Aureolic Acid Antibiotics: Synthesis of Model 2-Deoxy-β-glycosides of α-Hydroxytetralone

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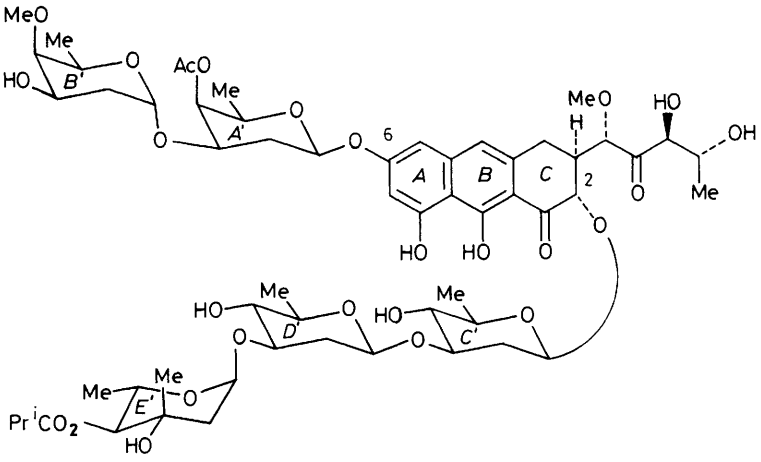
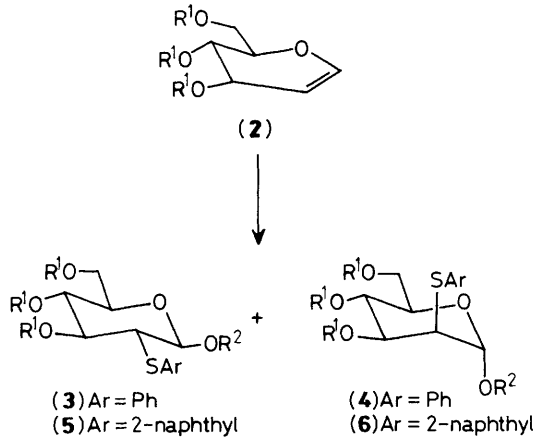
Glucals have been reacted with the naphthylsulphenate ester of 2-hydroxytetralone to afford 2-thio-β-glycosides, which are treated with Raney Ni to produce 2-deoxy-β-glycosides as models for the aureolic acid antibiotics.

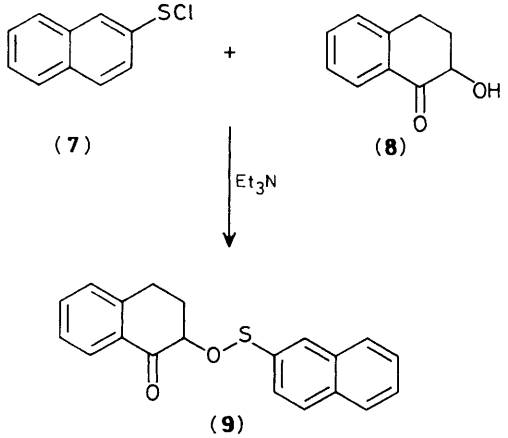
For many natural products, a link-up between an aglycone and a carbohydrate is the ultimate requirement for a total synthesis. The aureolic acid antibiotics, exemplified by olivomycin A (**1**), have two such connections, a β-linkage between the acyloin hydroxy group at C-2 and sugar *C'* (D-olivose) and a β-linkage between the phenolic OH at C-6 and sugar *A'* (4-acetyl-D-oliose).[1] Since syntheses exist of both the aglycone and carbohydrate components,[2] there remains the ultimate challenge of establishing these final glycoside bonds. Although there is extensive literature on glycosidation,[3] preparations of the specific 2-deoxy-β-glycosidic connections required for the aureolic acids, namely links to



(1) Olivomycin A



Scheme 1. *Reagents*: ArSOR, TMSOTf (1 equiv.), CH_2Cl_2, −20 °C.



Scheme 2

acyloins and phenols, are unknown or rare. Interestingly, one efficient method for producing the 2-deoxy-α-configuration directly from glucals has been published describing a model approach to the aureolic acid problem. Thus, *N*-iodosuccinimide (NIS) treatment of rhamnal diacetate in the presence of a 2-hydroxytetralone afforded only 2-iodo-α-glycosides with the unnatural anomeric configuration.[4] Of the β-glycoside syntheses reported in the recent literature,[5] we chose to employ the Ogawa method,[5c] (Scheme 1) because it used readily available glucals such as (**2**) as starting materials, to which were added phenylsulphenyl esters of the aglycones with $Me_3SiO_3SCF_3$ (TMSOTf) catalysis, affording moderate to good ratios of β-glycosides (**3a**) to α-isomers (**4**).

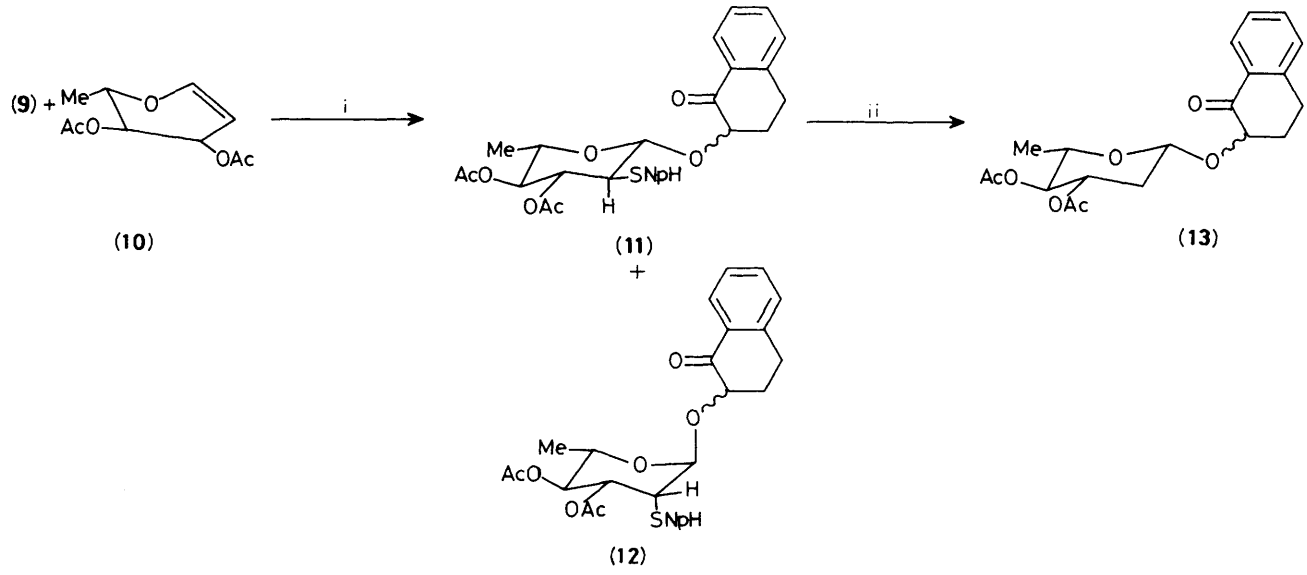
Our minor modification began with a search for a less volatile, stable, solid sulphenyl chloride. We settled on 2-naphthylsulphenyl chloride to prepare the sulphenate esters of aglycones. We observed that the 2-naphthylsulphenate esters of simple alcohols, upon reaction with glycals, afforded glycosides (**5**) and (**6**) with yields and β/α ratios comparable to those reported by Ogawa.

The unprecedented extension of the Ogawa method to an acyloin began with the preparation of the naphthylsulphenate (**9**) of 2-hydroxytetralone (**8**) in good yield *via* treatment of the acyloin with naphthylsulphenyl chloride (**7**) in ether at −78 °C, with exactly one equivalent of Et_3N as a base (Scheme 2).[6] The acyloin sulphenate ester is not very stable and must be used without purification within an hour of its preparation. Treatment of sulphenate (**9**) with diacetyl-L-rhamnal (**10**) and TMSOTf resulted in the formation of a 66% yield of a mixture of glycosides, with the β-isomer predominating in a 58/42 ratio (Scheme 3). Careful chromatography gave a single β-dia stereoisomer (**11**), a fraction containing one β and one α isomer, and finally the α-isomer (**12**). Four diastereoisomers are the expected result of using racemic acyloin and homochiral rhamnal.

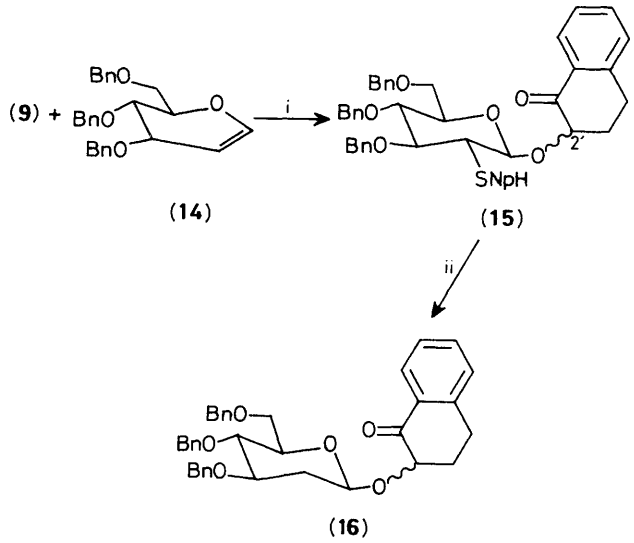
The β-stereochemistry of pure (**11**) and its acyloin epimer was easily identified by the two diaxial couplings exhibited by the unique proton at C-2, δ 3.45.† The naphthylthio group was

† *Selected n.m.r. data* for acyloin 2-naphthylthioglycosides: (**11**), C-1, δ 4.71 (d, *J* 8.86 Hz), C-2, δ 3.45 (dd, *J* 11.27, 8.86 Hz). C-2′ epimer of (**11**), C-1, δ 5.00 (d, *J* 8.86 Hz), C-2, δ 3.36 (dd, *J* 8.87, 11.23 Hz). (**12**), C-1, δ 5.64 (d, *J* 1.07 Hz), C-2, δ 4.43 (dd, *J* 5.55, 1.13 Hz). C-2′ epimer of (**12**), C-1, δ 5.30 [br.s (unresolved)], C-2, δ 4.26 (dd, *J* 4.69, 1.20 Hz). (**15**), C-1, δ 5.03 (d, *J* 8.67 Hz), C-2, δ 3.45 (dd, *J* 10.36, 8.74 Hz). C-2′ epimer of (**15**), δ 4.78 (d, *J* 8.56 Hz), C-2, δ 3.67 (dd, *J* 10.62, 8.52 Hz).

Data for acyloin deoxyglycosides: (**13**), C-1, δ 4.84 (dd, *J* 9.78, 1.98 Hz), C-2e, δ 2.49—2.25 (part of m), C-2a, δ 1.88 (td, *J* 9.78, 12.06 Hz). (**16**), C-1, δ 4.96 (dd, *J* 7.35, 2.47 Hz), C-2e, δ 2.74—2.68 (part of m), C-2a, δ 1.75 (ddd, *J* 11.68, 10.14, 7.41 Hz).



Scheme 3. *Reagents*: i, TMSOTf, CH_2Cl_2, −20 °C; ii, Raney Ni, EtOH, reflux.



Scheme 4. *Reagents*: i, TMSOTf (0.1 equiv.), CH_2Cl_2, −20 °C; ii, Raney Ni, EtOH, reflux.

removed with W-2 Raney Ni in refluxing ethanol to afford (**13**) in 65% yield. The stereoselectivity of the glycosylation with rhamnal diacetate is not high. However, when the reaction was carried out with sulphenate (**9**) and tribenzyl-D-glucal (**14**), a 78% yield of two diastereoisomeric (at acyloin C-2′) β-glycosides (**15**) could be isolated.‡ These were also cleanly desulphurized by Raney Ni treatment to afford (**16**) in 62% yield (Scheme 4).

In summary, we have demonstrated the practical conversion of glucals to 2-deoxy-β-glycosides of an acyloin representative of that found in the aureolic acid antibiotics. The extension of our methods to a total synthesis requires di- and tri-saccharide glycals and a suitable aglycone with C-2 and C-6 hydroxy groups available for derivatization.

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‡ Minor products are formed, but we have not conclusively proven them to be α-glycosides.

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