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SYNTHESIS OF DESTOMYCIN C, A PSEUDO-TRISACCHARIDE ANTIBIOTIC HAVING AN INTERGLYCOSIDIC SPIRO-ORTHOESTER LINKAGE

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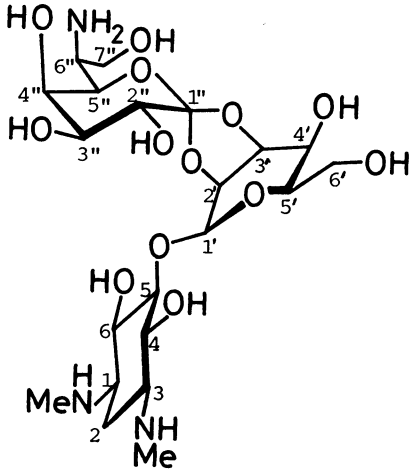
Destomycin C, a pseudo-trisaccharide antibiotic of orthosomycin family was synthesized *via* spiro-orthoester formation between 5-*O*-(β-D-mannopyranosyl)-2-deoxystreptamine and 6-amino-6-deoxyheptonolactone derivatives.

Interglycosidic spiro-orthoester linkage is the structural characteristics of so-called orthosomycins[1] and for its construction three synthetic methods have been developed independently.[2-4] In this paper we would like to report the first synthesis of a pseudo-trisaccharide antibiotic destomycin C (1),[5] using D-mannose as a starting compound for the talopyranose moiety which was linked with 6-amino-6-deoxy-L-*glycero*-D-*galacto*-heptonic acid (destomic acid) and *N,N'*-dimethyl-2-deoxystreptamine through spiro-orthoester and β-glycosidic linkages, respectively.



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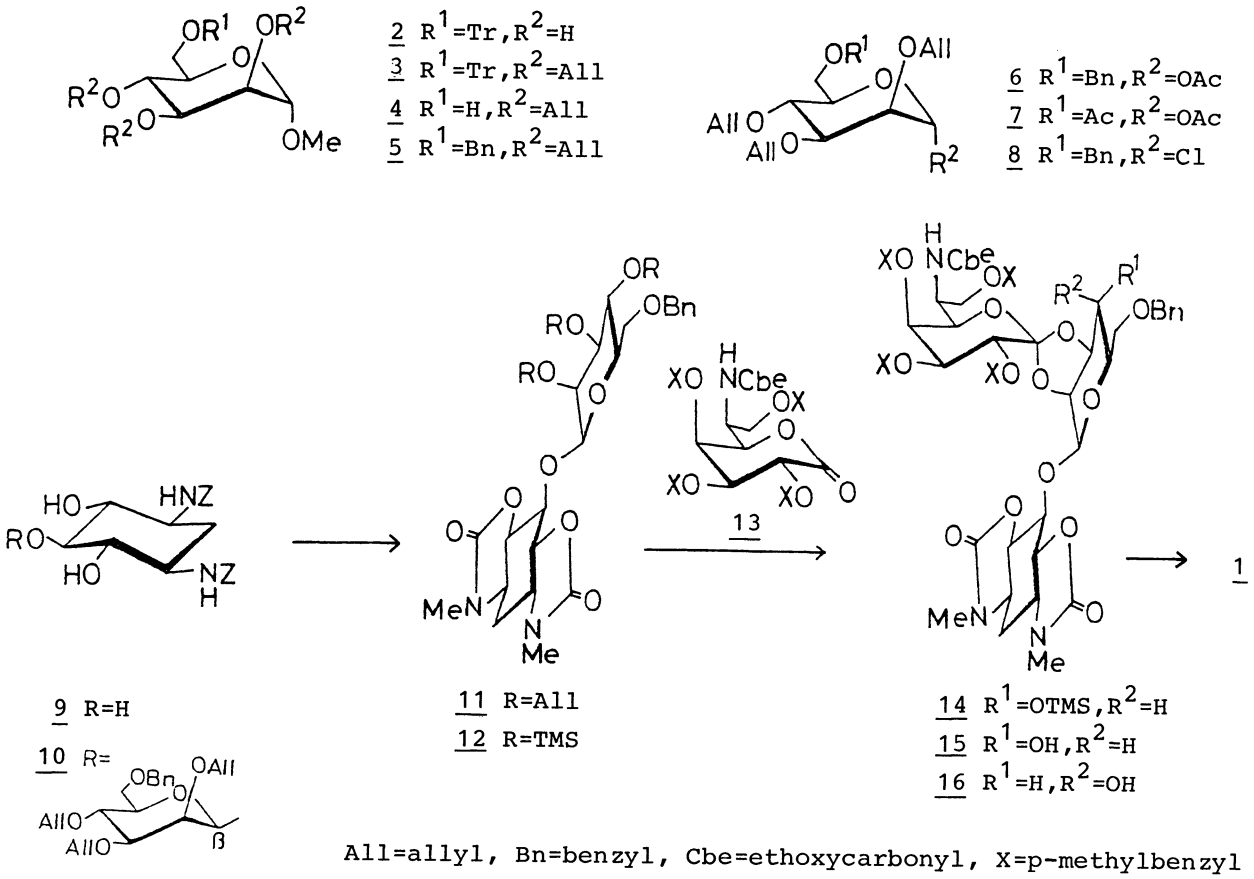
Methyl 6-*O*-trityl-α-D-mannopyranoside (2)[6] was treated with sodium hydride and allyl chloride in *N,N*-dimethylformamide (DMF) to give 2,3,4-tri-*O*-allyl derivative (3) in 86% yield. Treatment of 3 with 80% aqueous acetic acid at 60°C gave de-*O*-tritylated derivative (4) in 92% yield, and its conversion into 6-*O*-benzyl derivative (5) was performed with sodium hydride and benzyl chloride in DMF in 67% yield. Acetolysis of 5 with acetic anhydride and acetic acid containing



All=allyl, Bn=benzyl, Cbe=ethoxycarbonyl, X=p-methylbenzyl
TMS=trimethylsily, Tr=trityl.

concentrated sulfuric acid at room temperature gave the desired 1-acetate (6)[7] and 1,6-diacetate (7) in 67% and 30% yields, respectively. Treatment of 6 with hydrogen chloride in ether at 0 °C gave the corresponding α-chloride (8) in 74% yield.

Glycosylation of *N,N*-dibenzyloxycarbonyl-2-deoxystreptamine (9)[8] with 8 in tetrahydrofuran in the presence of silver triflate at -90 °C afforded the desired β-disaccharide (10)[9] together with the corresponding α-disaccharide[10] in 40% and 22% yields, respectively. Conversion of 10 into cyclic carbamate by intramolecular ester exchange using sodium hydride in DMF[11] at 0 °C, followed by methylation with methyl iodide gave 11 in 74% yield. De-*O*-allylation of 11 with palladium-charcoal and *p*-toluenesulfonic acid in methanol and successive trimethylsilylation gave 12 in 95% yield in two steps. On the other hand, destomic acid moiety was derived from destomycin A. The previously reported[12] tri-*N*-ethoxycarbonyl derivative was converted into octa-*O*-(*p*-methylbenzyl) derivative by treatment with *p*-methylbenzyl

bromide and silver oxide in DMF in 50% yield, and then hydrolyzed with 1 mol·dm^{-3} hydrochloric acid-acetic acid to give 13[13] in 67% yield.

According to the method of orthoester formation established by our previous work,[2] destomic acid derivative (13) was coupled with 12 in ether[14] in the presence of trimethylsilyl triflate at 3 °C for 3 d to give a single pseudo-trisaccharide (14) regio- and stereoselectively. Inversion of the configuration at C-4' was performed by oxidation of de-*O*-trimethylsilylated derivative (15) and successive reduction to give 16 in 36% yield in two steps. Then, the dicarbamate were hydrolyzed with aqueous barium hydroxide at 80 °C, and *p*-methylbenzyl and benzyl groups were hydrogenolyzed in water in the presence of palladium hydroxide. The deprotected product[15] was purified on a column of anion exchange resin [Dowex 1x2 (OH^-)], and proved to be identical with natural destomycin C (1) by comparison of their ^{1}H-NMR spectra at 500 MHz. The spectrum of 1 was fully analyzed at the first time in the aid of 2D J-resolved spectra and the data are summarized in the Table. The coupling constants indicate the slightly distorted $_0H^5$ conformation of the talopyranose moiety instead of the $B_{1,4}$ conformation, which was proved by X-ray analysis in the case of octa-*O*-acetyl-tris(*N*-ethoxycarbonyl)destomycin A.[12]

Table 1.

^{1}H NMR data of natural destomycin C in D_2O at 500 MHz

Proton	Chemical shift (ppm)	Coupling constant (Hz)
1,6	2.74-2.87 m	$J_{1,2a}=J_{2a,3}=12.3$
2a	1.22 q	$J_{1,2e}=J_{2e,3}=3.7$
2e	2.49 dt	$J_{2a,2e}=12.3$
4 }	3.61 dd	$J_{3,4}$ } 10.4
6 }	3.64 dd	$J_{6,1}$ } 10.2
5	3.84 t	$J_{4,5}=J_{5,6}=9.2$
1'	5.38 d	$J_{1',2'}=2.3$
2'	4.76 dd	$J_{2',3'}=5.9$
3'	4.86 t	$J_{3',4'}=5.9$
4'	4.12 dd	$J_{4',5'}=1.3$
5'	3.73 ddd	$J_{5',6'a}=3.6$
6'a	3.91 dd	$J_{6'a,6'b}=11.8$
6'b	4.03 dd	$J_{5',6'b}=8.2$
2"	4.24 d	$J_{2",3"}=10.2$
3"	4.05 dd	$J_{3",4"}=3.4$
4"	4.17 dd	$J_{4",5"}=1.3$
5"	3.89 dd	$J_{5",6"}=8.4$
6"	3.35 ddd	$J_{6",7"a}=6.4$
7"a	3.69 dd	$J_{7"a,7"b}=11.6$
7"b	3.86 dd	$J_{6",7"b}=4.3$
N-Me	2.56 s,2.58 s	

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7) $[\alpha]_D^{24}$ +41.6° (c 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.17 (d, $J_{1,2}$ 1.8 Hz, H-1) and 2.09 (s, 3 H, OAc).

8) Prepared by treatment of 2-deoxystreptamine dihydrochloride with benzyloxycarbonyl chloride and sodium carbonate in water. Mp 254-260 °C; IR (KBr): 1690 and 1540 cm^{-1}. cf., S. Umezawa and Y. Ito, Bull. Chem. Soc. Jpn., 34, 1540 (1961).

9) Separated on a silica-gel column with hexane-ethyl acetate (1:1). 10: Mp 216-217 °C, $[\alpha]_D^{24}$ -5.8° (c 1.0, $CHCl_3$), ^{13}C NMR ($CDCl_3$): δ 102.0 (d, C-1', J_{CH} 158.4 Hz).

10) Mp 128-129 °C, $[\alpha]_D^{24}$ +20.6° (c 2.2, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 99.96 (C-1').

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13) $[\alpha]_D^{23}$ +70.9° (c 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.47 (d, $J_{2,3}$ 9.4 Hz, H-2), ^{13}C NMR ($CDCl_3$): δ 170.0 (C-1).

14) Anomerization of the glycosidic bond of cyclohexyl 6-*o*-benzyl-2,3,4-tris-*o*-trimethylsilyl-β-D-mannopyranoside was observed on a preparatory glycosylidenation with 2,3,4,6-tetra-*o*-benzyl-D-gluconolactone in the presence of trimethylsilyl triflate. The anomerization occurred completely in dichloromethane and could be suppressed in ether under 20%.

15) Yield was about 40% in two steps.

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