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THE SYNTHESIS OF DESTOMYCIN C, A TYPICAL PSEUDO-TRISACCHARIDE OF DESTOMYCIN-GROUP ANTIBIOTICS*

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ABSTRACT

A synthesis is described of the pseudo-trisaccharide antibiotic, destomycin C, which contains orthoester and β-D-talopyranosidic linkages. A β-D-mannopyranosidic linkage was formed first in the presence of silver triflate in tetrahydrofuran. Glycosylidenation with trimethylsilyl triflate in ether proceeded successfully without anomerisation of the β-D-mannopyranosidic linkage. The *β-manno* → *β-talo* conversion was effected conventionally. Removal of the protecting groups then gave destomycin C.

INTRODUCTION

An interglycosidic spiro-orthoester linkage is a structural characteristic of the orthosomycins[1], which are divided into two sub-groups, namely, such oligosaccharide antibiotics as everninomicins and flambamycin, and such aminoglycoside (pseudo-trisaccharide) antibiotics as destomycins. The latter consists of 6 antibiotics, including destomycins A–C (**1**–**3**)[2–4]. Destomycins isolated from *Streptomyces rimofaciens* are used as anthelmintics for domestic fowls and animals. The configuration of the spiro-orthoester carbon of the major component, destomycin A, was shown to be *R* by our research group[5]. One of the minor components, destomycin C (**3**), has an additional *N*-methyl group in the aminocyclitol moiety, and was reported to show an antimicrobial spectrum[4] similar to that of destomycin A, although no data were given.

The major problems in the synthesis of destomycin C (**3**) concern the formation of the orthoester and β-D-talopyranosidic linkages. The latter linkage was created first in order to avoid possible steric hindrance by the orthoester linkage. If D-mannose is used as the precursor of the central unit of **3**, then the formation of the β-mannopyranosidic linkage will require subsequent creation of the orthoester linkage and inversion of configuration (*manno* → *talo*) or *vice versa*. Since attempted

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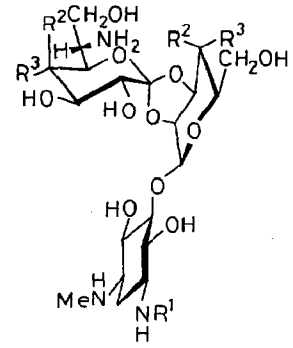


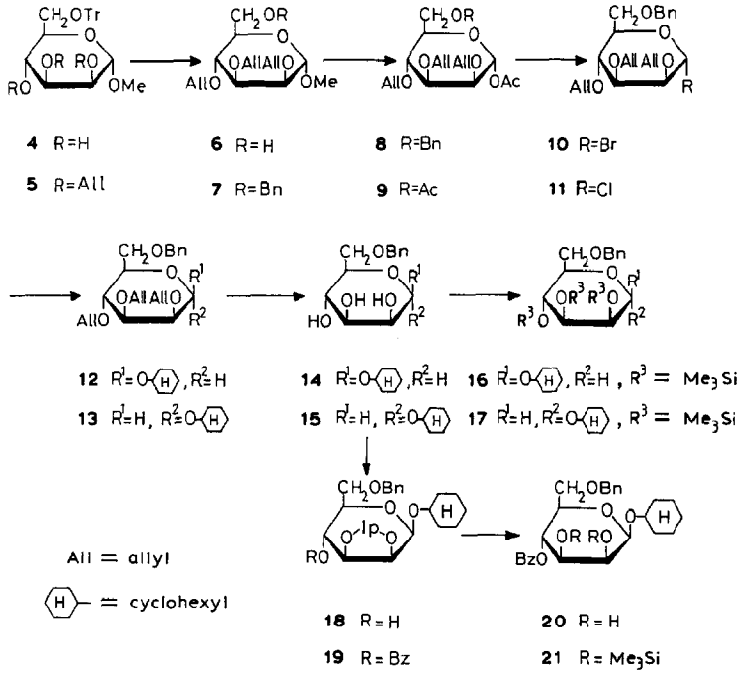
		R^1	R^2	R^3
1	destomycin A	H	OH	H
2	destomycin B	Me	H	OH
3	destomycin C	Me	OH	H

formation of a spiro-orthoester from 6-deoxy-6-ethoxycarbonylamino-2,3,4,7-tetra-*O*-(*p*-methylbenzyl)-L-*glycero*-D-*galacto*-heptonolactone (destominolactone, **40**) and the 2,3-bis-*O*-trimethylsilyl derivative of 5-[4,6-di-*O*-(*p*-methylbenzyl)-β-D-talopyranosyl]-1,3-di-*N*-ethoxycarbonyl-1-*N*-methyl-4,6-di-(*p*-methylbenzyl)-*O*-2-deoxystreptamine (**41**), which were derived from destomycin A, was not successful, the second sequence appeared to be more promising and was substantiated as reported in the preliminary communication[6]. The synthesis of destomycin C is now reported in detail.

RESULTS AND DISCUSSION

The D-mannopyranosyl donors were prepared as follows. Methyl 6-*O*-trityl-α-D-mannopyranoside[7] (**4**) was treated with sodium hydride and allyl chloride in *N,N*-dimethylformamide to give 86% of the 2,3,4-tri-*O*-allyl derivative **5**. Treatment of **5** with aqueous 80% acetic acid at 60° gave the *O*-detritylated derivative **6**, which, with sodium hydride and benzyl chloride in *N,N*-dimethylformamide, gave 67% of the 6-*O*-benzyl derivative **7**. Acetolysis of **7** with acetic anhydride–acetic acid–concentrated sulfuric acid at room temperature gave the desired 1-acetate **8** and the 1,6-diacetate **9** in yields of 70% and 30%, respectively. Treatment of **8** with titanium tetrabromide[8] in dichloromethane or hydrogen chloride in ether[9] gave good yields of the corresponding α-glycosyl bromide (**10**) or chloride (**11**), respectively.

The model acceptors, cyclohexyl 6-*O*-benzyl-2,3,4-tris-*O*-trimethylsilyl-β-D-mannopyranoside (**16**) and cyclohexyl 4-*O*-benzoyl-6-*O*-benzyl-2,3-bis-*O*-trimethylsilyl-β-D-mannopyranoside (**21**), were prepared as follows. Coupling of **10** with cyclohexanol in the presence of silver silicate[10] in dichloromethane at −20° gave 65% of the β-glycoside **12** and traces of the α-glycoside **13**. Silver triflate-promoted glycosylation of the less reactive **11** in tetrahydrofuran was effective at 0° to give **12** and **13** in yields of 21% and 42%, respectively. Reaction at −78° did not markedly



change the $\alpha\beta$-ratio (β, 6.8%; α, 23%). This glycosylation was more effective for the formation of the β-glycoside of an aminocyclitol derivative as described later. Each anomer **12** and **13** was *O*-deallylated (→ **14** and **15**) and then trimethylsilylated (→ **16** and **17**). Treatment of **14** with 2,2-dimethoxypropane and toluene-*p*-sulfonic acid in acetone gave the 2,3-*O*-isopropylidene derivative **18**, the 4-benzoate (**19**) of which was *O*-deisopropylidenated (→ **20**) in aqueous 80% acetic acid followed by trimethylsilylation to give **21** (84% from **14**).

Coupling of the trimethylsilylated *cis*-2,3-diols **16**, **17**, and **21** with 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (**22**) in the presence of trimethylsilyl triflate[11] gave the 2,3-*O*-glucosylidenemannopyranosides **23**, **25**, and **27**, respectively. The results are summarised in Table I and a serious problem was the anomerisation of the β-D-mannopyranosidic linkage during the reaction. In dichloromethane, the anomerisation proceeded rapidly to give the α-D-mannopyranosides such as **25** and **27** (entries 1 and 6). For **16**, the anomerisation could be suppressed substantially by using ether as the solvent, and the β-glycoside **23** preponderated (entry 3). This effect was also seen with **12** as a model compound (Fig. 1). Pretreatment of commercially available trimethylsilyl triflate with powdered molecular sieves (4 Å) also suppressed the anomerisation (Table I, entry 2), although the reason remains to be clarified. This pretreatment retarded the glucosylidenation in ether and required a higher reaction temperature to give the α-glycoside **25** preponderantly in higher yield (entry 4). The bis-*O*-trimethylsilyl-β-D-mannopyranoside derivative **21** required a

TABLE I

GLUCOSYLIDENATION OF TRIMETHYLSILYLATED MANNOPYRANOSIDES

Entry	*Mannopyranoside*	*Solvent*	*Catalyst*[a] *(mol %)*	*Temp. (°)*	*Time (days)*	*Product*	*Yield*[b] *(%)*	*Ratio of isomers*[c]
1	**16**	CH_2Cl_2	5	+3	3	**25**	28	1:1
2	**16**	CH_2Cl_2	20[d]	+3	2	**23**	24	1:1
						25	42	1:1
3	**16**	Ether	10	−15	3	**23**	35	1:1
						25	10	1:1
4	**16**	Ether	40[d]	r.t.	2	**23**	19	1:1
						25	44	1:1
5	**17**	Ether	10	−20	3	**25**	54	$R>>S$[e]
6	**21**	CH_2Cl_2	10	r.t.	3	**27**	22	5:9
7	**21**	1,4-Dioxane–CH_2Cl_2	20	+5	1	**27**	25	$R<<S$[e]

[a]Trimethylsilyl triflate. [b]Including the corresponding 4-trimethylsilyl ether. [c]Due to the asymmetry of the orthoester carbon. [d]Previously treated with molecular sieves (4 Å). [e]Over 10:1.

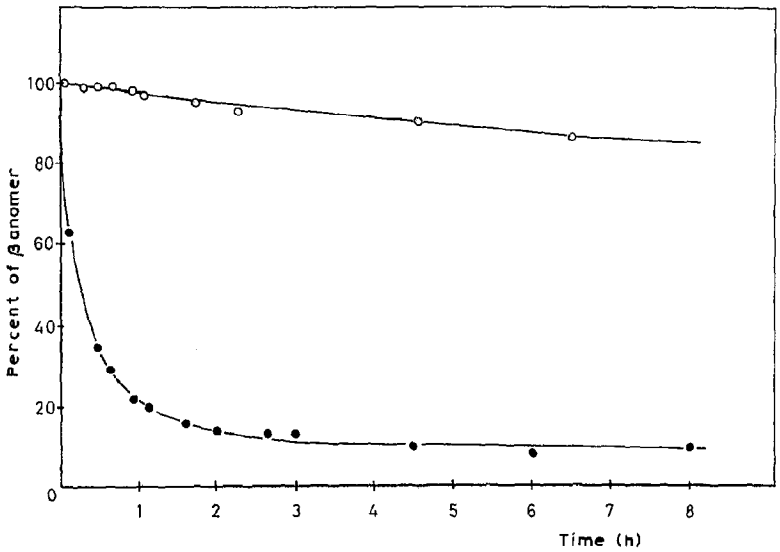
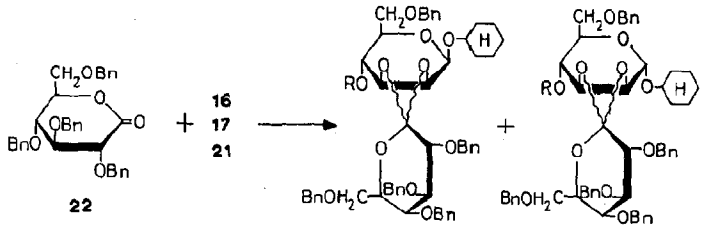


Fig. 1. Anomerisation of **12** in ether (o) and dichloromethane (●) in the presence of 44mM trimethylsilyl triflate at 17°. In the former, 40% of the β-anomer was present after 50 h, as deduced from the $[\alpha]_D$ value.

higher reaction temperature even in dichloromethane, presumably due to the electron-withdrawing effect of BzO-4. Due to the low solubility of **21** in ether and 1,4-dioxane, the reaction was carried out in a mixed solution with dichloromethane. However, only an anomerised product **27** was obtained (entry 7).

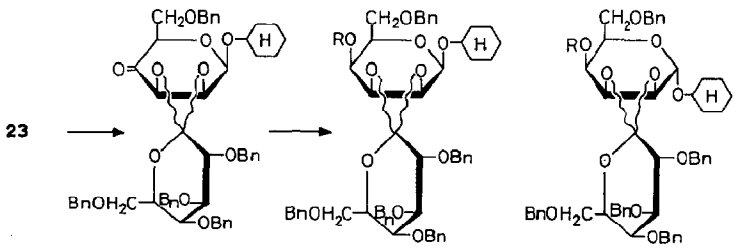
The configuration of the orthoester carbon was tentatively determined on the basis of the ^{13}C-n.m.r. chemical shifts and the empirical rule[12] for 2,3-*O*-glucosylidenated α-D-mannopyranoside that the carbon of the *R* isomer resonates at higher field ($\delta \sim 119$, *cf.* $\delta \sim 120$ for the *S* isomer). The result also accords with the mechanism, *i.e.*, the tendency that AlkO-4 leads to formation of the *R* isomer, and AcO-4 to the *S* isomer[12].



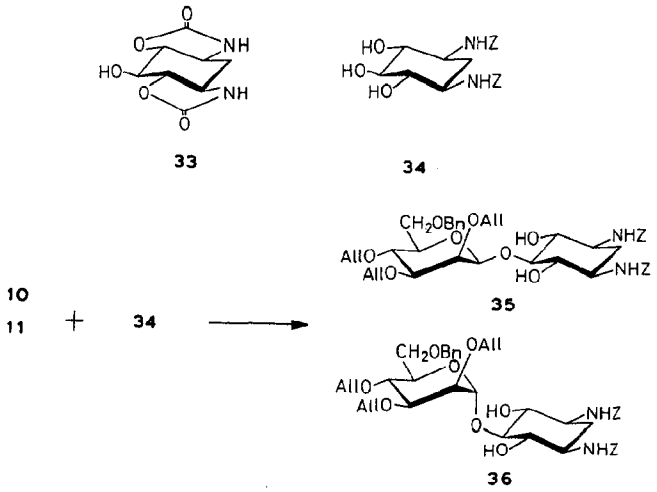
In the coupling of the α anomer **17** the *R* isomer preponderated, whereas the β-anomer **16** gave a 1:1 *RS*-mixture (Table I). The results indicate that anomerisation occurred after the formation of the orthoester linkage. Furthermore, the glucosylidenated β-D-mannopyranoside derivative may anomerise more rapidly than the parent compound.

A model reaction sequence for inversion of configuration at C-4 was carried out using the D-glucosylidene-β-D-mannopyranoside derivatives **23**. Oxidation of **23** with pyridinium chlorochromate followed by borohydride reduction gave solely the D-glucosylidene-β-D-talopyranoside derivative **29** (78% yield in two steps). The same conversion, when applied to the α-D-mannopyranoside derivative **25**, gave 82% of **31**. The configuration at C-4 was confirmed by the ^{1}H-n.m.r. data of the corresponding 4-acetates **30** and **32**.

The synthesis of destomycin C was approached *via* glycosylation of 2-deoxystreptamine derivatives. Silver triflate-promoted glycosylations in tetrahydrofuran, which was successfully used for preparation of the cyclohexyl β-D-mannopyranoside **12**, were applied to 1-*N*,6-*O*; 3-*N*,4-*O*-dicarbonyl- (**33**)[13] and 4,6-di-*N*-benzyloxycarbonyl-2-deoxystreptamine[14] (**34**). Although, by coupling of the chloride **11** in tetrahydrofuran with **33** at −90°, the pseudo-disaccharide was obtained in a yield of only 3%, the coupling of **11** with **34** under the same conditions afforded the desired β-pseudo-disaccharide **35** together with the corresponding α-disaccharide **36** in yields of 40% and 22%, respectively. This distinct difference in the reactivity of these two acceptors may be attributed to complex formation between the nitrogen and the neighboring oxygen atoms with silver ions. In the latter case, better β-selectivity was obtained to give **35** and **36** in yields of 52% and 14%, respectively, when the coupling was carried out at −78° at 2.7 times higher concentration. Furthermore, at higher reaction temperatures, the selectivity decreased, although a higher total yield was obtained at −30° to −50°[15]. At 0°, the α-anomer **36** (31%) was formed preponder-



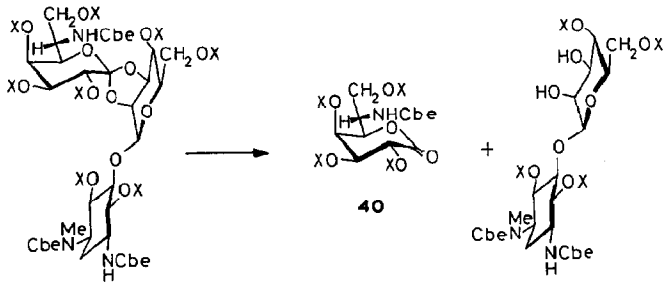
antly, together with the β-anomer **35** (10%) and 11-hydroxy-6-oxaundecyl 2,3,4-tri-*O*-allyl-6-*O*-benzyl-α-D-mannopyranoside (14%), by the reaction of **11** with **34** in tetrahydrofuran.



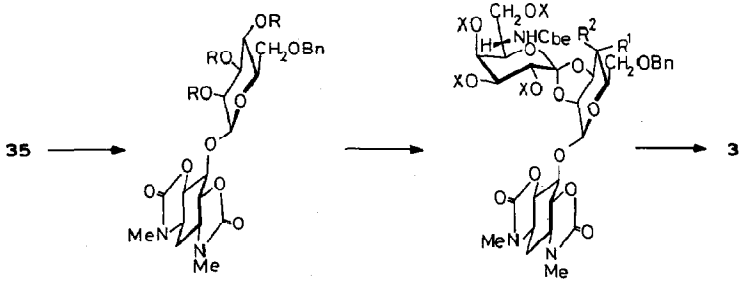
The deoxystreptamine moiety of the β-disaccharide derivative **35** was converted into the cyclic carbamate by intramolecular ester exchange using sodium hydride in *N,N*-dimethylformamide at 0°, followed by methylation with methyl iodide, to give 74% of **37**. *O*-Deallylation of **37** with Pd/C and toluene-*p*-sulfonic acid in methanol followed by trimethylsilylation gave the derivative **38** (95% yield in two steps). The destomic acid moiety was derived from destomycin A. Tri-*N*-ethoxycarbonyldestomycin A[5] was converted into the octa-*O*-(*p*-methylbenzyl) derivative **39** (50%) by treatment with *p*-methylbenzyl bromide and silver oxide in *N,N*-dimethylformamide, which was hydrolysed with M hydrochloric acid–acetic acid to give **40** and **41** in yields of 67% and 53%, respectively.

The coupling of destominolactone **40** with **38** in ether in the presence of trimethylsilyl triflate for 3 days at 3° was regio- and stereo-selective and gave a single pseudo-trisaccharide derivative **42**. ^{13}C-N.m.r. chemical shifts for the orthoester carbon in **42** (δ 120.3) and its *O*-desilylated derivative **43** (δ 120.5) indicate the unnatural *S*-isomer according to the above-described rule. However, the orthoester carbons of glucosylidenated β-pyranosides, especially those of *S* isomers, show a downfield shift of 0.5–1.3 p.p.m. in contrast to the corresponding α-glycoside as shown in Table II. Furthermore, the destomycin derivative **39** has a signal at δ 120.6 due to the orthoester carbon of *R* configuration. Thus, the configuration of the orthoester carbon in **39** was deduced to be *R* and this was confirmed by chemical conversion into destomycin C (**3**).

Inversion of the configuration at C-4′ was performed by oxidation of **43** and successive reduction to give **44** in 36% yield in two steps. Then, the carbamate moieties were hydrolysed with aqueous barium hydroxide at 80° and the *p*-methylbenzyl and benzyl groups were hydrogenolysed in aqueous ethanol in the presence of palladium hydroxide. When the product was purified on Dowex 1-X2 (HO^-) resin,



39 40 41



35 37 R = All
38 R = Me_3Si
42 R^1 = Me_3Si, R^2 = H
43 R^1 = OH, R^2 = H
44 R^1 = H, R^2 = OH
3

Cbe = ethoxycarbonyl

X = *p*-methylbenzyl

it proved to be identical with natural destomycin C (**3**) by comparison of their 500-MHz ^{1}H-n.m.r. spectra. The spectrum of **3** was fully analysed with the aid of 2D *J*-resolved spectra, and the data are summarised in Table III. The coupling constants indicate a slightly distorted $^0H^5$ conformation of the talopyranose moiety instead of the $B^{1,4}$ conformation, which was proved by X-ray analysis[5] in the case of octa-*O*-acetyltri-*N*-(ethoxycarbonyl)destomycin A.

EXPERIMENTAL

General methods. — All melting points are uncorrected. Solutions were concentrated under diminished pressure below 50° (bath). Optical rotations were measured with a JASCO DIP-4 polarimeter at 20 ± 5°. I.r. spectra were recorded with a Hitachi EPI-G2 grating spectrometer. ^{1}H-N.m.r. spectra were recorded with a JEOL PS-100 or Bruker AM-500 spectrometer, for solutions in $CDCl_3$ (internal Me_4Si) unless otherwise stated. ^{13}C-N.m.r. spectra were recorded with a JEOL FX-

TABLE II

^{13}C-N.M.R. CHEMICAL SHIFTS OF THE ORTHOESTER CARBON IN $CDCl_3$ AT 22.5 MHz

Compound	*Glycosylidene residue*		*Chemical shift*	
	Configuration	*Substituent at C-4*	R *isomer*	S isomer
23	*β-manno*	OH	119.4	120.6
24	*β-manno*	OAc	120.1	121.6
30	*β-talo*	OAc	119.8	121.7
25	*α-manno*	OH	118.9	120.1
26	*α-manno*	OAc	119.2	120.3
27	*α-manno*	OBz	119.3	120.7
31	*α-talo*	OH	118.4	120.1
32	*α-talo*	OAc	119.7	120.7
39	*β-talo*	OH	120.6	—
42	*β-manno*	OX[a]	120.3	—
43	*β-manno*	OX	120.5	—

[a]X = p-Methylbenzyl.

90Q spectrometer for solutions in $CDCl_3$ unless otherwise stated. Conventional chromatography as well as flash chromatography were performed on Kieselgel 60 (Merck), and preparative t.l.c. on Kieselgel 60HF (Merck).

*Methyl 2,3,4-tri-*O*-allyl-6-*O*-trityl-α-*D*-mannopyranoside* (**5**). — To a suspension of sodium hydride (50%; 6.22 g, 130 mmol) in dry *N,N*-dimethylformamide (20 mL) was added dropwise a solution of **4**[7] (9.42 g, 21.6 mmol) in the same solvent (20 mL). The mixture was stirred for 3.5 h at room temperature and then treated with a solution of allyl chloride (9.90 g, 129 mmol) in dry *N,N*-dimethylformamide (10 mL). After stirring for 3 h at room temperature, the solution was poured into ice–water and extracted with chloroform. Conventional processing of the extract and flash column chromatography (hexane–ethyl acetate, 15:1) of the residue gave **5** (10.3 g, 85.5%), isolated as a syrup, $[\alpha]_D$ +25° (*c* 1.7, chloroform). ^{1}H-N.m.r. data: δ 7.6–7.1 (m, 15 H, 3 Ph), 6.1–5.7 (m, 3 H, 3 =CH), 5.5–4.9 (m, 6 H, 3 $=CH_2$), 4.77 (d, $J_{1,2}$ 2.0 Hz H-1), 4.3–4.0 (m, 6 H, 3 OCH_2), 3.84–3.56 (m, 6 H, H-2,3,4,5,6a,6b), and 3.40 (s, 3 H, OMe).

Anal. Calc. for $C_{35}H_{40}O_6$: C, 75.51; H, 7.24. Found: C, 75.30; H, 7.26.

*Methyl 2,3,4-tri-*O*-allyl-α-*D*-mannopyranoside* (**6**). — A solution of **5** (1.57 g, 2.82 mmol) in aqueous 83% acetic acid (24 mL) was stirred for 35 min at 60°, and then concentrated with toluene. Flash column chromatography (hexane–acetone, 5:1) of the residue gave **6** (816 mg, 92%), isolated as a syrup, $[\alpha]_D$ +57.5° (*c* 1.1, chloroform). ^{1}H-N.m.r. data: δ 6.17–5.75 (m, 3 H, 3 =CH), 5.45–5.03 (m, 6 H, 3 $=CH_2$), 4,71 (d, $J_{1,2}$ 1.6 Hz, H-1), 4.49–4.09 (m, 6 H, 3 OCH_2), 3.89–3.49 (m, 6 H, H-2,3,4,5,6a,6b), 3.37 (s, 3 H, OMe), and 2.18 (bs, 1 H, HO-6).

Anal. Calc. for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 61.35; H, 8.48.

*Methyl 2,3,4-tri-*O*-allyl-6-*O*-benzyl-α-*D*-mannopyranoside* (**7**). — To a sus-

TABLE III

^{1}H-N.M.R. DATA OF NATURAL AND SYNTHETIC DESTOMYCIN C IN D_2O AT 500 MHz[a]

Proton	*Natural*			*Synthetic*		
	Chemical shift (p.p.m.)	*Coupling constant (Hz)*		*Chemical shift (p.p.m.)*	*Coupling constant (Hz)*	
1	2.74–2.78 m	$J_{1,2a}$	12.3	2.70–2.76 m	$J_{1,2a}$	12.0
		$J_{1,2e}$	3.7		$J_{1,2e}$	[b]
2*a*	1.22 q	$J_{2a,2e}$	12.3	1.15 q	$J_{2a,2e}$	12.0
2*e*	2.49 dt	$J_{2a,3}$	12.3	[b]	$J_{2a,3}$	12.0
3	2.74–2.87 m	$J_{2e,3}$	3.7	2.70–2.76 m	$J_{2e,3}$	[b]
4	3.61 dd	$J_{3,4}$	10.4	3.59 dd	$J_{3,4}$	8.3
5	3.84 t	$J_{4,5}$	9.2	3.83 dd	$J_{4,5}$	8.3
6	3.64 dd	$J_{5,6}$	9.2	3.61 t	$J_{5,6}$	10.6
		$J_{6,1}$	10.2		$J_{6,1}$	10.6
1′	5.38 d	$J_{1',2'}$	2.3	5.39 d	$J_{1',2'}$	2.4
2′	4.76 dd	$J_{2',3'}$	5.9	4.77 dd	$J_{2',3'}$	6.1
3′	4.86 t	$J_{3',4'}$	5.9	4.87 dd	$J_{3',4'}$	5.5
4′	4.12 dd	$J_{4',5'}$	1.3	4.12 dd	$J_{4',5'}$	< 1.0
5′	3.73 ddd	$J_{5',6'a}$	3.6	3.73 ddd	$J_{5',6'a}$	3.4
6′a	3.91 dd	$J_{6'a,6'b}$	11.8	3.91 dd	$J_{6'a,6'b}$	12.1
6′b	4.03 dd	$J_{5',6'b}$	8.2	4.03 dd	$J_{5',6'b}$	8.2
2″	4.24 d	$J_{2'',3''}$	10.2	4.25 d	$J_{2'',3''}$	10.3
3″	4.05 dd	$J_{3'',4''}$	3.4	4.06 dd	$J_{3'',4''}$	3.6
4″	4.17 dd	$J_{4'',5''}$	1.3	4.18 dd	$J_{4'',5''}$	< 1.0
5″	3.89 dd	$J_{5'',6''}$	8.4	3.89 dd	$J_{5'',6''}$	8.3
6″	3.35 ddd	$J_{6'',7''a}$	6.4	3.34 m	$J_{6'',7''a}$	6.6
7″a	3.69 dd	$J_{7''a,7''b}$	11.6	3.69 dd	$J_{7''a,7''b}$	11.6
7″b	3.86 dd	$J_{6'',7''b}$	4.3	3.86 dd	$J_{6'',7''b}$	3.9
NMe	2.56 s, 2.58 s			2.56 s, 2.58 s		

[a]Chemical shifts were calculated by using the HDO signal as internal standard. [b]Could not be completely analysed.

pension of sodium hydride (50%; 1.72 g, 35.8 mmol) in dry *N,N*-dimethylformamide (7 mL) was added dropwise a solution of **6** (7.50 g, 23.9 mmol) in the same solvent (13 mL) followed, after stirring overnight at room temperature, by a solution of benzyl chloride (4.53 g, 35.8 mmol) in dry *N,N*-dimethylformamide. The product obtained by processing as described for **5** was purified by flash chromatography (hexane–ethyl acetate, 8:1) to give **7** (7.19 g, 74.5%), isolated as a syrup, $[\alpha]_D$ +42° (*c* 1.3, chloroform). ^{1}H-N.m.r. data: δ 7.5–7.3 (m, 5 H, Ph), 6.18–5.66 (m, 3 H, 3 =CH), 5.46–5.02 (m, 6 H, 3 $=CH_2$), 4.76 (d, $J_{1,2}$ 1.8 Hz, H-1), 4.72 and 4.55 (ABq, *J* 12.2 Hz, CH_2Ph), 4.46–3.88 (m, 6 H, 3 OCH_2), 3.98–3.80 (m, 6 H, H-2,3,4,5,6a,6b), and 3.18 (s, 3 H, OMe).

Anal. Calc. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.04; H, 8.14.

1-O-Acetyl-2,3,4-tri-O-allyl-6-O-benzyl-α-D-mannopyranose (**8**). — To a solution of **7** (7.07 g, 17.5 mmol) in acetic anhydride (180 mL) was added a mixture of acetic acid (60 mL) and concentrated sulfuric acid (0.12 mL). The mixture was

stored for 1 h at room temperature, then poured into ice-water containing sodium hydrogencarbonate (0.5 g), and extracted with chloroform. The residue obtained by conventional processing of the extract was fractionated by flash chromatography on silica gel (hexane–ethyl acetate, 8:1) to give **8** (5.27 g, 70%) and 1,6-di-*O*-acetyl-2,3,4-tri-*O*-allyl-α-D-mannopyranose (**9**; 1.82 g, 30%), both as syrups.

Compound **8** had $[\alpha]_D$ +42° (*c* 1.5, chloroform); ν_{max} 1760 cm^{-1} (ester). ^{1}H-N.m.r. data: δ 7.5–7.3 (m, 5 H, Ph), 6.17 (d, $J_{1,2}$ 1.8 Hz, H-1), 6.13–5.65 (m, 3 H, 3 =CH), 5.47–5.01 (m, 6 H, 3 $=CH_2$), 4.71 and 4.53 (ABq, *J* 12.0 Hz, CH_2Ph), 4.4–4.0 (m, 6 H, 3 OCH_2), 3.9–3.6 (m, 6 H, H-2,3,4,5,6a,6b), and 2.09 (s, 3 H, OAc); ^{13}C, δ 168.9 (s, C=O) and 92.24 (d, C-1).

Anal. Calc. for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.68; H, 7.68.

Compound **9** had $[\alpha]_D$ +39° (*c* 1.8, chloroform); ν_{max} 1750 cm^{-1} (ester). ^{1}H-N.m.r. data: δ 6.11 (d, $J_{1,2}$ 2.0 Hz, H-1), 6.1–5.7 (m, 3 H, 3 =CH), 4.7–3.3 (m, 12 H, 3 OCH_2 and H-2,3,4,5,6a,6b), and 2.10 (s, 6 H, 2 OAc); ^{13}C, δ 168.7 and 170.6 (2 s, C=O), and 92.00 (d, C-1).

Anal. Calc. for $C_{19}H_{28}O_8$: C, 59.36; H, 7.34. Found: C, 59.02; H, 7.37.

2,3,4-Tri-O-allyl-6-O-benzyl-α-D-mannopyranosyl halides. — (*a*) ***Bromide*** (**10**). To a solution of **8** (3.55 g, 8.21 mmol) in dry dichloromethane (50 mL) was added dropwise at room temperature a solution of titanium(IV) bromide (2.09 g, 5.69 mmol) in dry dichloromethane (20 mL), and then, after 2 h, dry acetonitrile (150 mL) and sodium acetate (30 g). When the solution turned turbid, the mixture was diluted with toluene (80 mL), filtered, and concentrated. A solution of the residue in chloroform was washed with ice-water, dried, and concentrated to give **10** as a syrup quantitatively, which was used for glycosylation without any further purification. ^{1}H-N.m.r. data: δ 7.3–7.1 (m, 5 H, Ph), 6.44 (d, $J_{1,2}$ 1.5 Hz, H-1), 6.1–5.6 (m, 3 H, 3 =CH), 5.4–5.0 (m, 6 H, 3 $=CH_2$), 4.62 and 4.44 (ABq, *J* 12.0 Hz, CH_2Ph), 4.3–3.5 (m, 12 H, 3 OCH_2 and H-2,3,4,5,6a,6b).

(*b*) ***Chloride*** (**11**). An ice-cold solution of **8** (6.31 g, 14.6 mmol) in dry ether (120 mL) was saturated with hydrogen chloride, stored for 3 h at 0°, then diluted with ether, washed with cold water, aqueous sodium hydrogencarbonate, and cold water, dried, and concentrated. The syrupy residue was purified by flash chromatography (hexane–ethyl acetate, 8:1) to give **11** (4.43 g, 74%). ^{1}H-N.m.r. data: δ 7.5–7.0 (m, 5 H, Ph), 6.13 (s, H-1), 6.1–5.6 (m, 3 H, 3 =CH), 5.5–5.0 (m, 6 H, 3 $=CH_2$), 4.68 and 4.50 (ABq, *J* 12.0 Hz, CH_2Ph), and 4.4–3.5 (m, 12 H, 3 OCH_2 and H-2,3,4,5,6a,6b).

Anal. Calc. for $C_{22}H_{29}ClO_5$: C, 64.62; H, 7.15; Cl, 8.67. Found: C, 64.60; H, 7.38; Cl, 9.22.

Cyclohexyl 2,3,4-tri-O-allyl-6-O-benzyl-β-D-mannopyranoside (**12**). — A solution of freshly distilled cyclohexanol (79.8 mg, 0.80 mmol) in dry dichloromethane (5 mL) was stirred with newly prepared silver silicate (500 mg) for 1 h at room temperature in the dark and then cooled to −22°, and a solution of **10** derived from **8** (500 mg, 1.16 mmol) in dichloromethane (4 mL) was added. The mixture was kept at −22° for 30 min and then allowed to attain room temperature, dichloro-

methane was added, and insoluble material was removed by filtration. The residue obtained by conventional processing of the filtrate was purified by flash chromatography (hexane–acetone, 20:1) to give **12** (243 mg, 65%), $[\alpha]_D$ −51° (*c* 1.9, chloroform), −33° (*c* 0.9, ether), −42° (*c* 1.6, dichloromethane). N.m.r. data: ^{1}H, δ 7.4–7.2 (m, 5 H, Ph), 6.1–5.6 (m, 3 H, 3 =CH), 5.4–4.9 (m, 6 H, 3 $=CH_2$), 4.59 (s, 2 H, CH_2Ph), 4.46 (s, H-1), 4.4–3.2 (m, 13 H, 3 OCH_2, OCH, and H-2,3,4,5,6a,6b), 2.1–1.1 (m, 10 H, 5 CCH_2); ^{13}C, δ 99.1 (s, C-1).

Anal. Calc. for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 71.29; H, 8.61.

Coupling of **11** *and cyclohexanol in the presence of silver triflate.* — To a solution of cyclohexanol (0.5 mmol) in distilled tetrahydrofuran (10 mL) was added dry silver triflate (2.0 mmol) in the dark and then dropwise, at an appropriate temperature, a solution of **11** (0.75 mmol) in tetrahydrofuran (5 mL). After 30 min, the mixture was poured into an ice-cold 1:1 mixture of saturated aqueous sodium hydrogencarbonate and sodium chloride, filtered, and extracted with chloroform. The crude mixture of products obtained by conventional processing of the extract was fractionated, as described above, to afford **12** (22% at 0° and 6.8% at −78°) and cyclohexyl 2,3,4-tri-*O*-allyl-6-*O*-benzyl-α-D-mannopyranoside (**13**; 44% at 0° and 23% at −78°), $[\alpha]_D$ +53° (*c* 1.1, chloroform), +63° (*c* 1.2, ether), +50° (*c* 1.2, dichloromethane). ^{1}H-N.m.r. data: δ 7.4–7.1 (m, 5 H, Ph), 6.1–5.6 (m, 3 H, 3 =CH), 5.4–5.0 (m, 6 H, 3 $=CH_2$), 4.96 (d, $J_{1,2}$ 1.5 Hz, H-1), 4.65 and 4.50 (ABq, *J* 11.8 Hz, CH_2Ph), 4.4–3.9 (m, 6 H, 3 OCH_2), 3.9–3.4 (m, 7 H, OCH and H-2,3,4, 5,6a,6b), and 2.0–0.7 (m, 10 H, 5 CCH_2); ^{13}C, δ 96.0 (s, C-1).

Anal. Calc. for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 71.18; H, 8.61.

Cyclohexyl 6-O-benzyl-β-D-mannopyranoside (**14**). — A solution of **12** (493 mg, 1.04 mmol) in methanol (80 mL) was heated for 2 h at 50° in the presence of toluene-*p*-sulfonic acid (310 mg) and 10% Pd/C (150 mg). After the addition of aqueous sodium hydrogencarbonate (140 mg), the mixture was filtered and concentrated. The residue was purified on a column of silica gel with hexane–acetone (1:1) to give **14** (222 mg, 61%), m.p. 117.5–119° (from ethyl acetate–light petroleum), $[\alpha]_D$ −61° (*c* 1.4, chloroform). ^{1}H-N.m.r. data: δ 7.4–7.2 (m, 5 H, Ph), 4.58 (s, 2 H, CH_2Ph), 3.96–3.30 (m, 8 H, H-1,2,3,4,5,6a,6b and OCH), 2.1–1.1 (m, 10 H, 5 CCH_2).

Anal. Calc. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.93; H, 8.24.

Cyclohexyl 6-O-benzyl-α-D-mannopyranoside (**15**). — *O*-Deallylation of **13**, as described for **14**, afforded **15** (46%) as a syrup, $[\alpha]_D$ +58° (*c* 0.8, chloroform). ^{1}H-N.m.r. data: δ 7.4–7.2 (m, 5 H, Ph), 4.92 (s, H-1), 4.56 (s, 2 H, CH_2Ph), 4.6–3.3 (m, 7 H, H-2,3,4,5,6a,6b and OCH), and 2.0–1.0 (m, 10 H, 5 CCH_2).

Anal. Calc. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.56; H, 7.70.

Cyclohexyl 6-O-benzyl-2,3,4-tris-O-trimethylsilyl-α- (**17**) *and -β-D-mannopyranoside* (**16**). — To a solution of chlorotrimethylsilane (0.87 mL, 6.9 mmol) and imidazole (470 mg, 6.9 mmol) in dry *N,N*-dimethylformamide was added **14** (1.0 mmol). The mixture was stirred for 30 min at room temperature, and then diluted with ether, washed with water, dried, and concentrated. The residue was purified on

a column of silica gel with ether, to give **16** quantitatively as a syrup. ^{1}H-N.m.r. data: δ 7.3–7.1 (m, 5 H, Ph), 4.54 (s, 2 H, C*H*$_2$Ph), 4.40 (s, H-1), 3.9–3.2 (m, 7 H, H-2,3,4,5,6a,6b and OCH), 2.1–1.1 (m, 10 H, 5 CCH_2), 0.16, 0.14, and 0.08 (3 s, 27 H, 3 $SiMe_3$).

Trimethylsilylation of **15**, as described for **16**, gave **17** quantitatively as a syrup. ^{1}H-N.m.r. data: δ 7.4–7.2 (m, 5 H, Ph), 4.72 (d, $J_{1,2}$ 2.0 Hz, H-1), 4.57 (s, 2 H, C*H*$_2$Ph), 3.9–3.4 (m, 7 H, H-2,3,4,5,6a,6b and OCH), and 2.0–0.9 (m, 10 H, 5 CCH_2), 0.14, 0.11, and 0.08 (3 s, 27 H, 3 $SiMe_3$).

*Cyclohexyl 4-*O*-benzoyl-6-*O*-benzyl-β-*D*-mannopyranoside* (**20**). — To a solution of **14** (605 mg, 1.72 mmol) in dry acetone (2 mL) was added toluene-*p*-sulfonic acid (12 mg) and 2,2-dimethoxypropane (2 mL). The mixture was kept for 20 min at room temperature, then neutralised with aqueous sodium hydrogencarbonate, and concentrated, and a solution of crude **19** in ethyl acetate (50 mL) and concentrated ammonia (0.02 mL) was passed through a column of silica gel. Concentration of the eluate gave crude cyclohexyl 6-*O*-benzyl-2,3-*O*-isopropylidene-β-D-mannopyranoside (**18**). ^{1}H-N.m.r. data: δ 7.3–7.1 (m, 5 H, Ph), 4.77 (d, $J_{1,2}$ 2.5, H-1), 4.50 (s, 2 H, C*H*$_2$Ph), 4.2–3.3 (m, 7 H, H-2,3,4,5,6a,6b and OCH), 2.91 (d, *J* 2.5 Hz, OH), 1.52 and 1.35 (2 s, each 3 H, 2 CMe), and 2.1–1.0 (m, 10 H, 5 CCH_2).

To a solution of crude **18**, derived from **14** (605 mg), in dry pyridine (5 mL) was added benzoyl chloride (0.4 mL). The mixture was stirred for 20 min at room temperature and, after addition of methanol (0.2 mL), kept for a further 20 min, then diluted with chloroform, washed with water, dried, and concentrated. A solution of the residue in aqueous 80% acetic acid was kept for 7 h at 35° and then concentrated. The residue was purified on a column of silica gel (hexane–ethyl acetate, 3:2) to afford **20** (657 mg, 84%), isolated as a syrup, $[\alpha]_D$ −16° (*c* 0.7, chloroform); ν_{max} 3420 (OH) and 1720 cm^{-1} (ester). ^{1}H-N.m.r. data: δ 8.1–7.9 and 7.7–7.1 (m, 10 H, Ph), 5.34 (t, $J_{3,4} = J_{4,5}$ = 8.3 Hz, H-4), 5.2–4.8 (b, 2 H, HO-2,3), 4.69 (d, $J_{1,2}$ 1.0 Hz, H-1), 4.52 (s, 2 H, C*H*$_2$Ph), 4.05 (dd, $J_{2,3}$ 3.5 Hz, H-2), 3.82 (dd, H-3), 3.7–3.5 (m, 4 H, H-5,6a,6b and OCH), and 2.1–1.1 (m, 10 H, 5 CCH_2).

Anal. Calc. for $C_{26}H_{32}O_7$: C, 68.40; H, 7.07. Found: C, 68.23; H, 6.85.

*Cyclohexyl 4-*O*-benzoyl-6-*O*-benzyl-2,3-bis-*O*-trimethylsilyl-β-*D*-mannopyranoside* (**21**). — Trimethylsilylation of **20**, as described for **16**, gave **21** (96%), m.p. 148–150° (from hexane), $[\alpha]_D$ −54° (*c* 0.4, chloroform); ν_{max} 1730 cm^{-1} (ester). ^{1}H-N.m.r. data: δ 8.1–7.9 and 7.6–7.1 (m, 10 H, 2 Ph), 5.38 (t, $J_{3,4} = J_{4,5}$ = 9.0 Hz, H-4), 4.55 (s, H-1), 4.48 (s, C*H*$_2$Ph), 3.9–3.5 (m, 6 H, H-2,3,5,6a,6b and OCH), 2.1–1.1 (m, 10 H, 5 CCH_2), and 0.18 (s, 18 H, 2 $SiMe_3$).

Anal. Calc. for $C_{32}H_{48}O_7Si_2$: C, 63.95; H, 8.07. Found: C, 63.67; H, 8.22.

*Cyclohexyl 6-*O*-benzyl-2,3-*O*-(2,3,4,6-tetra-*O*-benzyl-*D*-glucopyranosylidene)-α-* (**25**) *and -β-*D*-mannopyranoside* (**23**). — To a solution of the dry lactone (**22**) (151 mg, 0.28 mmol) and **16** (243 mg, 0.42 mmol) in dry ether (0.7 mL) at −20° was added a solution of trimethylsilyl triflate (6.2 mg, 0.028 mmol) in ether (100 μL). The solution was kept for 3 days at −20° and then for 2 days at −15°, when t.l.c. showed that **16** had disappeared. After addition of pyridine (0.3 mL), the mixture

was diluted with chloroform, washed with aqueous sodium hydrogencarbonate and water, dried, and concentrated. The residue was treated with methanol in the presence of potassium carbonate and fractionated by flash chromatography (hexane–acetone, 6:1–3:1) to give **23** (syrup, 86 mg, 35%), *R*-**25** (13 mg, 5%), m.p. 134–136° (from acetone–light petroleum), and *S*-**25** (syrup, 13 mg, 5%). Partial ^{13}C-n.m.r. data: **23**, δ 119.4 (s, C-1′*R*) and 95.4 (d, C-1*R*), 120.6 (s, C-1′*S*) and 96.4 (d, C-1*S*); *R*-**25**, δ 118.9 (s, C-1′) and 93.9 (d, C-1); *S*-**25**, δ 120.1 (s, C-1′) and 93.9 (d, C-1).

Anal. Calc. for $C_{53}H_{60}O_{11}$: C, 72.91; H, 6.93. Found: **23**, C, 72.71; H, 6.91; *R*-**25**, C, 73.09; H, 7.01; *S*-**25**, C, 72.69; H, 6.78.

*Cyclohexyl 4-*O*-acetyl-6-*O*-benzyl-2,3-*O*-(2,3,4,6-tetra-*O*-benzyl-*D*-gluco-pyranosylidene)-β-*D*-mannopyranoside* (**24**). — Conventional acetylation of **23** gave **24** quantitatively. Partial n.m.r. data: ^{1}H, δ 5.39 (dd, *J* 7.1 and 9.9 Hz, H-4); ^{13}C, δ 120.1 (s, C-1′*R*), 97.1 (d, $J_{C\text{-}1,H\text{-}1}$ 156.5 Hz, C-1*R*), 121.6 (s, C-1′*S*), and 95.4 (d, $J_{C\text{-}1,H\text{-}1}$ 157.5 Hz, C-1*S*).

Anal. Calc. for $C_{55}H_{62}O_{12}$: C, 72.19; H, 6.83. Found: C, 72.19; H, 7.01.

Conventional acetylation of **25** (a mixture of *R* and *S* isomers) gave the corresponding 4-acetate **26** quantitatively, which was characterised only by the n.m.r. data: ^{1}H, δ 5.06 (s, H-1*R*), 5.06 (t, $J_{3,4} = J_{4,5} = 10.5$ Hz, H-4*R*), 5.18 (s, H-1*S*), and 5.02 (t, $J_{3,4} = J_{4,5} = 10.5$ Hz, H-4*S*); ^{13}C, δ 120.3 (s, C-1′*S*), 119.2 (s, C-1′*R*), and 94.1 (d, C-1*RS*).

*Cyclohexyl 4-*O*-benzoyl-6-*O*-benzyl-2,3-*O*-(2,3,4,6-tetra-*O*-benzyl-*D*-gluco-pyranosylidene)-α-*D*-mannopyranoside* (**27**). — To a solution of **22** (347 mg, 0.65 mmol) and **21** (583 mg, 0.97 mmol) in dry dichloromethane (1.5 mL) at −15° was added a solution of trimethylsilyl triflate (14.2 mg, 0.06 mmol) in dichloromethane (100 μL). The temperature was elevated gradually up to room temperature and the mixture was stored thereat for 3 days. The residue obtained by the processing, as described for **23** and **25**, was purified by flash chromatography (hexane–acetone, 6:1) to give **27** (141 mg, 22%) as an epimeric mixture. Partial n.m.r. data: ^{1}H, δ 5.35 (s, H-1*R*), 5.28 (dd, *J* 8.0 and 9.0 Hz, H-4*R*), 5.68 (dd, *J* 7.0 and 10.2 Hz, H-4*S*), 5.26 (s, H-1*S*); ^{13}C, δ 120.7 (s, C-1′*S*), 119.3 (s, C-1′*R*), and 94.3 (d, $J_{C\text{-}1,H\text{-}1}$ 171.5 Hz, C-1*RS*).

Anal. Calc. for $C_{60}H_{64}O_{12}$: C, 73.75; H, 6.60. Found: C, 73.78; H, 6.51.

*Cyclohexyl 4-*O*-acetyl-6-*O*-benzyl-2,3-*O*-(2,3,4,6-tetra-*O*-benzyl-*D*-gluco-pyranosylidene)-β-*D*-talopyranoside* (**30**). — To a solution of **23** (49.6 mg, 0.057 mmol) in dry dichloromethane (0.3 mL) was added pyridinium chlorochromate (80 mg) and powdered molecular sieves (4 Å, 30 mg), and the mixture was stirred

*Cyclohexyl 4-*O*-acetyl-6-*O*-benzyl-2,3-*O*-(2,3,4,6-tetra-*O*-benzyl-*D*-gluco-pyranosylidene)-β-*D*-talopyranoside* (**30**). — To a solution of **23** (49.6 mg, 0.057 mmol) in dry dichloromethane (0.3 mL) was added pyridinium chlorochromate (80 mg) and powdered molecular sieves (4 Å, 30 mg), and the mixture was stirred overnight at room temperature. The residue obtained by evaporation of the solvent was eluted from a column of silica gel–calcium sulfate with ether. Crude 4-ulose **28**, obtained by concentration of the eluate, was used further without purification. To a

solution of **28** in ethanol at 0° was added sodium borohydride (91 mg), and the mixture was stirred for 4 h at 0°, then diluted with acetone–water, saturated with carbon dioxide at 0°, and concentrated. The residue was eluted from a column of silica gel with ethyl acetate to give **29** (38.7 mg, 78%).

Conventional acetylation of **29** gave **30** quantitatively. Partial n.m.r. data: ^{1}H, δ 5.52 (t, $J_{3,4} = J_{4,5} = 4.5$ Hz, H-4*R*), 5.89 (t, $J_{3,4} = J_{4,5} = 5.5$ Hz, H-4*S*); ^{13}C, δ 119.8 (s, C-1′*R*), 98.9 (d, C-1*R*), 121.7 (s, C-1′*S*), and 98.3 (d, C-1*S*).

Anal. Calc. for $C_{55}H_{62}O_{12}$: C, 72.19; H, 6.83. Found: C, 72.06; H, 6.99.

*Cyclohexyl 4-*O*-acetyl-6-*O*-benzyl-2,3-*O*-(2,3,4,6-tetra-*O*-benzyl-*D*-gluco-pyranosylidene)-α-*D*-talopyranoside* (**32**). — Conversion of HO-4 in **25** (mixture of *R* and *S* isomers) was carried out as described above, to give **31** in 82% yield in two steps. ^{13}C-N.m.r. data: δ 118.4 (s, C-1′*R*), 94.3 (d, C-1*R*), 120.1 (s, C-1′*S*), and 94.8 (d, C-1*S*).

Conventional acetylation of **31** gave **32** quantitatively. N.m.r. data: ^{1}H, δ 5.53 (dd, *J* 4.7 and 5.4 Hz, H-4*R*), 5.02 (d, H-1*R*), 5.36 (dd, *J* 3.9 and 4.9 Hz, H-4*S*), and 5.13 (d, H-1*S*); ^{13}C, δ 119.7 (s, C-1′*R*), 95.3 (d, C-1*R*), 120.3 (s, C-1′*S*), and 94.8 (d, C-1*S*).

Anal. Calc. for $C_{55}H_{62}O_{12}$: C, 72.19; H, 6.83. Found: C, 72.20; H, 6.93.

*1,3-Di-*N*-benzyloxycarbonyl-5-*O*-(2,3,4-tri-*O*-allyl-6-*O*-benzyl-β-*D*-manno-pyranosyl)-2-deoxystreptamine* (**35**) *and 1,3-di-*N*-benzyloxycarbonyl-5-*O*-(2,3,4-tri-*O*-allyl-6-*O*-benzyl-α-*D*-mannopyranosyl)-2-deoxystreptamine* (**36**). — (*a*) *Coupling at 0°.* To a suspension of **34** (152 mg, 0.35 mmol) in dry tetrahydrofuran (20 mL) was added, in the dark, dry silver triflate (650 mg, 2.5 mmol) and then, at 0° dropwise, a solution of **11** (171 mg, 0.42 mmol) in dry tetrahydrofuran (4 mL) during 5 min. After 30 min, the mixture was poured into an ice-cold 1:1 mixture of saturated aqueous sodium hydrogencarbonate and sodium chloride, filtered, and extracted with chloroform. The residue obtained by usual processing of the extract was fractionated by flash chromatography (hexane–ethyl acetate, 1:1) to give **35** (27.9 mg, 9.9%), **36** (86.3 mg, 31%), 11-hydroxy-6-oxaundecyl 2,3,4-tri-*O*-allyl-6-*O*-benzyl-α-*D*-mannopyranoside[15] (33.6 mg, 14%), and 2,3,4-tri-*O*-allyl-6-*O*-benzyl-*D*-mannopyranose (25.9 mg, 16%).

Compound **35** had m.p. 216–217° (from acetone–hexane), $[\alpha]_D$ −5.8° (*c* 1, chloroform); ν_{max} 3600–3100 (OH and NH), 1690 and 1540 cm^{-1} (urethane). N.m.r. data: ^{1}H, δ 7.4–7.2 (m, 15 H, 3 Ph), 6.1–5.6 (m, 3 H, 3 =CH), 5.4–4.9 (m, 6 H, 3 =CH_2), 5.08 and 5.06 (2 s, each 2 H, CH_2Ph), 4.60 (s, H-1′), 4.57 and 4.44 (ABq, *J* 11.8 Hz, CH_2Ph), 4.35–3.3 (m, 17 H, H-1,3,4,5,6, H-2′,3′,4′,5′,6a′,6b′, and 3 OCH_2), 2.53 (m, 1 H, H-2*e*), and 1.26 (m, 1 H, H-2*a*); ^{13}C, δ 156.9 and 156.3 (2 s, C=O), and 102.1 (d, $J_{C\text{-}1,H\text{-}1}$ 158.4 Hz, C-1′).

Anal. Calc. for $C_{44}H_{54}N_2O_{12}$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.99; H, 6.85; N, 3.40.

Compound **36** had m.p. 128–129° (from acetone–light petroleum), $[\alpha]_D$ +21° (*c* 2.2, chloroform); ν_{max} 3600–3150 (OH and NH), 1730 and 1700 (urethane), 1550, and 1510 cm^{-1}. N.m.r. data: ^{1}H, δ 7.4–7.2 (m, 15 H, 3 Ph), 6.1–5.6 (m, 3 H, 3

=CH), 5.4–4.9 (m, 7 H, 3 $=CH_2$ and H-1'), 5.08 and 5.06 (2 s, 4 H, 2 CH_2Ph), 4.52 (s, 2 H, CH_2Ph), 4.4–3.2 (m, 17 H, H-1,3,4,5,6, H-2',3',4',5',6a',6b', and 3 OCH_2), 2.47 (m, 1 H, H-2*e*), and 1.27 (m, 1 H, H-2*a*); ^{13}C, δ 156.7 and 156.4 (2 s, C=O), and 100.0 (d, $J_{C\text{-}1',H\text{-}1'}$ 170.9 Hz, C-1').

Anal. Calc. for $C_{44}H_{59}N_2O_{12}$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.93; H, 6.95; N, 3.28.

(*b*) *Coupling at* $-78°$. To a suspension of **34** (153 mg, 0.36 mmol) in dry tetrahydrofuran (7 mL) was added at $-78°$ dry silver triflate (639 mg, 2.5 mmol) and then a solution of **11** (212 mg, 0.52 mmol) in dry tetrahydrofuran (2 mL). After 5 h, the mixture was processed in the same manner as described above, to give **35** (147 mg, 52%), **36** (38.5 mg, 14%), and the 11-hydroxy-6-oxaundecyl α-D-mannopyranoside derivative (53.5 mg, 18%).

1-N,*6*-O:*3*-N,*4*-O-*Dicarbonyl-1,3-di*-N-*methyl-5*-O-*(2,3,4-tri*-O-*allyl-6*-O-*benzyl-β*-D-*mannopyranosyl)-2-deoxystreptamine* (**37**). — To a chilled solution of **35** (497 mg, 0.62 mmol) in dry *N,N*-dimethylformamide (11 mL) was added sodium hydride (50%, 1.0 g, 21 mmol) and then methyl iodide (1.2 mL, 19 mmol) after 30 min. After 10 min, acetic acid (1.3 mL) and aqueous sodium hydrogencarbonate were added, and the mixture was extracted with chloroform. Conventional processing of the extract gave a residue which was purified by flash chromatography (hexane–acetone, 2:1) to afford **37** (280 mg, 74%), m.p. 107–108° (from ethyl acetate–hexane), $[\alpha]_D$ $-35°$ (*c* 2.7, chloroform); ν_{max} 1760 and 1740 cm^{-1} (urethane). ^{1}H-N.m.r. data: δ 7.5–7.2 (m, 5 H, Ph), 6.1–5.6 (m, 3 H, 3 =CH), 5.5–5.0 (m, 6 H, 3 $=CH_2$), 4.76 (s, H-1'), 4.62 (s, 2 H, CH_2Ph), 4.6–2.8 (m, 17 H, H-1,3,4, 5,6, H-2',3',4',5',6a',6b', and 3 OCH_2), 2.81 and 2.72 (2 s, 6 H, 2 NMe), 2.28 (dt, $J_{1,2e} = J_{2e,3} = 3.5$ Hz, H-2*e*), and 1.46 (q, $J_{1,2a} = J_{2a,2e} = J_{2a,3} = 12.0$ Hz, H-2*a*).

Anal. Calc. for $C_{32}H_{42}N_2O_{10}$: C, 62.52; H, 6.88; N, 4.56. Found: C, 62.33; H, 7.04; N, 4.51.

5-O-*(6*-O-*Benzyl-2,3,4-tris*-O-*trimethylsilyl-β*-D-*mannopyranosyl)-1*-N,*6*-O:*3*-N,*4*-O-*dicarbonyl-1,3-di*-N-*methyl-2-deoxystreptamine* (**38**). — *O*-Deallylation of **37** (502 mg, 0.82 mmol) was performed in methanol (30 mL) in the presence of toluene-*p*-sulfonic acid (90 mg) and Pd/C (10%, 200 mg) for 4 h at 45° as described for **14**. *O*-Trimethylsilylation as described for **16** then gave **38** (549 mg, 95%) after purification on a column of silica gel (ethyl acetate). ^{1}H-N.m.r. data: δ 7.4–7.2 (m, 5 H, Ph), 4.64 (s, H-1'), 4.53 and 4.39 (ABq, *J* 10.0 Hz, CH_2Ph), 4.0–2.7 (m, 11 H, H-1,3,4,5,6, H-2',3',4',5',6a',6b'), 2.78 (s, 6 H, 2 NMe), 2.22 (m, 1 H, H-2*e*), 1.42 (q, $J_{1,2a} = J_{2a,2e} = J_{2a,3} = 11.0$ Hz, H-2*a*), 0.10 and 0.06 (2 s, 27 H, 3 $SiMe_3$).

5-O-{*2,3*-O-*[6-Deoxy-6-ethoxycarbonylamino-2,3,4,7-tetra*-O-*(*p-*methylbenzyl)*-L-glycero-D-galacto-(R)-*heptopyranosylidene]-4,6-di*-O-(p-*methylbenzyl)-β*-D-*talopyranosyl*}-1,3-di-N-*ethoxycarbonyl-1*-N-*methyl-4,6-di*-O-(p-*methylbenzyl) - 2-deoxystreptamine* (**39**). — To a solution of the tri-*N*-ethoxycarbonylated derivative[5], derived from destomycin A (2.47 g, 4.7 mmol), in *N,N*-dimethylformamide (20 mL) was added, in the dark, freshly prepared silver oxide (11.2 g) and *p*-methylbenzyl bromide (9.33 g). The mixture was stirred for 3 h at room tem-

perature and then, after the addition of ethanol (5 mL), for a further 1 h. Insoluble material was collected and washed with acetone and chloroform. The residue obtained by concentration of the filtrate and washings was fractionated by flash chromatography (hexane–acetone, 6:1), to give **39** (3.68 g, 50%) and, presumably, its 3-*N*-(*p*-methylbenzyl) derivative (660 mg, 8%).

Compound **39** was a syrup, $[\alpha]_D$ +29° (*c* 3.1, chloroform); ν_{max} 3400 (NH) and 1700 cm^{-1} (urethane). Partial ^{13}C-n.m.r. data: δ 156.4, 156.3 (2 s, C=O), 120.6 (s, C-1″), and 95.5 (d, C-1′).

Anal. Calc. for $C_{93}H_{113}N_3O_{19}$: C, 70.84; H, 7.22; N, 2.66. Found: C, 71.01; H, 7.12; N, 2.54.

The 3-*N*-(*p*-methylbenzyl) derivative of **39** was a syrup, $[\alpha]_D$ +14° (*c* 1, chloroform); ν_{max} 1700 cm^{-1} (urethane). Partial ^{13}C-n.m.r. data: δ 156.4 (s, C=O), 120.6 (s, C-1″), and 95.5 (d, C-1′).

Anal. Calc. for $C_{101}H_{121}N_3O_{19}$: C, 72.17; H, 7.26; N, 2.50. Found: C, 72.49; H, 7.11; N, 2.41.

6-Deoxy-6-ethoxycarbonylamino-2,3,4,7-tetra-O-(p-*methylbenzyl*)-L-glycero-D-galacto-*heptono-1,5-lactone* (**40**) *and 5-[4,6-di*-O-(p-*methylbenzyl*)-β-D-*talopyranosyl]-1,3-di*-N-*ethoxycarbonyl-1*-N-*methyl-4,6-di*-O-(p-*methylbenzyl*)-*2-deoxystreptamine* (**41**). — To a solution of **39** (2.90 g, 1.84 mmol) in acetic acid (120 mL) was added M hydrochloric acid (40 mL), and the mixture was kept for 40 min at 50°. The residue obtained by concentration of the solvent was fractionated by flash chromatography (hexane–acetone, 8:1–2:1), to give **40** (864 mg, 67%) and **41** (867 mg, 53%).

Compound **40** was a syrup, $[\alpha]_D$ +71° (*c* 1.6, chloroform). N.m.r. data: ^{1}H, δ 7.35–7.10 (m, 16 H, ArH), 5.16 (d, NH), 5.11 and 4.58 (ABq, *J* 11.8 Hz, C*H*$_2$Ar), 4.86 and 4.55 (ABq, *J* 10.4 Hz, C*H*$_2$Ar), 4.73 and 4.30 (ABq, *J*, 11.4 Hz, C*H*$_2$Ar), 4.41 (s, 2 H, C*H*$_2$Ar), 4.47 (d, $J_{2,3}$ 9.4 Hz, H-2), 4.47 (m, H-5), 4.07 (m, $J_{6,NH}$ 8.0 Hz, H-6), 3.96 (m, H-4), 4.03 (q, *J* 7.0 Hz, OC*H*$_2$Me), 3.84 (dd, $J_{3,4}$ 2.0 Hz, H-3), 3.47 (dd, $J_{6,7}$ 6.0, $J_{7,7'}$ 9.4 Hz, H-7), 3.33 (dd, $J_{6,7'}$ 4.0 Hz, H-7′), 2.36 and 2.33 (s, 12 H, 4 Ph*Me*), and 1.16 (t, CMe); ^{13}C, δ 170.0 and 156.2 (s, C=O), 137.7, 137.5, 134.8, and 134.5 (4 s, aromatic), 129.1–127.6 (many d, aromatic), 80.6 (d, C-5), 77.0, 76.3, 73.9 (3 d, C-2,3,4), 74.9, 73.9, 73.2, 72.9 (4 t, *C*H$_2$Ar), 68.4 (t, C-7), 60.9 (t, *C*H$_2$Me), 51.9 (d, N-C), 21.2 (q, Ph*Me*), and 14.4 (q, C*Me*).

Anal. Calc. for $C_{42}H_{49}NO_8$: C, 72.50; H, 7.10; N, 2.01. Found: C, 72.73; H, 6.96; N, 2.01.

Compound **41** was a syrup, $[\alpha]_D$ −16° (*c* 1.8, chloroform). ^{1}H-N.m.r. data: δ 7.3–6.9 (m, 16 H, Ar), 5.20 (b s, NH), 5.04 (d, 1 H, *J* 10.2 Hz, one of C*H*$_2$Ar), 4.88–2.90 (m, 31 H), 2.78 (b s, 4 H, NMe and one of CH_2), 2.34 (s, 13 H, 4 PhMe and one of CH_2), 1.26 and 1.22 (2 t, 6 H, 2 CMe).

Anal. Calc. for $C_{51}H_{66}N_2O_{12}$: C, 68.13; H, 7.40; N, 3.12. Found: C, 67.86; H, 7.53; N, 2.85.

5-O-{*6*-O-*Benzyl-2,3*-O-*[6-deoxy-6-ethoxycarbonylamino-2,3,4,7-tetra*-O-(p-*methylbenzyl*)-L-glycero-D-galacto-(R)-*heptopyranosylidene]*-β-D-*mannopyranosyl*}

*-1-*N,*6-*O:*3-*N,*4-*O-*dicarbonyl-1,3-di-*N-*methyl-2-deoxystreptamine* (**43**). — To a solution of dry **38** (549 mg, 0.77 mmol) and **40** (359 mg, 0.52 mmol) in dry ether (3 mL) was added at −23° a solution of trimethylsilyl triflate (22.8 mg, 0.10 mmol) in ether (100 μL), and the temperature was elevated gradually to 3°. The mixture was stored for 3 days at 3°, dry pyridine (2 mL) was added, and the mixture was worked-up as described for **23** and **25**. Fractionation of the product by flash chromatography (hexane–acetone, 4:1–3:1) gave the pseudo-trisaccharide **42** (162 mg, 30%) and **40** (120 mg, 34%). Partial n.m.r. data: ^{1}H, δ 7.5–7.0 (m, 21 H, ArH), 2.84 (s, 6 H, 2 NMe), 2.35 and 2.32 (2 s, 9 H and 3 H, 4 Ph*Me*), and 0.20 (s, 9 H, $SiMe_3$); ^{13}C, δ 159.5, 159.4, and 156.3 (3 s, C=O), 120.3 (s, C-1″), 95.0 (d, $J_{C\text{-}1',H\text{-}1'}$ 155.0 Hz, C-1′), 21.2 (q, PhMe), and 16.4 (q, CMe).

A solution of **42** (73.7 mg, 0.059 mmol) in dry methanol (3 mL) was stirred for several min at room temperature in the presence of a small amount of potassium carbonate and then concentrated. The residue was purified on a column of silica gel (ethyl acetate–acetone), to afford **43** (62 mg, 89%) as a syrup, $[\alpha]_D$ +24° (*c* 1.6, methanol), +16° (*c* 0.5, chloroform); ν_{max} 1750 cm^{-1} (urethane). Partial n.m.r. data: ^{1}H, δ 7.5–6.9 (m, 21 H, ArH), 2.73 (s, 6 H, 2 NMe), 2.34, 2.32, and 2.30 (3 s, 3, 6 and 3 H, 4 Ph*Me*); ^{13}C, δ 159.8, 157.1, and 156.4 (3 s, C=O), 120.5 (s, C-1″), 97.7 (d, $J_{C\text{-}1',H\text{-}1'}$ 157.5 Hz, C-1′), 21.2 (q, PhMe), and 14.5 (q, CMe).

Anal. Calc. for $C_{65}H_{77}N_3O_{17}$: C, 66.59; H, 6.62; N, 3.58. Found: C, 66.34; H, 6.75; N, 3.44.

*5-*O-{*6-*O-*Benzyl-2,3-*O-*[6-deoxy-6-ethoxycarbonylamino-2,3,4,7-tetra-*O-(*p-methylbenzyl)-*L-glycero-D-galacto-(R)-*heptopyranosylidene]-β-*D-*talopyranosyl}-1-*N,*6-*O:*3-*N,*4-*O-*dicarbonyl-1,3-di-*N-*methyl-2-deoxystreptamine* (**44**). — Oxidation of **43** (59.8 mg, 0.042 mmol) was performed with pyridinium chlorochromate (50 mg) in dry dichloromethane (0.5 mL) in the presence of powdered molecular sieves (3 Å, 30 mg) for 1 day at room temperature. Crude 4-ulose, obtained as described for **30**, was reduced with sodium borohydride (200 mg) in ethanol (4 mL) for 100 min at 0°. Processing as described for **30** and purification by flash chromatography (hexane–acetone, 5:2) gave **44** (18 mg, 40%) as a syrup, $[\alpha]_D$ +25° (*c* 0.2, chloroform). Partial ^{1}H-n.m.r. data: δ 7.4–7.0 (m, 21 H, ArH), 2.79 and 2.74 (2 s, 6 H, 2 NMe), 2.35 and 2.32 (2 s, each 6 H, 4 Ph*Me*).

Anal. Calc. for $C_{65}H_{77}N_3O_{17}$: C, 66.59; H, 6.62; N, 3.58. Found: C, 66.61; H, 6.95; N, 3.35.

Destomycin C (**3**). — To a solution of **44** (17 mg, 0.014 mmol) in 1,4-dioxane (1 mL) was added dropwise at 80° 0.1M barium hydroxide. The mixture was kept for several h at 80°, then neutralised with 0.25M sulfuric acid (0.4 mL), and adjusted to a slightly basic pH with aqueous sodium hydrogencarbonate. Insoluble material was removed, the filtrate was concentrated under 45°, and a solution of the residue in ethanol (1 mL) and water (1.5 mL) was hydrogenolysed in the presence of 20% palladium hydroxide for 2 days. Conventional processing and purification on Dowex 1-X2 (HO^-) resin by elution with water afforded **3** (3 mg, 40%), which was characterised by ^{1}H-n.m.r. data as shown in Table III.

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