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SYNTHESIS OF THE DISACCHARIDE C-D FRAGMENT FOUND IN EVERNINOMICIN-C AND -D, AVALAMYCIN-A AND -C, AND CURAMYCIN-A: STEREOCHEMISTRY AT THE SPIRO-ORTHOLACTONE CENTER

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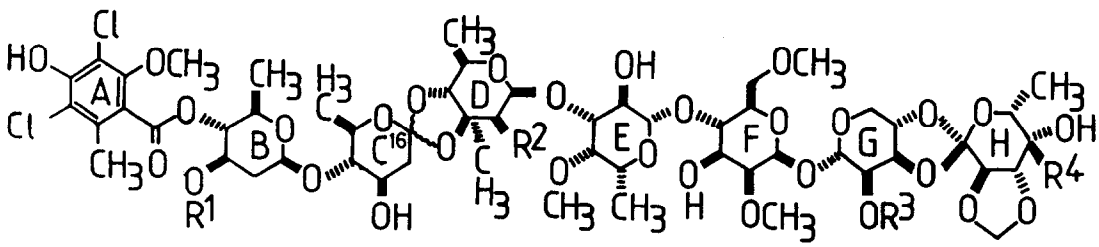
Summary *The two isomers at the spiro-ortholactone center of the disaccharide C-D fragment of orthosomycins have been synthesized. Their mild acidic hydrolysis was under stereoelectronic control with each isomer leading to only one ester. It is therefore possible, from these results, to deduce the absolute configuration of the spiro-center in natural antibiotics.*

An oligosaccharide group of antibiotics, the orthosomycins,[1] are structurally characterized by the presence of one or two unique interglycoside spiro-ortholactone linkages, replacing the traditional acetalic junctions. Flambamycin (**1**), everninomicins (**2-5**), avilamycins (**6, 7**) and curamycin-A (**8**) are the esters of dichloroisoeverninic acid (residu A) which figure among the members of this oligosaccharide group (Scheme 1). The structure of everninomicin-D[2] (**4**) and



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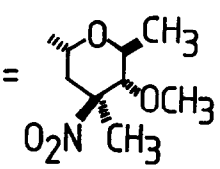
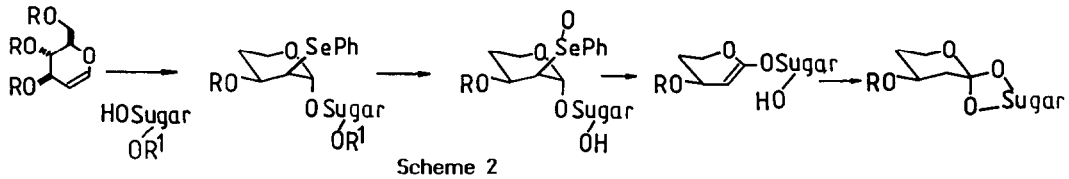


1 R^1 H, R^2 OH, R^3 $COCH(CH_3)_2$, R^4 $COCH_3$ Flambamycin
2 R^1 L, R^2 OH, R^3 CH_3, R^4 $CH(OCH_3)CH_3$ Everninomicin-B
3 R^1 L, R^2 H, R^3 CH_3, R^4 $CH(OCH_3)CH_3$ Everninomicin-C
4 R^1 L, R^2 H, R^3 CH_3, R^4 (S)-$CH(OCH_3)CH_3$ Everninomicin-D
5 R^1 R^2 H, R^3 CH_3, R^4 (S)-$CH(OCH_3)CH_3$ Everninomicin-2
6 R^1 R^2 H, R^3 $COCH(CH_3)_2$, R^4 $COCH_3$ Avilamycin-A
7 R^1 R^2 H, R^3 $COCH(CH_3)_2$, R^4 (S)-$CH(OH)CH_3$ Avilamycin-C
8 R^1 R^2 H, R^3 R^4 $COCH_3$ Curamycin-A

Scheme 1

avilamycin-A and -C[3] (**6, 7**) has been elucidated[4] although the absolute configuration at the ortholactone center of residue C (C-16) remained unknown. Mild acidic hydrolysis of oligosaccharide antibiotics **1-8** results in the selective cleavage of spiro-center C-16, giving an ester located at the O-4 position of residue D (D-evalose or 2-deoxy-D-evalose). This remarkable behavior may well be attributed to the configuration at C-16 in which, according to work done by Deslongchamps[5], stereoelectronic effects have the potential to influence the selectivity of the cleavage. Hydrolytic studies of synthetic models — isomers of a known configuration at the spiro-center — could thus provide valuable stereochemical information. We now report the first synthesis of the two possible isomers at C-16 of the disaccharide C-D fragment[6] and the study of their hydrolysis under acidic conditions.

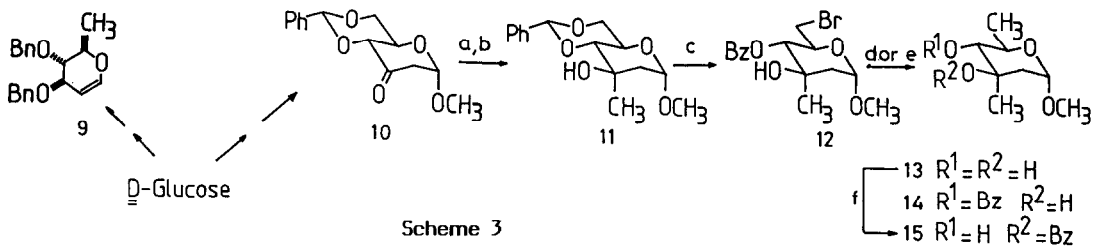
The synthetic scheme adopted follows a procedure previously reported by our group[7] (Scheme 2). Glycosyloxyselenation[8] of a suitably protected sugar, oxydation at selenium, and regiospecific syn-elimination of the resulting selenoxide lead to a transient ketene acetal. Cyclization



Scheme 2

by an intramolecular nucleophilic attack of a properly positioned hydroxy-group then occurs, yielding the desired spiro-ortholactone function.

A routine exchange of protecting groups (MeOH, MeONa, room temperature, 1 h, then BnBr, NaH, DMF, room temperature, 4 h) from 3,4-di-O-acetyl-1,5-anhydro-2,6-dideoxy-D-arabino-hex-1-enitol[9] provided cristalline 3,4-di-O-benzyl-D-rhamnal **9**, $[\alpha]_D$ -33°[10], precursor of unit C, in 85% yield. Methyl α-D-evermicoside **13** (methyl 2-deoxy-α-D-evaloside), was best prepared from ulose **10**[11] by Wittig olefination, mercuration-demercuration[12] (→**11**), N-bromosuccinimide treatment (→**12**) and lithium aluminum hydride reduction (Scheme 3). Alternatively, treat-

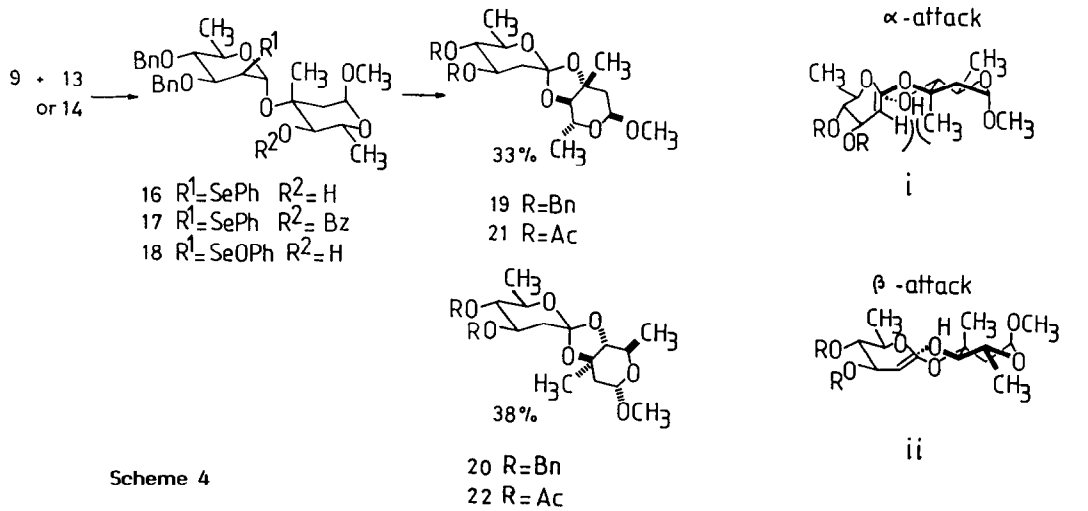


Scheme 3

a) Ph_3PCH_3Br, $NaNH_2$, THF, 20°C, 15 min, 75%; b) $Hg(OAc)_2$, THF-water, 20°C, 30 min then aqueous NaOH, $NaBH_4$, 20°C, 5 min, 90%; c) NBS, CCl_4, $BaCO_3$, reflux, 6 h, 95%; d) $LiAlH_4$ THF, reflux, 6 h, 84%; e) W2 Raney nickel, AcOEt, MeOH, Et_3N, room temperature, 10 h, 79%; f) Bu_3SnO, $PhCH_3$, reflux, 4 h then PhCOCl, Et_3N, room temperature, 1 h, 80%.

ment of bromide **12** by W2 Raney nickel led to the known[13] 4-O-benzoate **14**, $[\alpha]_D$ +136°, in 79% yield. Isomeric tertiary 3-O-benzoate **15**, $[\alpha]_D$ +116° was easily obtained by regioselective benzoylation via the O-dibutylstannylene acetal[14] derived from diol **13** in 80% yield[15].

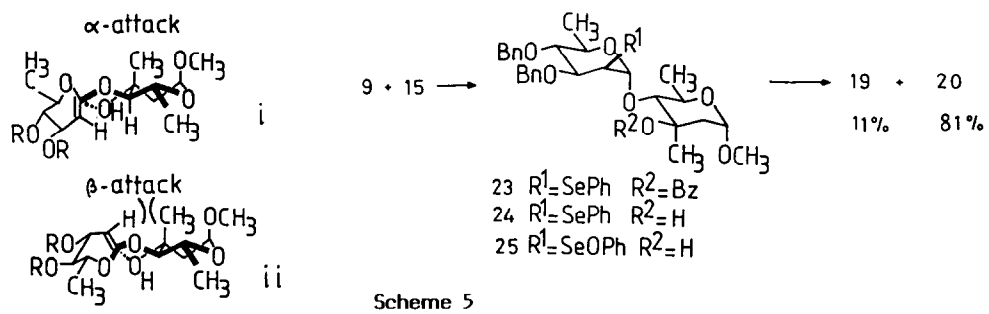
When glycal **9** (1.3 equiv.) was reacted with methyl α-D-evermicoside **13** (1 equiv.) following our glycosyloxyselenation procedure (PhSeCl, CH_3CN, sym-collidine, 0°C, 1 h), 1',2'-trans diaxial (1→3) linked disaccharide **16**, $[\alpha]_D$ +60°, was obtained in 70% yield (Scheme 4). The unexpected regiospecificity of this reaction was confirmed by condensation of alcohol **14** with activated glycal **9** (room temperature, 10 h) which nicely provided the α-linked disaccharide **17**, $[\alpha]_D$ +25°, in 83% yield. Debenzoylation led to the same disaccharide **16** (92% yield) as described above. Subsequent oxidation ($NaIO_4$, MeOH-water, 20°C, 1 h) afforded the corresponding selenoxides **18** (98% yield) as a mixture of diastereoisomers at selenium (ratio, 2:1). Heating (120°C, 2 h) selenoxides **18** in toluene-vinyl acetate[16]-di-isopropylamine (sealed system) resulted in the formation of both ortholactones **19**, $[\alpha]_D$ +93.6° (33%), and **20**, $[\alpha]_D$ +92.7° (38%)[17]. Debenzylation (Na, NH_3, 1,2-dimethoxyethane) of **19** and **20** followed by acetylation (Ac_2O, pyridine) provided ortholactones **21**, $[\alpha]_D$ +114°, m.p. 114°C and **22**, $[\alpha]_D$ +121°, m.p. 92°C in 89% and 83% yield respectively. This unanticipated total lack of selectivity may be explained by looking at the conformational



Scheme 4

models for the intermediate ketene acetal (Scheme 4). In the two possible modes of attack (α or β), the oxygen at C-4 should be roughly perpendicular to the sp^2 system for C-O bond formation. During this process, a strong steric interaction develops between the vinylic H-2' and the methyl group at C-3 in the electronically favored α-attack (**i**, Scheme 4). This steric congestion is not felt in the electronically unfavorable β-attack (**ii**, Scheme 4). In this spiro-cyclization, the gain of selectivity supplied by steroelectronic control is thus balanced by steric factors.

The stereochemical situation should be reversed in the case where the ketene acetal is derived from a (1→4) disaccharide. Again, inspection of the models showed that electronic and steric factors were acting together so that the desired ortholactone might be selectively produced (**i** and **ii**, Scheme 5). Indeed a similar sequence of reactions with 3-O-benzoate **15** and glycal **9**

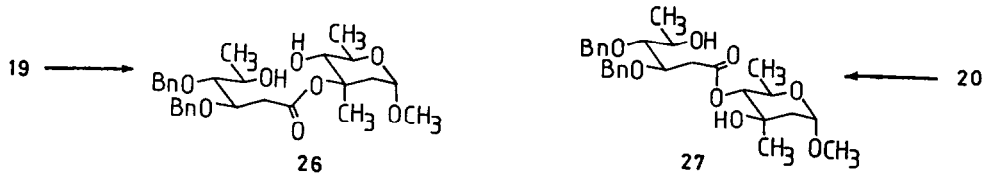


Scheme 5

provided successively 2'-phenylseleno α-linked disaccharide **23** (75%), $[\alpha]_D$ +7.8°, debenzoylated product **24**, $[\alpha]_D$ +99° (88%), selenoxides **25** (98%, diastereoisomeric ratio, 4:1) and selectively ortholactone **20** in an excellent yield (81%). Isomeric ortholactone **19** was also isolated in 11% yield.

With both isomeric C-D fragments in hand, attention was then focused on their hydrolytic behavior. Mild acidic hydrolysis (1 mM TsOH, H_2O in p-dioxane) of ortholactone **20** produced a single ester **27** located at O-4 of the 2-deoxy-D-evalose residue while, under identical conditions,

ortholactone **19** produced only ester **26** located at the tertiary O-3 of residue D (Scheme 6).



Scheme 6

In both cases the axially oriented C-O bond relative to residue C is cleaved. This clear-cut behavior strongly suggests that the absolute configuration at C-16 of natural antibiotics is the one displayed by ortholactone **20**.

References and notes

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