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NEW APPROACH TO THE TOTAL SYNTHESIS OF SHOWDOMYCIN. STEREOCHEMISTRY STUDY OF THE INTERMEDIATE AND RELATED PRODUCTS.

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The present paper describes a new, easy and versatile synthesis of showdomycin , and investigates several important features of the stereochemistry of its intermediate products. The absolute configurations on C-2 of following and similar compounds were determined by ^{1}H-NMR spectroscopy and/or methods of Molecular Mechanics: Methyl 3,6-anhydro-2-deoxy-2-bromo-4,5-O-isopropylidene--7-O-trityl-D-glycero-D-allo- and -D-glycero-D-altro-heptonates (3R and 3S) and methyl 2,7:3,6-dianhydro-4,5-O-isopropylidene-D-glycero-D-allo- and -D-glycero-D-altro-heptonates (10R and 10S).

INTRODUCTION

The stereochemistry in the formation of the C-C bond at the anomeric center of sugar derivatives[1], is the subject of many recently published works. Many synthetic studies are orientated towards the preparation of C-glycosides as a) intermediates in the preparation of naturally occurring C-nucleosides and their analogues[2]; and b) as chiral templates[3].

One of the more effective processes is the Wittig reaction between stabilized phosphorus ylides and reducing monosaccharide derivatives. The reactions of 2,3-O-isopropylidene ribose and mannose derivatives and ylides Ph_3P=CHX (X=CO_2R, CN, $COCH_2CO_2R$) have been widely studied, the mechanism is partially established and the anomeric configuration is confirmed by spectroscopic methods[4].

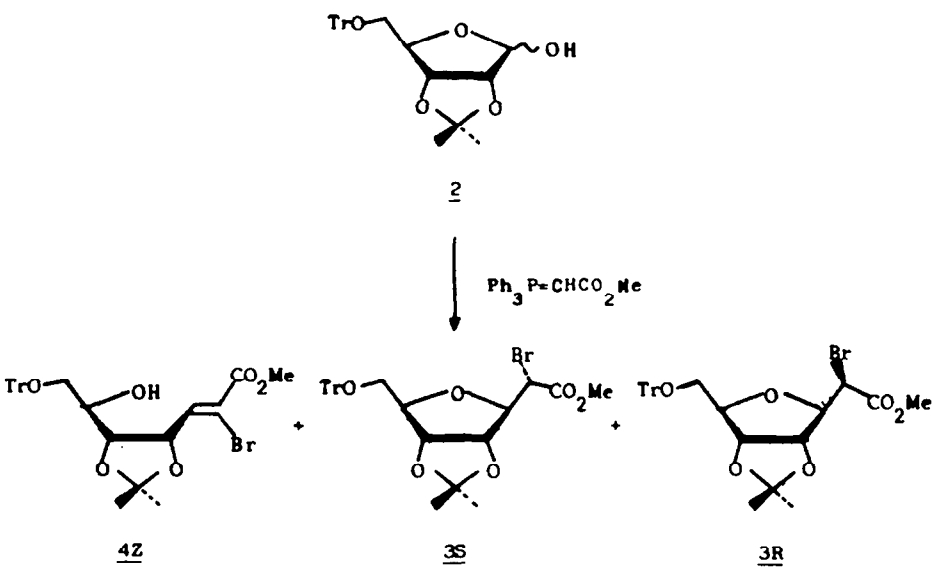
In connection with our work on C-glycosides[5a,5b] and C-nucleosides antibiotic formation[5c], we have employed the ylide Ph_3P=$CBrCO_2Me$ for several purposes: a) to synthesize C-glycosides containing two functional groups at the C-α of the aglycone so that they could act as new and interesting chiral templates; b) to determine the stereochemistry of the two new chiral centers and the stereoselectivity of the reaction; c) to study the reactivities of the resulting compounds; and d) their applications to the showdomycin synthesis.

Results and Discussion

We have reacted 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose (2) with methoxycarbonylbromomethylenetriphenylphosphorane in several solvents and under different reaction conditions. The best yield was obtained with anhydrous benzene in the presence of a catalytic amount of benzoic acid[6]. Three reaction

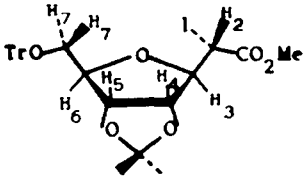
products were isolated : the two C-2 epimers of methyl 3,6-anhydro-2-deoxy-2--bromo-4,5-O-isopropylidene-7-O-trityl-D-glycero-D-allo- and -D-glycero-D-altro--heptonates (3R) and (3S)[7], in a ratio R:S (1.7:1), and methyl (Z)-2,3-dideoxy--2-bromo-4,5-O-isopropylidene-7-O-trityl-D-ribo-hept-2-enonate (4Z).

Scheme I



The assignment of β-C-ribofuranosyl configuration (D-allo) of 3R and 3S was supported by the fact that the value of $^{3}J_{5,6}$ (1 Hz) and the values for the methyls of the isopropylidene group fit the pattern established ($\Delta\delta$ = 1.8 Hz). The ^{13}C NMR data also fall in the established regions for the β-anomer[4].

The absolute configuration at C-2 of 3S (not determined for similar compounds in the literature)[7], was assigned by comparison with the similar product 5S, prepared in our laboratory[8]. Compound 5S was obtained by iodine intramolecular cyclization, and in accordance with the probable mechanism of this reaction[9], we can assume the β-S configuration.



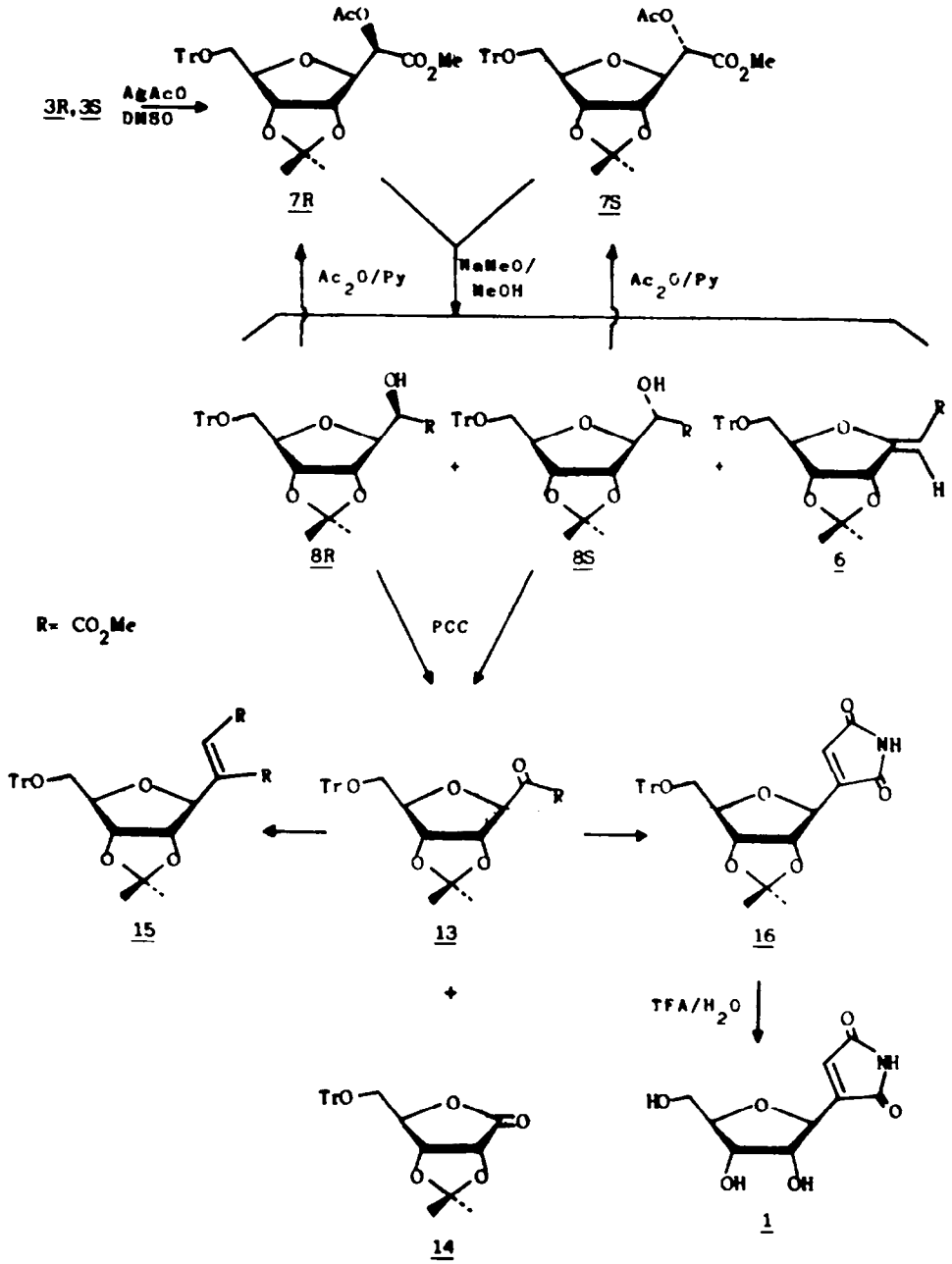
The assignment of the Z configuration of 4 was in agreement with the theoretical shift of the vinyl proton for the two possible configurations[10] (the contribution of the sugar moiety was calculated from the analogous compound without bromine)[8,11] .

Compound 4Z closes to form 3R and 3S in the presence of NaOH/dioxane. 3R is the predominant isomer. In fact, the major isomer has the greater value of $^{3}J_{2,3}$, which suggests a preferential antiperiplanar Br-O conformation; in this position, the Br-O dipolar repulsion and the steric hindrance of the

substituents at C-2 are minimal. On the other hand, the preferential conformation of the minor isomer β-S would be that illustrated in Figure 1a, with greater dipolar and steric interactions between CO_2Me and H-4.

To study the reactivity of these C-glycosides, a series of reactions aimed at showdomycin synthesis[12-18] were tested.

Scheme II



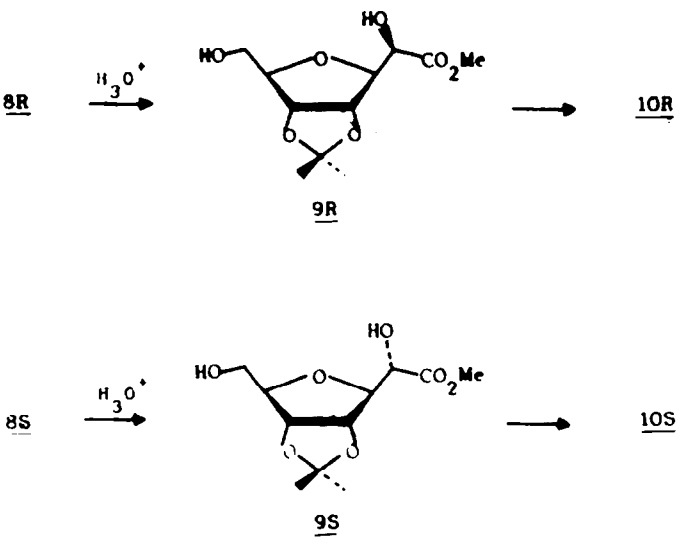
The low reactivity of the bromine atom, which proved to be resistant to hydrolysis by aqueous or alcoholic basic media, was noted. This fact may be interpreted as a result of the great steric hindrance to the nucleophile "endo" approach in a SN_2 process; due to the "exo" position of the bromine atom. The Moffatt oxidation of 3R,S gives a very low yield even when performed at high temperatures. DMSO-$NaHCO_3$ treatment gave the hydroxy derivatives 8R,S as major products (52.6%), together with the elimination product 6. The formation of 8R,S can be explained by the low nucleophilicity of the DMSO. The ^1H NMR data for compound 6 were consistent with the assigned stereochemistry.

While this work was in progress, a similar synthetic approach was published in a preliminary letter, by N. Katagiri and co-workers[19], but there are many important differences, data, and conclusions in our work, which prompted us to report our study. We preferred the use of AgOAc in DMSO in order to help a SN_1 process. The mixture of the acetoxy derivatives 7R,S obtained from each one of the 3R or 3S isomers could not be resolved by either tlc or hplc.

The methanolysis (NaOMe/MeOH) of these acetoxy derivatives led to the corresponding hydroxy derivatives 8R and 8S , which were separated by thick layer chromatography. Later acetylation (Ac_2O/py) of these, yielded pure 7R and 7S. The anomeric configuration of all these derivatives (7R, 7S, 8R and 8S) is according to ^1H NMR and ^{13}C NMR data.

The absolute configurations of these products were easily confirmed by selectively hydrolysis of the trityl group in each one of the hydroxy derivatives 8R and 8S, by TFA treatment, in the hope of obtaining the 10R and 10S anhydro derivatives. The study of the bidimensional non-scalar correlation (NOESY, Figure 2) provided an unequivocal assignment of the absolute configuration at C-2 of 10R and 10S, and also determined the configuration of their precursors (7R,S), (8R,S), and (9R,S).

Scheme III



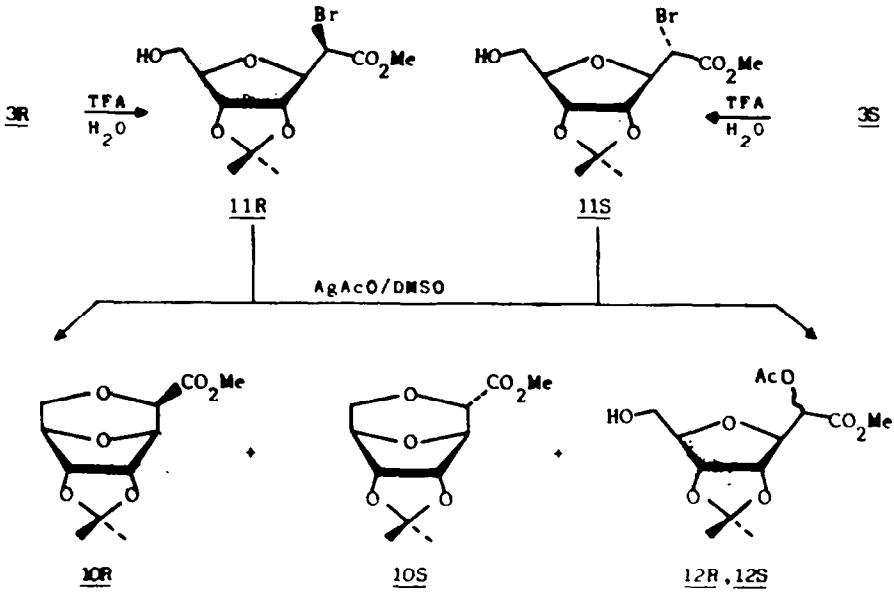
In this way, the NOESY experiment (2D NOE Spectroscopy)[20] for the 10S isomer shows cross-peaks for the following pairs of protons H-2:H-4 and

H-5:H-7_{endo}. but not for the H-5:H-7_{exo} pair. A similar experiment for the 10R isomer only reveals cross-peaks for the H-2:H-7_{exo} pair, but not for the pair H-5:H-7_{endo}. These cross-peaks are in agreement with the close spacial proximity of these pairs of protons as figure 2 shows, for the chair conformations of both isomers. Moreover, proton H-7_{endo} of 10S , shows a W coupling constant with proton H-2 in the COSY experiment (Homonuclear Shift Correlated Spectroscopy[21], figure 2c), and a dipolar correlation with proton H-5 in the NOESY experiment, as we can hope for the endo methylene H-7 proton in the chair conformation.

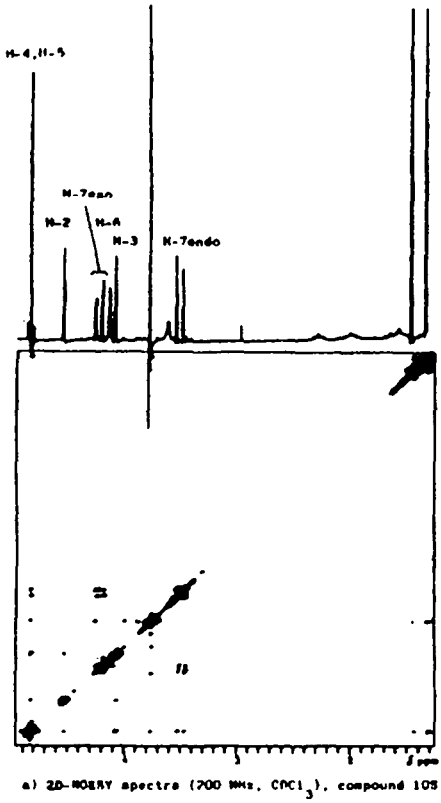
These results also agree with the results obtained from the theoretical study (MMP2, Molecular Mechanic [22]) which show us that these are the most stable conformers for both isomers. Moreover, the theoretical torsion angles obtained permitted the calculation[23] of the corresponding theoretical, and very similar vicinal coupling constants (table IV). The only large difference was a greater coupling constant $J_{2,3}$ for the 2(R) isomer, in agreement with the experimental values and the axial-equatorial nature of these coupling protons in 2(R).

As an extension of the above studies, the selective hydrolysis of the trityl ether in each one of the bromo derivatives 3R and 3S, was carried out and gave the bromo-hydroxy derivatives 11R and 11S respectively. Their configuration at C-2 was confirmed by treating them with AgOAc in DMSO, and in fact, the product 11S yielded an almost equimolecular mixture of the corresponding derivatives 12R and 12S, with a minor amounts of 10R and 10S. On the other hand, 11R preferentially produced the anhydro derivative 10S, and a small amounts of 10R and 12S with traces of 12R.

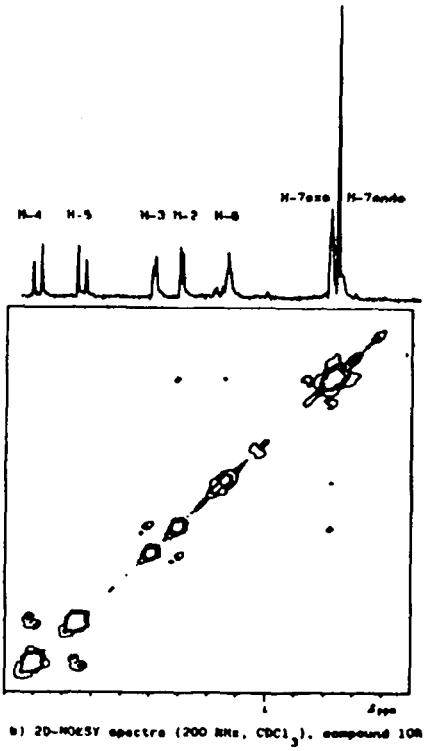
Scheme IV



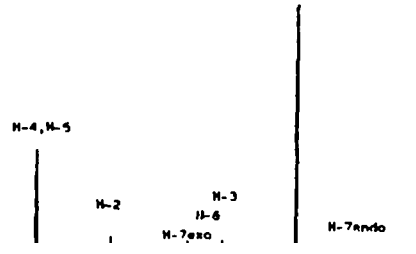
Several observations in the ^1H NMR spectra are consistent with this present structural assignment. Thus, with the exception of the acetoxy derivatives 7R,S, all the C-2(R) derivatives show a larger chemical shifts for H-3 than for H-2. Inversely, all the C-2(S) derivatives have larger chemical shifts for H-2 than for H-3. In addition, δ H-2(R isomers) < δ H-2(S isomers), δ H-3(R isomers) > δ H-3(S isomers).

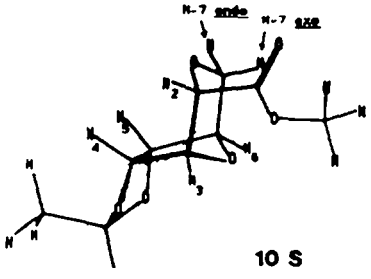


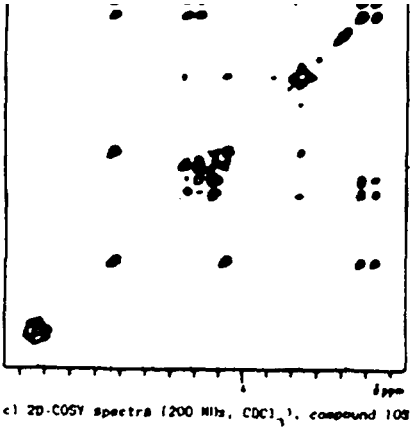
a) 2D-NOESY spectra (200 MHz, $CDCl_3$), compound 10S



b) 2D-NOESY spectra (200 MHz, $CDCl_3$), compound 10R







c) 2D-COSY spectra (200 MHz, $CDCl_3$), compound 10S

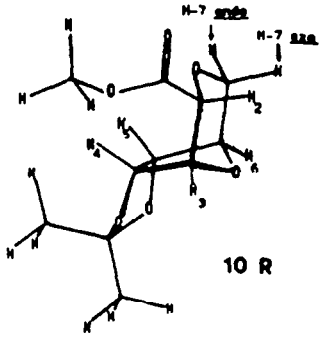
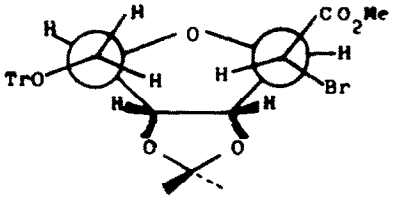


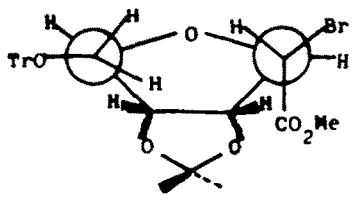
Figure 2

Consideration of the expected conformers of 11R and 11S shows the more suitable disposition of the terminal hydroxyl group of 11R, to trap the ion pair resulting from the interaction Br-Ag, and the consequent facile ether formation. This again confirms the assignment at C-2.

Figure 1

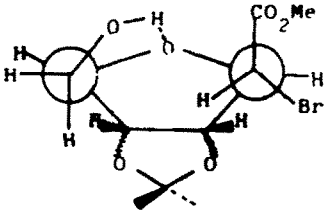


3R β, C-2(R)

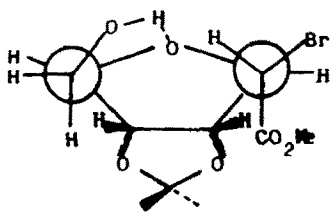


3S β, C-2(S)

Fig a



11R



11S

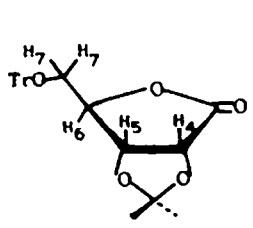
Fig b

The oxidation of the epimer mixture 7R,S was examined by the different methods reported [13], however, these do not permit the purification of the desired α-ketoester 13. Consequently, the use of pyridinium chlorochromate (PCC), was studied. The best yield was obtained when the oxidant was intimately mixed with neutral Al_2O_3, and gave the chromatographically pure α-ketoester in 55.7% yield. The only by-product detected in this method, was the ribonolactone derivative 14 (21%), from which 13 was easily separated by thick layer chromatography over neutral Al_2O_3. The structure of 14 was confirmed because the same product was obtained by oxidizing 2 with PCC.

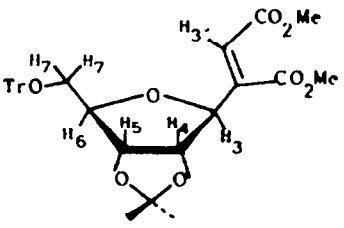
The 1H NMR spectra of pure 13 could be obtained for the first time, although NMR monitoring showed that it decomposed rapidly and yielded the lactone 14 as the only product. Because of the rapid decomposition we could not carry out an elemental analysis. The oxidation procedure was studied under several different conditions. It was observed that when 7R,S was mixed with silica gel, considerable hydrolysis of the trityl group occurred and 14 was not formed. This prompted the use of a more basic medium, but it caused a considerable formation of 14. This may be explained by considering a mechanism which could lead to 14, for example; the formation of a chromate at C-3 via the enolate of 13, followed by the normal steps of the oxidation of glycols.

Finally, pure 13 or mixture of 13 and 14 was reacted with either $Ph_3P{=}CHCO_2Me$ or $Ph_3P{=}CHC(O)NH_2$ in anhydrous chloroform and yielded 15 or 16 respectively. These were purified by thick layer chromatography.

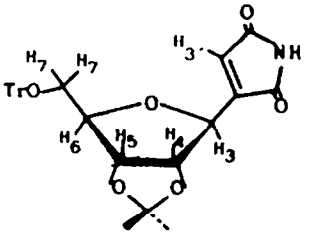
Acid hydrolysis [16] of 16 yielded showdomycin, which was confirmed by comparison with the ^1H NMR spectra with that reported in the literature[24].



14



15



16

Figure 3. Numeration employed in NMR Tables for maintaining the ring numbers of the serie.

TABLE I

^1H-NMR chemical shifts of products 3 to 16 (in $CDCl_3$, δ ppm)

Product	H-2	H-3	H-4	H-5	H-6	H-7a	H-7b	CMe2	MeO	Trityl	Others
3R	4.33 d	4.43 dd	4.82 dd	4.64 dd	4.22 ddd	3.21 dd	3.14 dd	1.49	1.30	3.73	7.23-7.38	
3S	4.55 d	4.42 dd	5.00 dd	4.69 dd	4.18 ddd	3.27 dd	3.15 dd	1.54	1.35	3.68	7.22-7.42	
4I	---	7.35 d	5.15 dd	4.33 dd	3.78 m	3.35 d		1.34	1.32	3.81	7.25-7.42	2.5 (OH)
5R	4.63 d	4.3 dd	4.97 dd	4.72 dd	4.18 ddd	3.25 dd	3.14 dd	1.52	1.34	3.62	7.2-7.5	
6I	5.57 d	---	5.93 dd	4.53 dd	4.58 dd	3.50 dd	2.93 dd	1.42	1.35	3.74	7.15-7.38	
7R	5.28 d	4.47 dd	4.75 m		4.21 ddd	3.36 dd	3.12 dd	1.56	1.37	3.80	7.20-7.45	1.88 (AcO)
7S	5.37 d	4.39 dd	4.80 dd	4.65 dd	4.21 ddd	3.29 dd	3.13 dd	1.55	1.30	3.70	7.20-7.45	1.94 (AcO)
8R	4.26 d	4.38 dd	4.82 dd	4.60 dd	4.06 dd	3.24 dd	3.12 dd	1.45	1.25	3.78	7.20-7.38	3.11 (OH)
8S	4.38 d	4.22 dd	4.71 dd	4.56 dd	4.08 dd	3.24 dd	3.18 dd	1.51	1.32	3.68	7.22-7.38	3.11 (OH)
9R	4.32 d	4.39 dd	4.84 dd	4.71 dd	4.08 dd	3.83 dd	3.65 dd	1.52	1.35	3.78		
9S	4.48 d	4.33 dd	4.65 dd	4.72 dd	4.15 dd	3.82 dd	3.64 dd	1.48	1.30	3.80		4.74 (OH)
10R	4.32 d	4.42 d	4.82 d	4.67 d	4.16 m	3.81 d		1.48	1.31	3.80		
10S	4.35 bs	4.10 d	4.84 d		4.15 m	4.24 dd	3.52 ddd	1.47	1.34	3.78		
11R	4.30 d	4.42 dd	4.69 dd	4.74 dd	4.17 ddd	3.77 dd	3.64 dd	1.53	1.34	3.79		3.8 (OH)
11S	4.51 d	4.33 dd	4.84 dd	4.72 dd	4.11 ddd	3.85 dd	3.65 dd	1.53	1.34	3.79		3.65 (OH)
13	---	4.34 d	4.53 dd	4.90 dd	4.15 m	3.26 dd	3.13 dd	1.45	1.28	3.87	7.20-7.50	
14	---	---	4.98 d	4.42 d	4.58 dd	3.73 dd	3.06 dd	1.46	1.33		7.20-7.45	
15	---	4.59 dd	4.78 dd	4.56 dd	4.16 ddd	3.34 dd	3.14 dd	1.50	1.29	3.76	7.20-7.50	3.71 (MeO) 6.24 (H-3')
16	---	4.67 dd	4.73 dd	4.60 dd	4.31 ddd	3.27 dd	3.19 dd	1.57	1.33		7.20-7.50	7.40 d(NH) 6.67 dd (H-3')

TABLE II

^{13}C-NMR chemical shifts of products 3, 6, 7, 8, 9, 10 y 14 (in $CDCl_3$, δ ppm)

Product	C-1	C-2	C-3	C-4	C-5	C-6	C-7	CMe2	CMe2	MeO	Others
3S	168.5	44.5	85.0	82.5	81.6	84.9	64.1	113.6	27.5	25.6	52.0	87 (C-Tr) 144,129,128,127 (Tr)
3R	168.0	44.6	85.6	84.6	82.6	85.0	64.6	114.0	27.4	25.6	53.0	87 (C-Tr) 143.7,129,128,127 (Tr)
6I	167.5	92.8	174.2	80.2	80.0	86.8	64.0	112.5	26.7	25.6	51.0	87 (C-Tr) 143.2,128.5,128,127.2 (Tr)
7R	167.7	71.8	83.1	80.7	81.9	83.8	64.1	114.0	27.6	25.7	52.5	87 (C-Tr) 143.9,128.8,127,127.8 (Tr) 170.2 (AcO)
7S	167.8	72.2	83.2	80.6	81.5	84.2	64.1	114.0	27.4	25.5	52.5	87 (C-Tr) 143.8,127.7,127.9,127.2 (Tr) 170 (AcO)
8S	172.0	71.8	86.0	82.0	80.9	84.0	64.0	114.0	27.7	26.0	53.0	87 (C-Tr) 143.5, 127.5, 128, 129 (Tr)
8R	172.5	71.1	85.0	81.7	81.7	84.6	64.0	114.0	27.6	25.6	52.7	87 (C-Tr) 143.8, 127, 128.8,127.8 (Tr)
9R	173.0	71.5	85.7	81.9	81.8	86.0	62.5	114.0	27.5	25.5	52.5	
10S	168.5	73.7	80.7	81.0	82.2	82.5	65.3	112.5	26.1	24.7	52.2	
14	---	---	175.5	76.0	78.5	81.8	63.0	113.5	27.3	25.6	---	87 (C-Tr) 142.5, 127.5, 128, 128.8 (Tr)

TABLE III

Coupling Constants (Hz) of products 3 to 16

Product	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7a}$	$J_{6,7b}$	$J_{7a,7b}$	Others
3R	9.9	3.6	6.6	2.9	3.4	3.6	10.0	
3S	5.8	3.6	6.6	4.6	3.2	4.85	10.3	
4Z	---	3.0	4.0	3.1	2.0	2.0	---	
5S	6.5	3.5	6.4	4.7	3.2	5.0	10.3	
6Z	---	---	6.1	0	2.6	2.1	10.4	$J_{2,4}$ 0.5
7R	3.0	4.8	6.4	5.0	3.8	4.5	10.0	
7S	3.0	4.5	6.4	3.9	3.8	4.8	10.0	
8R	1.8	3.4	6.4	4.6	3.4	4.5	10.2	
8S	3.3	3.9	6.5	4.3	3.8	4.7	10.2	
9R	1.9	3.3	6.3	3.4	2.8	2.8	12.0	
9S	3.0	3.3	6.3	3.5	2.5	2.8	12.3	
10R	2.0	0	5.6	0	1.4	1.4	0	
10S	1.0	0	5.7	0	1.0	1.0	11.8	
11R	8.4	2.6	6.5	2.5	5.3	3.3	12.0	
11S	4.4	4.2	6.7	4.2	2.8	3.8	12.1	
13	---	3.0	6.5	5.0	4.0	6.0	12.0	
14	---	---	5.6	0	2.5	1.7	10.7	
15	---	5.0	6.5	4.0	3.3	4.5	10.3	$J_{3,3'}$ 1.7
16	---	4.1	6.4	3.5	3.9	5.4	10.2	$J_{3,3'}$ 1.8 $J_{3',NH}$ 1.8

TABLE IV

Theoretical coupling constants and interatomic distances for 10R and 10S

Product	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7a}$	$J_{6,7b}$	d_{2-4}	d_{2-7b}	d_{5-7a}
10R	1.58	0.78	8.06	0.82	1.28	2.55	---	2.60	---
10S	0.76	0.78	8.06	0.82	1.35	2.48	2.55	---	2.61

7a = 7endo; 7b = 7exo; interatomic distances in Angstroms

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded with a Beckman Aculab IV spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with a Bruker WP 200 SY spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Mass spectra were obtained with a Kratos MS-25 or a Hewlett Packard 5988A. Elemental analyses were carried out in the Microanalysis Service of the University of Málaga, in a Perkin Elmer 240. The solvent systems used were as follows: A, 6:2.5 hexane/ethyl acetate; B, 1:1 hexane/ethyl ether; C, 15:1 hexane/ethyl acetate; D, 8:1:1 hexane/ethyl acetate/ethyl ether; E, 7:2 hexane/ethyl acetate; F, 10:1 carbon tetrachloride/ethyl acetate; G, 1:2 hexane/ethyl acetate.

Methyl 3,6-anhydro-2-deoxy-2-bromo-4,5-O-isopropylidene-7-Otrityl-D-glycero-D-allo- and D-glycero-D-altro-heptonates (3R) and (3S), and Methyl (Z)-2,3-dideoxy-2-bromo-4,5-O-isopropylidene-7-Otrityl-D-ribo-hept-2-enonate (4Z). 5.42 g (10 mmol) of 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose (2) were refluxed in anhydrous benzene (40 mL) with 6.58 g (16 mmol) of methoxycarbonylbromomethylenetriphenylphosphorane and 1 mg of benzoic acid. After 4 h, an NMR of a concentrated sample showed a major proportion of 4, which partially cyclized into the reaction medium. After removing solvent, the resultant syrup was chromatographed on silica gel (Merck 9385, solvent B). Three fractions were obtained: 0.6 g of 3S, 5.25 g of a mixture of 3S and 3R, and 1.06 g of 4Z. Slower chromatography causes a more cyclization to 3R and 3S. Total yield, 6.76 g (89.5 %).

In another procedure, starting from 4.42 g of 2 (10 mmol), using the same reactive proportions, without catalyst, and after 6.5 h, the reaction mixture was poured into 100 mL of solvent B and filtered with suction through 20 g of silica (Merck 7734). The silica was washed (4 x 25 mL solvent B), and the

combined filtrates were concentrated to a syrup (5.08 g, 87.4% yield) which showed by TLC (solvent A) the presence of three products. This mixture was dissolved in dioxane (40 mL) and 10% NaOH (30 mL) was added. After 1 h, the mixture was neutralized with $KHSO_4$, extracted with ether (2 x 25 mL) and evaporated, obtaining 4.62 g (84.16%) of a mixture of 3R and 3S at high purity. The isomers were separated by thick layer chromatography in solvent B (three elutions).

3S : R_f 0.67 (solvent A); $(\alpha)_{20}^{D}$ +6 (c 0.509, MeOH)

3R : R_f 0.64 (solvent A); $(\alpha)_{20}^{D}$ +5.3 (c 0.7, MeOH).

3R and 3S :UV λ_{max} 218 nm (ϵ 8105, MeOH); NMR data are in tables. The remainded data are the same reported[6].

4Z: R_f 0.57 (solvent A); mp 40 C; UV λ_{max} 224 nm (ϵ 9049, MeOH); IR ν_{max} (KBr): 3500, 1750, 1650, 820; MS, m/e 568 ($^{81}BrM^+$), 566 ($^{79}BrM^+$), 553 ($^{81}BrM^+$-Me), 551 ($^{79}BrM^+$-Me);

Anal. Calc. for $C_{30}H_{31}O_6Br$: C, 63.49; H, 5.51. Found: C, 62.70; H, 5.69.

Methyl 3,6-anhydro-2-acetyl-4,5-O-isopropylidene-7-O-trityl-D-glycero-D-allo and D-glycero-D-altro-heptonates (7R and 7S) and by-product (6). A mixture of 3R and 3S (5 g, 8.8 mmol), $NaHCO_3$ (3.7 g, 44 mmol) and AgOAc (1.5 g, 8.8 mmol) were refluxed in DMSO in a light protected flask. The reaction was monitored by TLC using solvent A, showing the presence of three new products. After 4 h,the mixture was filtered, and the precipitated washed with AcOEt (2 x 20 mL). Solvent was removed under vacuo to give 4.63 g of a mixture of 7R and 7S contaminated by 6 (11:1). Total yield of 7R and 7S, 88.42%. 7R and 7S were separated from 6 by thick layer chromatography, using solvent C.

7R and 7S: Rf 0.49 (solvent A);IR vmax (KBr): 1740,1380; MS m/e 547 (M^++1), 546 (M^+), 531 (M^+-Me), 487 (M^+-CO_2Me).

Anal. Calc. for $C_{32}H_{34}O_8$: C, 70.31; H, 6.26. Found: C, 70.22; H, 6.39.

6: R_f 0.53 (solvent A); UV λ_{max} 207 (ϵ 18620,MeOH), λ_{max} 235 (ϵ 11520,MeOH); IR ν_{max} (KBr): 1700, 1640; $(\alpha)_{20}^{D}$ -55.78 (c 0.095, MeOH); MS m/e 486 (M^+), 454 (M^+-MeOH).

Methyl 3,6-anhydro-4,5-O-isopropylidene-7-O-trityl-D-glycero-D-allo- and -D-glycero-D-altro-heptonates (8R) and (8S). The mixture 7R and 7S (3.91 g, 7.15 mmol), were dissolved in anhydrous methanol (20 mL) and treated successively with three portions of 0.174 N NaOMe every two hours (0.5, 0.2 and 0.2 mL). After 12 h, the solution was diluted with ether (10 mL) and neutralized ($KHSO_4$). The organic layer was washed with water (10 mL), and dried (Na_2SO_4), to give a mixture of 8R, 8S and 6, (58.1, 33.2 and 8.7% respectively; total yield 91.15), which was separated by thick layer chromatography (solvent D).

8R: R_f 0.42 (solvent A); UV λ_{max} 217 nm (ϵ 11000, MeOH); IR ν_{max} (film): 3440, 1750; $(\alpha)_{20}^{D}$ +3.02 (c 0.794, MeOH); MS m/e 504 (M^+), 489 (M^+-Me), 456 (M^+-2Me-H_2O).

Anal. Calc. for $C_{30}H_{32}O_7$: C, 71.41; H, 6.39. Found: C, 71.49; H, 6.32.

8S: R_f 0.28 (solvent A); UV λ_{max} 217 nm (ϵ 11000, MeOH); IR ν_{max} (film): 3450, 1750; $(\alpha)_{20}^{D}$ +10.84 (c 0.507, MeOH); MS m/e 489 (M^+-Me),458 (M^+-Me-MeO).

Anal. Calc. for $C_{30}H_{32}O_7$: C, 71.41; H, 6.39. Found: C,71.52; H, 6.51.

Methyl 3,6-anhydro-4,5-O-isopropylidene-D-glycero-D-allo- and -D-glycero-D-altro-heptonates (9R) and (9S), and Methyl 2,7:3,6-dianhydro-4,5-O-isopropylidene-D-glycero-D-allo- and -D-glycero-D-altro heptonates (10R) and (10S). A solution of 8R (260 mg, 0.516 mmol), chloroform (3 mL), water (1 mL) and TFA (15 drops) were stirred at room temperature for 2.15 h.

Then the reaction was diluted in chloroform (5 mL) and neutralized ($NaHCO_3$). The organic layer was washed with water (3 mL), and dried (Na_2SO_4) to give 177 mg of mainly 10R contaminated with 9R and triphenylmethanol. 9R and 10R were purified by thick layer chromatography, using solvent E.

The products 9S and 10S were obtained following the same procedure as with 8S

9R: R_f 0.20 (solvent G); UV λ_{max} 206 nm (ϵ 558, MeOH); IR ν_{max} (film): 3500, 1720; $(\alpha)_{20}^{D}$ -13.17 (c 1.04, MeOH); MS m/e 247 (M^+-Me), 203 (M^+-CO_2Me).

9S: R_f 0.16 (solvent G); UV λ_{max} 206 nm (ϵ 3500, MeOH); IR ν_{max} (film): 3500, 1720; $(\alpha)_{20}^{D}$ +1.76 (c 1.02, MeOH).

10R: R_f 0.54 (solvent G); UV λ_{max} 206 nm (ϵ 3790, MeOH); IR ν_{max} (film): 1735; $(\alpha)_{20}^{D}$ +5.4 (c 0.24, MeOH).

10S: R_f 0.49 (solvent G); UV λ_{max} 206 nm (ϵ 2974, MeOH); IR ν_{max} (film): 1735; $(\alpha)_{20}^{D}$ +4.2 (c 0.63, MeOH); MS m/e 244 (M^+), 229 (M^+-Me), 185 (M^+-CO_2Me)

Methyl 3,6-anhydro-2-deoxy-2-bromo-4,5-O-isopropylidene-Dglycero-D-allo- and

11R: R_f 0.16 (solvent A); UV λ_{max} 206 nm (ε 304, MeOH); $(\alpha)_{20}D$ -10.95 (c 0.146, MeOH).
11S: R_f 0.12 (solvent A); UV λ_{max} 211 nm (ε 328, MeOH); $(\alpha)_{20}D$ +6.15 (c 0.325, MeOH).
11R and 11S: IR ν_{max} (KBr): 3400, 1720; MS m/e 311 ($^{81}BrM^+$-Me), 309 ($^{79}BrM^+$-Me); Anal. Calc. for $C_{11}H_{17}O_6Br$: C, 40.63; H, 5.27. Found: C, 40.61; H, 5.32.

Methyl 3,6-anhydro-4,5-O-isopropylidene-D-allo-2-heptulosonate (13), and 2,3-O-isopropylidene-5-O-trityl-1,4-ribonolactone (14). A mixture of 8R and 8S (130 mg, 0.26 mmol) were refluxed in anhydrous benzene (5 mL) with a mixture of 111 mg (0.51 mmol) of pyridinium chlorochromate and 250 mg of neutral Al_2O_3 that had previously been thoroughly mixed in a mortar. After 2.5 h, the solution was filtered, and the precipitate washed with ether (2 x 5 mL). The combined filtrates were evaporated and purified by thick layer chromatography (neutral Al_2O_3, Merck 1092, solvent E), giving 50 mg of 13 (55.7 %) and 23 mg of 14 (21 %). Compound 14, was obtained from 2: 139.4 mg (0.32 mmol) of 2 were refluxed in anhydrous benzene (2 mL) with a mixture of 139 mg (o.64 mmol) of pyridinium chlorochromate and 375 mg of $NaHCO_3$ thoroughly mixed in a mortar. After 9 h, the solution was filtered and the precipitate washed with ether (2 x 5 mL). The combined filtrates were evaporated and purified by thick layer chromatography using solvent E, giving 102 mg of 14 (73.6 %), with the same analytical and spectral data as the compound isolated from 8.
13: R_f 0.22 (solvent A); IR ν_{max} (KBr): 1750, 1740 .
14: R_f 0.47 (solvent A); UV λ_{max} 204 nm (ε 4760, MeOH); IR ν_{max}(KBr): 1750; MS m/e 430 (M^+), 415 (M^+-Me).
Anal. Calc. for $C_{27}H_{26}O_5$ x 1/2 H_2O: C, 70.88; H, 6.39. Found: C, 70.74; H, 6.28.

Dimethyl 2-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)maleate (15). A solution of 13 (30 mg, 0.10 mmol), and methoxycarbonylmethylenetriphenylphosphorane (23.8 mg, 13.86 mmol) were refluxed in anhydrous chloroform, overnight, TLC indicated the absence of 13, and the presence of 15 (R_f 0.6, solvent A). The reaction mixture was concentrated and purified by thick layer chromatography (solvent F).
15 : R_f 0.6 (solvent A); UV λ_{max} 209 (ε 3500,MeOH); IR ν_{max} (film): 1715,1700; $(\alpha)_{20}D$ +12.94 (c 0.17, MeOH); MS m/e 558 (M^+), 543 (M^+-Me).

2-(2,3-O-Isopropylidene-5-O-trityl-β-D-ribofuranosyl)-maleimide (16) and showdomycin (1). A solution of 13 (40 mg, 0.08 mmol) and carbamoylmethylenetriphenylphosphorane (25 mg, 0.08 mmol), in dry chloroform (2 mL) were stirred at room temperature for 2 h. Then, the solvent was evaporated and the residue was purified by thick layer chromatography (solvent D), giving 25 mg of 16 (61.6 %).
16: R_f 0.3 (solvent A); UV λ_{max} 214 nm (ε 7050, MeOH); IR ν_{max} (KBr): 3450-3360, 1720, 1610; $(\alpha)_{20}D$ -3.8 (c 1.8 10^{-3}, MeOH); MS m/e 415(M^+-$C_4H_2NO_2$, maleimide rest), 267 (M^+-Tr+1).
Anal. Calc. for $C_{31}H_{29}O_6N$. $2H_2O$: C, 67.99; H, 6.07; N, 2.5 . Found: C, 67.93; H, 6.12; N, 2.04.
Removal of the protecting group was made following the procedure of Just and col.[13], giving 1, whose NMR and IR matched those reported previously[14].

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