A Synthesis of Aryl *C*-Glycosides *via* Polyketides†

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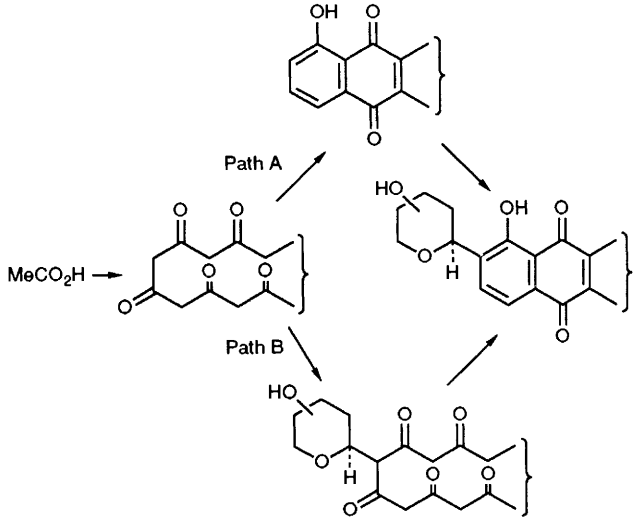
3,5,9,11-Tetraoxotridecanedioates containing *C*-glycoside units on the side chain were generated from 1-hydroxy sugars, β-ketoglutarate and acetoacetate; intramolecular condensation of the polyketide compounds gave *C*-glycosidic naphthalene-1,8-diols regio- and stereo-selectively.

A number of polycyclic aromatic natural products with the *C*-glycoside moiety have recently been isolated.[1] Taking into account the fact that many of them are of polyketide origin, two possible routes can be presented for the regioselective biosynthesis of the aryl *C*-glycosidic linkages (Scheme 1). The first route involves the introduction of the *C*-glycoside to the aromatic nuclei (path A). The second route consists of the aromatization of the *C*-glycosidic polyketide, which may be formed by the Knoevenagel-type reaction of the β-carbonyl compound and the sugar (path B). We have been studying the aromatization of synthetic polyketides,[2] which we have now applied to the synthesis of aryl *C*-glycosides through the 'biomimetic' route B reaction.

The idea was first examined with a simple lactol **1a**[3] (Scheme 2). Racemic lactol **1a** was condensed with β-oxoglutarate under Knoevenagel condition giving the pyran **2a**, the ketone moiety of which was reduced with $NaBH_4$ in ethanol at −78 °C giving the β-hydroxyglutarate **3a**. The 3,5,9,11-tetraoxotridecanedioate **4a** was generated by treating **3a** with acetoacetate dianion. Here, the use of a 1:1 mixture of THF and HMPA as solvent is essential for the condensation; a smaller proportion of HMPA did not give satisfactory results. The polyketide intermediate **4a** without isolation was aromatized with $Ca(OAc)_2$ in refluxing methanol giving the *C*-glycosidic naphthalene-1,8-diol **5a** in 50% yield as a single isomer, m.p. 138–139 °C (from EtOAc–hexane).

Optically active sugar derivatives were next employed in the synthesis. The 2-deoxy-1-hydroxy sugars **1b** and **1c**, conveniently prepared from L-rhamnal and D-glucal respectively,§ were converted to the glutarates **3b** and **3c**. Similar



Scheme 1

† *Abbreviations used*: THF, tetrahydrofuran; HMPA, hexamethylphosphoric triamide; MOM = methoxymethyl; NBS = *N*-bromosuccinimide; DMSO = dimethyl sulfoxide; AIBN = azoisobutyronitrile.

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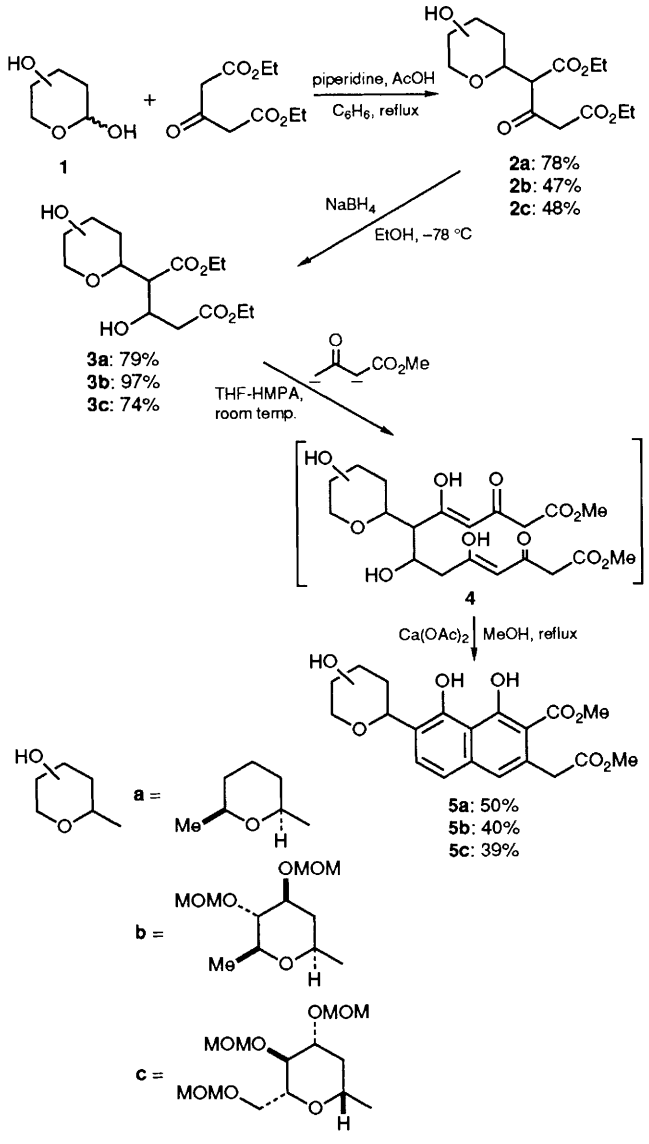
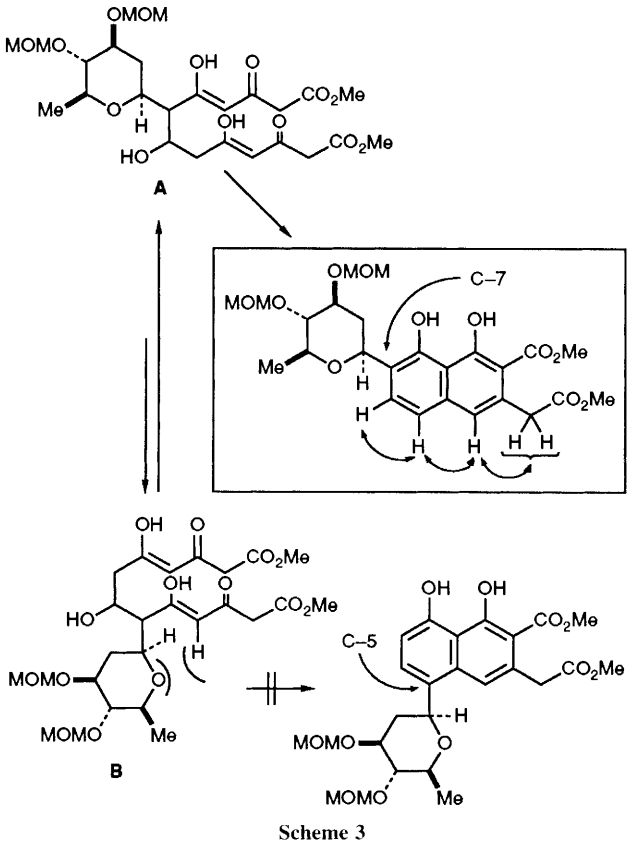
§ 1-Hydroxy sugars were synthesized from MOM protected L-rhamnal or D-glucal: (i) NBS, DMSO, H_2O, room temp.; 94% for the former, 91% for the latter; (ii) Bu^n_3SnH, AIBN, benzene, reflux; 95% for the former, 89% for the latter.



Scheme 2



Scheme 3

procedures to those described above gave the expected *C*-glycosides **5b** and **5c**, again as single isomers. For example, under nitrogen, to a THF (140 ml) and HMPA (140 ml) solution of the lithium–sodium dianion of acetoacetate (121 mmol) was added a THF (5 ml) solution of **3b** (8.1 mmol) at 0 °C. The mixture was stirred for 2.5 h at room temperature, and quenched by adding to 2 mol dm^{-3} HCl. The crude polyketide obtained after normal extraction procedures was refluxed under nitrogen in methanol (30 ml) with $Ca(OAc)_2 \cdot 2H_2O$ (12 mmol) for 2.5 h. The *C*-glycoside **5b** was chromatographically purified as the diacetate (Ac_2O, Et_3N, CH_2Cl_2; 0 °C; 2 h), and then **5b** was regenerated (1.64 g, 40%) with K_2CO_3–methanol, m.p. 135–136 °C (from EtOAc–hexane), $[\alpha]_D^{20}$ −117 (*c* 1.0, $CHCl_3$), **5c**: m.p. 109–110 °C (from EtOAc–hexane), $[\alpha]_D^{20}$ +98 (*c*. 1.0, $CHCl_3$).

The introduction of the *C*-glycosidic linkage at the 7-position of the naphthalenediol was confirmed by 2D NMR studies. The regioselectivity can be explained as follows (Scheme 3). The 5- and 7-substituted products may be formed *via* conformation **A** and **B**, respectively, in which the 1,3-diketone moieties exist in their enol form with intramolecular hydrogen bonding. The steric repulsion between the vinylic hydrogen at the 4-position and the 6-substituents disfavour the conformation **B**, and preferential formation of 7-substituted products *via* conformation **A** takes place. This type of regioselectivity could be predicted from our studies on the polyketide condensation.[2]

The β-configuration of the anomeric centres was determined from the coupling constants (*J* 2, 10 Hz). It is considered that the stereochemistry was established at the stage of the Knoevenagel condensation as the thermodynamically stable equatorial isomer. In fact, the Knoevenagel products **2b** and **2c** were mixtures of two isomers (^{13}C NMR), although two new asymmetric centres were generated from **1b** and **1c**. These chiral centres disappeared at the aromatization stage giving the *C*-glycoside as a single isomer.

Friedel–Crafts-type reactions of aromatic compounds with sugar derivatives have been extensively studied for the synthesis of aryl *C*-glycosides.[4] The diverse reactivities of aromatic compounds towards electrophilic substitution, however, have prevented the development of general methods with a wide applicability. Highly reactive electron-rich aromatic nuclei tend to give polyalkylated products, and aromatic rings which possess strongly electron-withdrawing groups such as quinones are inert to the reaction. Some organometallic approaches have been reported utilizing either metallated sugars or metallated arenes.[5] Another type of *C*-glycoside synthesis involves the construction of aromatic nuclei from precursors containing the *C*-glycoside moiety.[6] The utilization of *C*-glycosidic polyketides is a promising approach in this category. In fact, **5b** has been used in the synthesis of a natural benz[*a*]anthracene antibiotic.[7]

It should also be noted that the above reactions suggest the possibility of the presence of *C*-glycosidic polyketides in biological systems.

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