP,72%; ii: NH$_4$F, MeOH, 83%; iii: a)TsCl, py; b) NaI, EtCOMe, Δ; c) Bu$_3$SnH, 80%; iv: a) LiN^{i}Pr$_2$, -78°C; b) MeOCOOMe, 87%; v: a) LN; b) PhSSPh, 70%

Scheme 2

With both monomeric units in hand, attention was turned to the potentially problematic formation of the disaccharide. In the event the glycosyl acceptor (8) was coupled to the donor (13) with the aid of silver triflate in dichloromethane at room temperature in the presence of 4Å molecular sieves, resulting in a complex (5:3:2:2) mixture of 4 diastereoisomeric disaccharides (14) with a combined yield of 20% (Scheme 3). A number of other methods for the formation of glycosidic bonds to ulosonic and sialic acids were surveyed[11] but none gave a significant yield in the present example. The formation of glycosidic linkages to ulosonic and sialic acids is a notorious problem for all but the most simple alcohols and the low yield in the formation of 14 was not unexpected.[12] Saponification of 14 to 15 was essentially quantitative. Finally the diacid 15 was subjected to the Barton reductive decarboxylation protocol.[13] Thus, treatment of 15 with 2 equivalents each of triethylamine and the heterocyclic salt 16 gave the corresponding bis-thiohydroxamate derivative that was treated *in situ* with an excess of t-butylmercaptan and the whole photolysed under nitrogen with a 250W sunlamp in a circulating cold water bath. After completion, indicated by decolourization of the lemon yellow reaction mixture, the target disaccharide 1 was isolated by preparative tlc on silica gel in 76% yield (Scheme 3). Examination of the disaccharide by ^1H and ^{13}C NMR spectroscopy revealed that it was contaminated with approximately 15% of a second and 5% of a third disaccharide. The first of these byproducts is assigned as the β(1-3)-α-OMe -isomer of 1 and the less important, second byproduct as the α(1-3)-β-OMe -diastereoisomer.



i: AgOTf, CH_2Cl_2, 4A sieves, 20%; ii: NaOH, H_2O, THF, 99%; iii: a) 16, Et_3N, CH_2Cl_2, b) ^{t}BuSH, hυ, 8 °C, 76%

Scheme 3

This synthesis, with its transformation of a complex mixture of 4 diastereoisomers into one very major diastereoisomer of the product, serves to underline the potential of alkoxyglycosyl radicals in the preparation of 2-deoxy-β-glycosidic linkages. At the same time the main fault in the current system is clearly identified as being the inefficient formation of glycosidic bonds to ulosonate esters. This very general problem, also relevant to the chemistry of sialic acids, is currently under investigation in this laboratory.

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