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SYNTHESIS OF N^1-(*p*-GLYCOSYLOXYCINNAMOYL)SPERMIDINES*

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ABSTRACT

The synthesis of *O*-glycosylated N^1-(*p*-hydroxycinnamoyl)spermidines was investigated. *p*-Hydroxycinnamate glycosides of some amino sugars, including a synthetic intermediate of a unique antibiotic, cinodine, were prepared and converted into the amide of spermidine.

INTRODUCTION

Spermidine is one of the important and widely distributed polyamines in the animal kingdom and in microorganisms[1,2], and appears to participate in cellular differentiation and proliferation[3,4]. In plants, several alkaloids that have spermidine incorporated in their structures have been discovered[5,6] and in these the nitrogen atoms are often substituted with cinnamoyl or modified cinnamoyl groups, as in maytennine and celacinnine. The glycocinnamoylspermidines LL-BM123 β, and γ_1 and γ_2 (cinodines) isolated from an unidentified species of Nocardia[7], are examples of the fascinating spermidine conjugates and broad-spectrum antibiotics. The γ_1 and γ_2 components are of special interest in view of their potent activity against Gram-negative organisms and their protective effects against infection. Recently, a pseudo-disaccharide analog of cinodine, glycocinnaspermicin D[8], was also reported, and the ureylene linkage was revised from α to β. In this paper some *O*-glycosylated N^1-(*p*-hydroxycinnamoyl)spermidines, including a synthetic intermediate for cinodine, were selected as targets in order to establish a general synthetic method for this new type of conjugate between sugar, *p*-hydroxycinnamic acid, and spermidine.

RESULTS AND DISCUSSION

As previously reported[9], ethyl *p*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyloxy)cinnamate (**3**) was prepared effectively in 59% yield, together

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TABLE I

COUPLING[a] OF **1** AND **13** WITH **9** IN THE PRESENCE OF SILVER SALTS

Runs	*Molar ratios[b] of reactants*						*Temperature (degrees)*	*Products (%)*				
	9	*Promoters*				*Ratios[c]*		*Glycosides*		*α/β*	*Byproducts*	
Coupling of **1**[b]								**3**	**7**		**5**[d]	**12**
1	2.0	$AgClO_4$	0.5	Ag_2CO_3	2.0	4.0	r.t.	43	10	4.3	6	26
2[e]	2.0	$AgClO_4$	1.0	Ag_2CO_3	1.7	1.7	r.t.	53	9.7	5.5	*f*	*f*
3[g]	2.0	$AgClO_4$	1.1	Ag_2CO_3	1.8	1.6	r.t.	50	12	4.2	9	29
4	1.5	$AgClO_4$	1.5	Ag_2CO_3	0.75	0.5	r.t.	31	3.5	8.8	*f*	*f*
5	1.5	$AgClO_4$	2.0	Ag_2CO_3	0.75	0.38	r.t.	30	3.6	8.3	*f*	*f*
6	2.0	$AgClO_4$	1.1			0	r.t.	41	5.7	7.2	*h*	0
7	2.0	$AgClO_4$	1.1			0	−32 to −35	84	2.3	37	*h*	0
8	2.0	$AgClO_4$	1.0	$CdCO_3$	1.7	1.7	r.t.	49	13	2.3	2	38
9	2.0	AgOTf	1.0	Ag_2CO_3	2.0	2.0	−42 to −45	33	7.1	4.6	25	27
10	2.0	AgOTf	1.0			0	−42 to −45	71	13	5.5	6	0
Coupling of **13**[b]								**14**	**14β**[i]		**15**	**16**
11	2.0	$AgClO_4$	1.5	Ag_2CO_3	0.75	0.5	r.t.	28	6.8	4.1	3	21
12	2.0	$AgClO_4$	1.0			0	−30 to −35	59	2.9	20	*f*	*f*

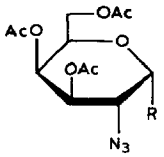
[a]The reactions were performed in CH_2Cl_2 for 24–30 h. [b]Mol of glycosyl chloride was 1.0. [c]Carbonate/perchlorate or triflate. [d]Isolated after acetylation. [e]Ref. 7. [f]Isolation was not attempted. [g]Silver perchlorate was first added after 12 h. [h]Could not be isolated. [i]β Anomer of **14**.

with the β anomer **7** (14%), by coupling 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl chloride (**1**) and ethyl *p*-(trimethylsilyloxy)cinnamate (**9**) in the presence of $AgClO_4$ and Ag_2CO_3. The yield of this coupling reaction is affected considerably by the ratio of the two silver salts, prompting us to examine the effects of some silver salts on this glycosylation (Table I).

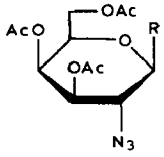
Mixtures of $AgClO_4$ and Ag_2CO_3 have frequently been used for promotion of the Koenigs–Knorr glycosylation with ratios selected according to the reactivity of the glycosyl moiety[10]. First of all, the effect of molar ratio of Ag_2CO_3 to $AgClO_4$ on the yields of **3** and **7** was examined. The best result was obtained with the ratio of 1.6 (run 3), which coincided with previous results (run 2). As Ag_2CO_3 did not promote the glycosylation and seems to act mainly as a supplier of silver cation or insoluble acid acceptor, it may be significant that increase of the carbonate (run 1) or the perchlorate (run 4 and 5) both resulted in lower yield. In the former instance a new type of byproduct, diglycosyl carbonate **12**, was isolated in 26% yield together with a small proportion of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactose (**5**). Furthermore, the formation of a relatively large amount of **12** in run 3 may be due to the delayed addition (after 12 h) of $AgClO_4$. While **12** was also formed in significant yield by the glycosylation with $AgClO_4$ and $CdCO_3$ (run 8) as well as with silver triflate and Ag_2CO_3 (run 9), **12** was not formed at all in the absence of Ag_2CO_3 (runs 6 and 7).

The structure of **12** was confirmed by ^{1}H- and ^{13}C-n.m.r. and i.r. data. The carbonate signal was observed in the ^{13}C-n.m.r. spectrum at δ 151.4 and H-1 signals in the ^{1}H-n.m.r. at 6.28 ($J_{1,2}$ 3.9 Hz), which indicated the di-*O*-glycosyl (α,α) structure. Compound **12** was, however, shown to be contaminated with the α,β and/or the β,β isomer by another H-1 signal at 5.35 ($J_{1,2}$ 8.4 Hz) and also by 5 minor signals for C-1–C-5, which were assigned to those of a β-glycosyl moiety. Furthermore, a similar side-reaction was observed in the reaction of the glycosyl chloride **13** to give a mixture of α-glycoside **14** and its β anomer, and the di-*O*-glycosyl carbonate **16**. Although the mechanism of formation of the diglycosyl carbonate remains to be established, the best promoter for this glycosylation turned out to be $AgClO_4$ at lower temperature, which gave **3** and **7** in 84% and 2.3% yields, respectively (run 7).

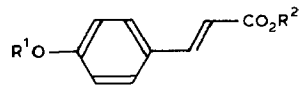
Next, glycosylation with the (more-reactive) glycosyl α-bromide **2** and β-chloride **6** were further examined as alternative methods, using ethyl *p*-hydroxycinnamate (**8**) and the sodium salt **11** of *tert*-butyl *p*-hydroxycinnamate (**10**), respectively, as the aglycon sources. The glycoside **4**, having a *tert*-butyl ester group, offers additional scope in synthesis because de-esterification may be effected smoothly under acidic conditions instead of the basic conditions required for **3**. Compound **10** was prepared from *tert*-butyl ethyl malonate[11] in 2 steps. Knoevenagel reaction of this half ester with *p*-hydroxybenzaldehyde in pyridine in the presence of piperidine gave **10** in 75% yield. Although the coupling reactions of **2** and **8** in the presence of such mercuric salts as cyanide and bromide or of silver triflate–Ag_2CO_3 gave poorer yields, SN2 substitution of **6** with sodium phenoxide



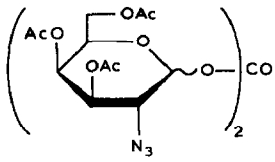
1 R = Cl
2 R = Br
3 R = OCn(Et)
4 R = OCn(Bu^t)
5 R = OH



6 R = Cl
7 R = OCn(Et)



8 R^1 = H, R^2 = Et
9 R^1 = Me$_3$Si, R^2 = Et
10 R^1 = H, R^2 = Bu^t
11 R^1 = Na, R^2 = Bu^t



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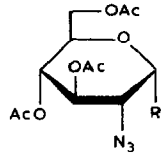
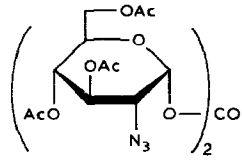


13 R = Cl
14 R = OCn(Et)
15 R = OH



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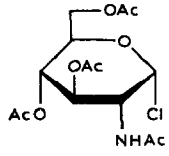

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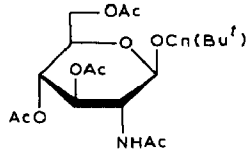

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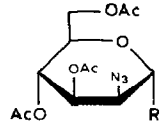
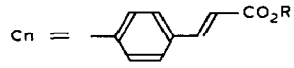


19 R = Cl
20 R = OCn(Et)

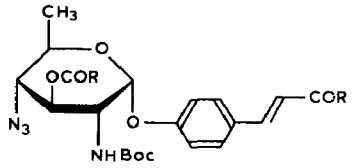


R = Et : Cn(Et), R = Bu^t : Cn(Bu^t)

11 gave exclusively the glycoside **4** in moderate yields (Table II). Furthermore the same SN2 reaction of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (**17**) with **11** in *N*,*N*-dimethylformamide gave the β-glycoside **18** in 57% yield. On the other hand, the $AgClO_4$–Ag_2CO_3-promoted coupling of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl (**13**) and -α-D-mannopyranosyl chloride (**19**) with **9** gave mainly the α-glycosides **14** and **20**, in 35–40% yield.

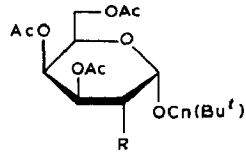
For the coupling of *O*-glycosylated *p*-hydroxycinnamate with spermidine derivatives, the following four glycosyl groups were selected: (*a*) 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl, (*b*) 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-α-D-galactopyranosyl, (*c*) 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-β-D-glucopyra-

21	22	23	24	25	
26	—	27	28	—	
29	30	—	31	32	
33	34	35	36	37	



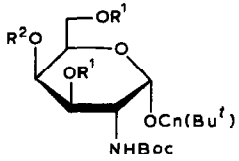
R = HN–(CH2)4–N(Boc)–(CH2)4–NHBoc

38



39 R = NH_2

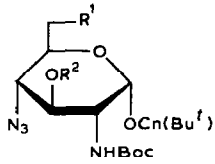
40 R = NHAc



41 $R^1 = R^2 = H$

42 R^1 = Bz, R^2 = H

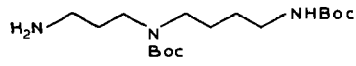
43 R^1 = Bz, R^2 = Ms



44 R^1 = OBz, R^2 = Bz

45 R^1 = OTs, R^2 = H

46 $R^1 = R^2 = H$



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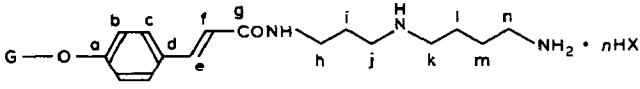
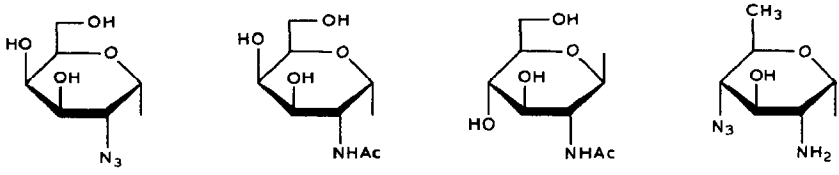


G = 

48 49 50 51

TABLE II

PREPARATION OF *p*-(GLYCOSYLOXY)CINNAMATE DERIVATIVES

Glycosyl halides	*Cinnamate derivatives*	*Promoters*	*Solvents*	*Products and yields (%)*			
2	**8**	$AgOTf–Ag_2CO_3$	CH_2Cl_2	**3**	20	**7**	7
2	**8**	$Hg(CN)_2$	$C_6H_6–CH_3NO_2$	**3**	34	**7**	5
2	**8**	$HgBr_2$	$C_6H_6–CH_3NO_2$	**3**	23	**7**	2
6	**11**		HMPA		**4**	32	
6	**11**		DMF		**4**	55	
17	**11**		DMF		**18**	57	

nosyl, and (*d*) 4-azido-2-(*tert*-butoxycarbonyl)amino-2,4,6-trideoxy-α-D-glucopyranosyl. For coupling with the spermidine derivative **47**, the free acids **21** and **23** were prepared by treatment of the *tert*-butyl esters **4** and **18**, respectively, with 90% CF_3CO_2H at room temperature. The 2-acetamido-2-deoxy analog (**22**) of **21** was also obtained from **4**. Selective and catalytic hydrogenation of **4** in the presence of palladium–barium sulfate and quinoline[9] gave the 2-amino derivative **39**, which was converted into its *N*-acetyl derivative **40** in 76% yield from **4**. Acidic de-esterification of **40** as just described provided **22** in 78% yield.

Compound **46** is an alternative synthetic intermediate, which can provide another possibility in the introduction of necessary functional groups for the total synthesis of cinodines, and was prepared from **4** by the same conversion previously reported for the synthesis of the corresponding ethyl ester[9]. Compound **4** was successively deacetylated, selectively hydrogenolyzed in the presence of palladium–barium sulfate and quinoline, and *tert*-butoxycarbonylated with 2-(*tert*-butoxycarbonylthio)-4,6-dimethylpyrimidine to give the 2-(*tert*-butoxycarbonylamino) derivative **41**, which was converted into the 3,6-dibenzoate **42** in 53% yield from **4**. Its 4-methanesulfonate **43** was subjected to SN2 substitution with sodium azide in hexamethylphosphoric triamide (HMPA) at 80° to give the 4-azide **44** in 78% yield. Debenzoylation of **44** followed by selective tosylation gave the 6-*p*-toluenesulfonate **45** in 76% yield.Selective reduction of **45** with sodium cyanoborohydride in the presence of sodium iodide in HMPA at 70° gave the 6-deoxy derivative **46** in 80% yield. The *tert*-butyl ester and *tert*-butoxycarbonyl groups of **46** were removed under acidic conditions and then the *N*-*tert*-butoxycarbonyl group was reintroduced to give **24**. This compound was also obtained in high yield by treatment of the corresponding ethyl ester[9] of **46** with 0.2M KOH (6–10 equivalents) in methanol.

The four glycosyloxycinnamic acids (**21–24**) were coupled with N^2,N^3-di-*tert*-butoxycarbonylspermidine[12] (**47**) by four different methods. Direct formation of the amide by coupling of the acid with **47** in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) or 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ)

TABLE III

COUPLING REACTIONS OF **21–25** WITH **47**

Acids	*Products*	*Yields (%)*			
		DCC[a]	*EEDQ*[b]	*MTT*[c]	*CDI*[d]
21	**33**	32 (60 h)[e]	40 (120 h)	37 (44 h)	70 (22 h)
22	**34**		33 (120 h)		65 (20 h)
23	**35**		51 (60 h)	69 (24 h)	
			77 (120 h)	71 (70 h)	
24	**36**			27 (40 h)	59[f] (20 h)
25	**37**				63 (20 h)

[a]DCC, DMAP–CH_2Cl_2, [b]EEDQ, DMAP–CH_2Cl_2, [c]MTT, EEDQ–CH_2Cl_2, [d]CDI–THF. [e]Reaction time, [f]Containing 3-*O*-(N^2,N^3-di-*tert*-butoxycarbonylspermidine)carbamoyl derivative (**38**).

gave poorer yields in the cases of **21** and **22**, whereas the amide **35** was formed in good yield from **23** (Table III). Furthermore, active acyl intermediate, for instance, the 3-acylthiazoline-2-thiones[13] **26–28** and 1-acylimidazoles[14] **29–32**, were prepared by the coupling of **21–25** with 2-mercaptothiazoline in the presence of EEDQ and with carbonyldiimidazole (CDI), respectively. Although the former gave results almost identical with those of the direct coupling, the latter gave much better yields. In the coupling of **24** by the CDI method, the 3-*O*-carbamoyl derivative (**38**) was also formed and was converted into the desired compound (**36**) by treatment with NaOMe. This difficulty was avoidable *via* the coupling of the 3-acetate (**25**), which gave **37** in 63% yield. The difference in the reactivities of α-glycosyloxy- (**21, 22,** and **24**) and β-glycosyloxy-cinnamic acids (**23**), as shown in the couplings by the EEDQ and acylthiazoline-2-thione methods, presumably reflects the stereo-electronic, *i.e.*, anomeric effect transmitted through the conjugated π-electron system.

Deprotection of the amides **33–37** was performed conventionally with NaOMe in MeOH for deacylation and with CF_3CO_2H for de(*tert*-butoxycarbonyl)-ation. Because of the alkali-sensitive nature of the glycoside, careful deacylation (a

TABLE IV

^{13}C-N.M.R. CHEMICAL SHIFTS[a] OF N^1-(*p*-GLYCOSYLOXYCINNAMOYL)SPERMIDINES IN D_2O

Carbon		**48**	**49**	**50**	**51**
Glycon	1	97.71	97.32	100.39	94.93d
	2	60.91	51.05	56.76	55.00d
	3	69.99*[c]	68.86	74.72	69.30d*
	4	69.16*	69.70	71.01	68.57d*
	5	73.21	73.16	77.36	70.13d*
	6	62.18	62.33	61.84	18.40q
	N–$COCH_3$		175.90	175.99	
			23.23	23.48	
Aglycon[b]	a	158.47	158.91	159.20	157.64d
	b	130.85	130.89	130.94	131.00d
	c	118.70	118.50	118.06	118.35d
	d	130.46	130.26	130.55	131.00s
	e	141.83	141.93	141.73	141.73d
	f	119.87	119.77	119.92	120.26d
	g	170.28	170.38	170.28	170.28s
	h	40.07	40.12	40.12	40.12s
	i	26.94	26.99	26.94	26.94t
	j	46.37	46.41	46.37	46.22t
	k	48.17	48.17	48.17	48.22t
	l	23.96*	24.01*	23.96*	24.01t*
	m	25.13*	25.18*	25.18*	25.18t*
	n	37.48	37.53	37.53	37.58t

[a]From external Me_4Si in p.p.m. [b]Notation of carbons in the aglycon moiety is shown in the structural formulas. [c]Assignment of signals denoted by asterisks may be interchanged.

strictly catalytic amount of NaOMe) was necessary. The free glycosyloxycinnamoylspermidines (**48–51**) were obtained as hydrogen chloride salts, and were fully characterized by ^{13}C-n.m.r. spectroscopy (Table IV); their biological activities are under investigation.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Solutions were concentrated under diminished pressure at 50° (bath). Optical rotations were measured at ambient temperature (20 ±5°) with a Carl Zeiss LEP-Al polarimeter. 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 spectrometer 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-90Q spectrometer for solutions in $CDCl_3$ unless otherwise stated. Chromatography was performed on Wakogel C-200, flash chromatography on Wakogel C-300, and preparative t.l.c. on Kieselgel HF_{254} Type 60 (Merck).

Ethyl p-*(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-*D*-galactopyranosyloxy)cinnamate* (**3**) *and its β anomer* (**7**). — The previous method[9] was improved with two different promoters. (*a*) *Silver perchlorate as promoter.* To a mixture of α-chloride[9] **1** (414 mg, 1.18 mmol), **9** (650 mg, 2.46 mmol), and 4Å molecular sieve (1 g) in CH_2Cl_2 (5 mL) was added $AgClO_4$ (268 mg, 1.29 mmol) under argon at −32 to −35°. The mixture was stirred for 20 h at the same temperature, and filtered after dilution with CH_2Cl_2 (15 mL). The filtrate was washed successively with water, $NaHCO_3$, and water, dried, and evaporated to give a syrupy mixture, which was separated on a column of silica gel with PhMe followed by 9:1 PhMe–EtOAc to give **3** (501 mg, 84%) and **7** (14 mg, 2.3%). The physical and spectral data were consistent with those previously reported[9].

(*b*) *Silver triflate as promoter.* The coupling of **1** (320 mg, 0.91 mmol) and **9** (485 mg, 1.84 mmol) was performed in the presence of silver triflate (259 mg, 1.01 mmol) and 4A molecular sieve (0.3 g) at −42 to −45°. The mixture was processed as just described to give **3** (328 mg, 71%) and **7** (62 mg, 13%).

tert-*Butyl* p-*(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-*D*-galactopyranosyloxy)cinnamate* (**4**). — To a solution of **11** (2.83 g, 11.7 mmol) in *N,N*-dimethylformamide (DMF, 23 mL) was added dropwise at room temperature with stirring a solution of β-chloride **6** (2.04 g, 5.83 mmol) in DMF (6 mL). After being kept for 65 h at the same temperature, the solution was poured into ice–water and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to give a syrupy mixture, which was separated on a column of silica gel with 3:1 hexane–EtOAc to give **4** (1.71 g, 55%), m.p. 81.5–82.5°, $[\alpha]_D$ +150° (*c* 1.1, $CHCl_3$); ν_{max}^{KBr} 2120 (azido), 1750 and 1702 (ester), and 1635 cm^{-1} (alkene); ^{1}H-n.m.r.: δ 5.67 (d, $J_{1,2}$ 4.0 Hz, H-1), 3.86 (dd, $J_{2,3}$ 10.0 Hz, H-2), 5.58 (dd, H-3), 1.53 (s, Bu), 1.95, 2.10 and 2.18 (each s, OAc), 6.27 and 7.53 (each d, *J* 16.1 Hz, alkenic), 7.09 and 7.47 (each d, *J* 8.0 Hz, aromatic).

2,3,4-Tri-O-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl bromide (**2**). — To a solution of 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranose[15] (1.03 g, 2.75 mmol) in CH_2Cl_2 (10 mL) and Ac_2O (0.5 mL) was added at 0° dropwise a 30% solution of HBr in AcOH. The mixture was kept for 1 h at the same temperature and further in a refrigerator for 20 h. The mixture was processed conventionally to give compound[16] **2** as crystals, ν_{max}^{KBr} 2110 (azido) and 1750 (ester) cm^{-1}; ^{1}H-n.m.r.: δ 6.42 (d, $J_{1,2}$ 3.6 Hz, H-1), 3.96 (dd, $J_{2,3}$ 10.4 Hz, H-2), 5.33 (dd, $J_{3,4}$ 3.0 Hz, H-3), 5.47 (dd, $J_{4,5}$ 1.6 Hz, H-4), 4.47 (dt, $J_{5,6} = J_{5,6'}$ 5.6 Hz, H-5), 4.04 (dd, $J_{6,6'}$ 12.4 Hz, H-6), 4.19 (dd, H-6'), 2.08 and 2.17 (each s, 6 H and 3 H, respectively, OAc).

3,4,6-Tri-O-acetyl-2-azido-2-deoxy-β-D-galactopyranosyl chloride (**6**). — Compound **6** was prepared from **2** by using Et_4NCl instead of Bu_4NCl; m.p. 128–129°, $[\alpha]_D$ −31.8° (*c* 1.1, $CHCl_3$). Lit.[17] m.p. 98–99°, $[\alpha]_D^{20}$ −16° (*c* 1, $CHCl_3$); lit.[15] m.p. 102–104°, $[\alpha]_D^{20}$ −16.5° (*c* 1, $CHCl_3$).

tert-*Butyl* p-*hydroxycinnamate* (**10**). — To a solution of *tert*-butyl ethyl malonate (151 g, 0.80 mol) in EtOH (400 mL) was added a solution of KOH (54.0 g, 0.96 mol) in EtOH (400 mL), and the mixture was heated overnight under reflux. The mixture was processed conventionally to give crude *tert*-butyl hydrogenmalonate (98 g) contaminated with a small amount of ethyl hydrogenmalonate. This ester was used for the following Knoevenagel reaction.

p-Hydroxybenzaldehyde (13.0 g, 0.11 mol) and piperidine (8 mL) was added under cooling with ice–water to a solution of *tert*-butyl hydrogenmalonate (16.2 g, 0.10 mol) in C_5H_5N (80 mL), and the mixture was heated at 70–80° until evolution of CO_2 ceased. After dilution with PhMe the mixture was washed with 10% citric acid and water, dried, and evaporated to give crude **10**, which was purified on a column of silica gel; yield 14.8 g (66%), m.p. 100–101°; ν_{max}^{KBr} 3260 (OH), 1675 (ester), 1635 (alkene) and 1605 cm^{-1} (phenyl), ^{1}H-n.m.r.: δ 1.56 (s, Bu), 6.18 and 7.49 (each d, *J* 15.8 Hz, alkenic), 6.80 and 7.34 (each d, *J* 8.0 Hz, aromatic).

Anal. Calc. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.82; H, 7.22.

Formation of bis(3,4,6-tri-O-acetyl-2-azido-2-deoxy-D-galactopyranosyl) carbonate (**12**). — A mixture of **1** (323 mg, 0.92 mmol) and **9** (485 mg, 1.8 mmol) was dried by azeotropic distillation of PhMe. To the mixture was added 4A molecular sieve (0.3 g), Ag_2CO_3 (453 mg, 1.6 mmol), and dry CH_2Cl_2 (10 mL), and the mixture was stirred for 12 h at room temperature. After the addition of $AgClO_4$ (202 mg, 1.0 mmol) stirring was continued for 71 h. The mixture of products obtained by the same treatment as described previously was separated on a column of silica gel with 9:1 PhMe–EtOAc to give **3** (233 mg, 50%), **7** (57 mg, 12%) and **12** (92 mg, 29%). Compound **12** was a syrup (the ratio of α,α and α,β isomers was estimated by ^{1}H-n.m.r. signals to be 1:1), ν_{max}^{NaCl} 2110 (azido) and 1750 cm^{-1} (ester); ^{1}H-n.m.r. (500 MHz): data for α,α isomer: δ 6.242 (d, $J_{1,2}$ 3.9 Hz, H-1), 4.005 (dd, $J_{2,3}$ 11.1 Hz, H-2), 5.373 (dd, $J_{3,4}$ 3.4 Hz, H-3), 5.524 (dd, $J_{4,5}$ 1.3 Hz, H-4), 4.363 (broad t, H-5), 4.085 (dd, $J_{5,6}$ 6.4 Hz, $J_{6,6'}$ 11.5 Hz, H-6), 4.138 (dd, $J_{5,6'}$ 6.4 Hz, H-6'), 2.036, 2.085, and 2.173 (each s, OAc); data for α,β isomer: (α-glycosyl moiety) δ 6.238 (d, $J_{1,2}$ 3.4 Hz, H-1), 4.028 (dd, $J_{2,3}$ 11.1 Hz, H-2), 5.335 (dd, $J_{3,4}$ 3.4 Hz, H-3),

5.509 (dd, $J_{4,5}$ 1.3 Hz, H-4), 4.363 (broad t, H-5), 4.089 (dd, $J_{5,6}$ 6.6 Hz, $J_{6,6'}$ 11.3 Hz, H-6), and 4.145 (dd, $J_{5,6'}$ 6.0 Hz, H-6'); (β-glycosyl moiety) δ 5.428 (d, $J_{1,2}$ 8.6 Hz, H-1), 3.871 (dd, $J_{2,3}$ 10.7 Hz, H-2), 4.941 (dd, $J_{3,4}$ 3.4 Hz, H-3), 5.400 (dd, $J_{4,5}$ 0.9 Hz, H-4), 4.040 (t, H-5), 4.138 (dd, $J_{5,6}$ 6.4 Hz, $J_{6,6'}$ 11.5 Hz, H-6), and 4.175 (dd, $J_{5,6'}$ 7.3 Hz, H-6'); 2.048, 2.051, 2.075, 2.085, 2.175 and 2.188 (each s, OAc); ^{13}C-n.m.r.: data for the α,α-isomer: δ 95.12 (d, C-1), 56.81 (d, C-2), 68.52 (d, C-3), 66.77 (d, C-4), 69.35 (d, C-5), and 60.91 (t, C-6), 20.45 (q, Me), 151.39 (s, carbonate), 169.35, 169.70, and 170.07 (each s, Ac); data added for α,β- isomer: δ 96.56 (d, C-1), 59.59 (d, C-2), 71.35 (d, C-3), 66.09 (d, C-4), 71.79 (d, C-5).

Anal. Calc. for $C_{25}H_{32}N_6O_{17}$: C, 43.61; H, 4.68; N, 12.21. Found: C, 43.60; H, 4.34; N, 11.83.

Ethyl p-*(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-*D*-glucopyranosyloxy)cinnamate* (**14**). — As described for **3**, the α-chloride[18] **13** (600 mg, 1.72 mmol) and **9** (920 mg, 3.48 mmol) were coupled in CH_2Cl_2 (9 mL) in the presence of $AgClO_4$ (392 mg, 1.89 mmol) and 4A molecular sieve (1.6 g). The anomeric mixture was separated on a column of silica gel with hexane–EtOAc to give **14** (510 mg, 59%) and its β anomer (25 mg, 3%). Compound **14** was a syrup, $[\alpha]_D$ +162° (*c* 2.0, $CHCl_3$); ν_{max}^{NaCl} 2110 (azido), 1750 and 1710 (ester), 1635 (alkene), and 1605 cm^{-1} (phenyl); ^{1}H-n.m.r.: δ 5.62 (d, $J_{1,2}$ 3.6 Hz, H-1), 3.51 (dd, $J_{2,3}$ 10.2 Hz, H-2), 5.65 (dd, $J_{3,4}$ 9.0 Hz, H-3), 5.11 (dd, $J_{4,5}$ 10.5 Hz, H-4), 3.9–4.4 (m, 3 H, H-5, H-6, and H-6'), 1.32 (t, *J* 8.0 Hz, Me in Et), 2.00, 2.02, and 2.11 (each s, OAc), 4.24 (q, CH_2 in Et), 6.30 and 7.58 (each d, *J* 16.0 Hz, alkenic), 7.08 and 7.46 (each d, *J* 8.0 Hz, aromatic).

Anal. Calc. for $C_{23}H_{27}N_3O_{10}$: C, 54.65; H, 5.38; N, 8.31. Found: C, 54.33; H, 5.24; N, 8.27.

*Formation of bis(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-*D*-glucopyranosyl) carbonate* (**16**). — The diglycosyl carbonate **16** was formed in the coupling of **13** and **9**, and isolated in the same manner as described for **12**. Compound **16** was a syrup, $[\alpha]_D$ +159° (*c* 1.2, $CHCl_3$); ν_{max}^{NaCl} 2120 (azido) and 1760 cm^{-1} (ester); ^{1}H-n.m.r.: δ 6.24 (d, $J_{1,2}$ 3.6 Hz, H-1), 3.73 (dd, $J_{2,3}$ 10.0 Hz, H-2), 5.54 (t, $J_{3,4}$ 10.0 Hz, H-3), and 5.15 (dd, $J_{4,5}$ 10.0 Hz, H-4), and 4.0–4.5 (m, 3 H, H-5, H-6, and H-6'). ^{13}C-N.m.r.: δ 94.79 (d, C-1), 60.38 (d, C-2), 70.43 (d, C-3), 67.57 (d, C-4), 70.61 (d, C-5), 61.16 (t, C-6), 20.54 (q, Me), 151.23 (s, carbonate), 169.52, 169.78, and 170.30 (each s, Ac).

Anal. Calc. for $C_{25}H_{32}N_6O_{17}$: C, 43.61; H, 4.68; N, 12.21. Found: C, 43.76; H, 4.70; N, 11.81.

tert-*Butyl* p-*(2-acetamido-2,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyloxy)cinnamate* (**18**). — To a solution of NaOEt prepared from Na (29 g, 0.126 mol) and abs. EtOH (200 mL), was added **10** (27.8 g, 0.126 mol). The sodium phenoxide obtained by evaporation of the solvent was dissolved in dry DMF (500 mL), and to this solution was added chloride[18] **17** (38.6 g, 0.105 mol). The mixture was kept for 20 h at room temperature, and poured into water (1 L). The precipitate was filtered off, washed with water and triturated with hot PhMe to give **18** (39.2 g, 68%), m.p.

197.5–198°, $[\alpha]_D$ −7.9° (*c* 2.1, $CDCl_3$); ν_{max}^{KBr} 1750 and 1720 (ester), 1665 (amide), 1640 (alkene), and 1610 cm^{-1} (phenyl); ^{1}H-n.m.r.: δ 5.35 (d, $J_{1,2}$ 8.0 Hz, H-1), 3.9 (m, H-2), 5.45 (t, $J_{2,3}$ 10.0 Hz, $J_{3,4}$ 9.6 Hz, H-3), 5.13 (dd, $J_{4,5}$ 8.9 Hz, H-4), 4.0–4.4 (m, 3 H, H-5, H-6, and H-6′), 1.55 (s, Bu), 1.95 (s, NAc), 2.05 and 2.08 (each s, 9 H, OAc), 5.95 (d, *J* 9.0 Hz, NH), 6.24 and 7.51 (each d, *J* 16.0 Hz, alkenic), 6.96 and 7.41 (each d, *J* 9.0 Hz, aromatic).

Anal. Calc. for $C_{27}H_{35}NO_{11}$: C, 59.01; H, 6.42; N, 2.55. Found: C, 58.99; H, 6.31; N, 2.49.

Ethyl p-*(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-*D*-mannopyranosyloxy)cinnamate* (**20**). — This compound was obtained in 29% yield by coupling of chloride **19** with **9** as described for **13**. Compound **20** was a syrup, $[\alpha]_D$ +65.0° (*c* 1.8, $CHCl_3$); ν_{max}^{NaCl} 2100 (azido), 1740 and 1700 (ester), 1630 (alkene), and 1600 cm^{-1} (phenyl); ^{1}H-n.m.r.: δ 5.59 (s, H-1), 5.61 (dd, $J_{2,3}$ 3.3 Hz, $J_{3,4}$ 9.0 Hz, H-3), 5.41 (t, $J_{4,5}$ 9.0 Hz, H-4), 3.9–4.3 (m, H-2, H-5, H-6, and H-6′), 1.34 (t, *J* 6.9 Hz, Me in Et), 2.02, 2.05, and 2.14 (each s, Ac), 4.26 (q, CH_2 in Et), 6.34 and 7.64 (each d, *J* 16.1 Hz, alkenic), 7.10 and 7.50 (each d, *J* 8.5 Hz, aromatic).

Anal. Calc. for $C_{23}H_{27}N_3O_{10}$: C, 54.65; H, 5.38; N, 8.31. Found: C, 54.25; H, 5.31; N, 8.05.

p-*(3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-*D*-galactopyranosyloxy)cinnamic acid* (**21**). — Compound **4** (207 mg, 0.39 mmol) was dissolved in 90% CF_3CO_2H (1 mL), and the solution was kept for 40 min at room temperature. The solution was mixed with $CHCl_3$ (20 mL) and EtOAc (10 mL), washed three times with water, dried, and evaporated to give **21** (166 mg, 90%), m.p. 163–165°, $[\alpha]_D$ +157° (*c* 1.8, $CDCl_3$); ν_{max}^{KBr} 2950 (broad, OH), 2110 (azido), 1740 (ester) 1680 (carboxyl), 1630 (alkene), and 1605 cm^{-1} (phenyl); ^{1}H-n.m.r.: δ 5.70 (d, $J_{1,2}$ 2.5 Hz, H-1), 3.88 (dd, $J_{2,3}$ 10.0 Hz, H-2), 5.55 (broad s, 2 H, H-3 and H-4), 4.0–4.5 (m, 3 H, H-5, H-6, and H-6′), 1.96, 2.13 and 2.21 (each s, OAc), 6.33 and 7.75 (each d, *J* 16.0 Hz, alkenic), 7.14 and 7.54 (each d, *J* 8.0 Hz, aromatic), and 8.84 (broad s, CO_2H).

Anal. Calc. for $C_{21}H_{23}N_3O_{10}$: C, 52.83; H, 4.86; N, 8.80. Found: C, 52.88; H, 4.86; N, 8.63.

p-*(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-*D*-galactopyranosyloxy)cinnamic acid* (**22**). — Compound **40** was de-esterified as described for **21** except for the reaction time (1 h) to give **22** in 78% yield, m.p. 218.5–219.5°, $[\alpha]_D$ +192° (*c* 1.0, $CDCl_3$); ν_{max}^{KBr} 3560 and 3350 (OH and NH), 1755 (ester), 1710 (carboxyl), 1640 (alkene), and 1610 cm^{-1} (phenyl); ^{1}H-n.m.r.: δ 5.76 (d, $J_{1,2}$ 3.6 Hz, H-1), 4.64 (m, H-2), 5.35 (dd, H-3), 5.46 (broad d, H-4), 4.0–4.6 (m, 3 H, H-5, H-6, and H-6′), 1.88 (s, NAc), 1.92, 1.96 and 2.16 (each s, OAc), 6.41 and 7.63 (each d, *J* 16.0 Hz, alkenic), 7.19 and 7.67 (each d, *J* 9.0 Hz, aromatic).

Anal. Calc. for $C_{23}H_{27}NO_4$: C, 55.98; H, 5.51; N, 2.84. Found: C, 55.92; H, 5.35; N, 2.50.

p-*(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyloxy)cinnamic acid* (**23**). — Compound **18** (5.5 g, 10 mmol), was dissolved in 90% CF_3CO_2H (5 mL) and CH_2Cl_2 (10 mL). After being kept for 3 h at room temperature, the solu-

tion was evaporated and the residue dissolved in EtOAc. The solution was washed with water, dried, and evaporated to give **23** (4.4 g, 88%), m.p. 234° (decomp.), $[\alpha]_D$ −14.0° (*c* 2.2, MeOH); ν_{max}^{KBr} 3340 (OH and NH), 1755 (ester), 1670 (carboxyl), 1640 (alkene), and 1610 cm^{-1} (phenyl); ^{1}H-n.m.r. ($CDCl_3$–Me_2SO-d_6): δ 5.38 (d, $J_{1,2}$ 8.4 Hz, H-1), 5.30 (dd, $J_{2,3}$ 9.2 Hz, $J_{3,4}$ 8.8 Hz, H-3), 4.99 (dd, $J_{4,5}$ 9.2 Hz, H-4), 3.9–4.4 (m, 4 H, H-2, H-5, H-6, and H-6'), 1.84 (s, NAc), 2.00 (s, 9 H, OAc), 6.34 and 7.54 (each d, *J* 16.0 Hz, alkenic), 7.40 and 7.56 (each d, *J* 8.0 Hz, aromatic).

Anal. Calc. for $C_{23}H_{27}NO_9$: C, 59.86; H, 5.90; N, 3.04. Found: C, 59.85; H, 5.95; N, 3.12.

p-[*4-Azido-2-(*tert*-butoxycarbonyl)amino-2,4,6-trideoxy-α-*D*-glucopyranosyloxy]cinnamic acid* (**24**). — (*a*) *From ethyl ester.* To a solution of ethyl *p*-[4-azido-2-(*tert*-butoxycarbonyl)amino-2,4,6-trideoxy-α-D-glucopyranosyloxy]cinnamate[9] (311 mg, 0.64 mmol) in MeOH (20 mL) was added M KOH (6 mL). After being kept for 12 h at room temperature, the mixture was poured into water, acidified with M hydrochloric acid, and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to give **24** (292 mg, 96%), m.p. 188° (decomp.), $[\alpha]_D$ +218° (*c* 0.75, MeOH); ν_{max}^{KBr} 3420 (broad, OH and NH), 2120 (azido), 1690 (urethane and carboxyl), 1635 (alkene), and 1610 cm^{-1} (phenyl); ^{1}H-n.m.r. (acetone-d_6): δ 5.81 (d, $J_{1,2}$ 4.0 Hz, H-1), 1.26 (d, $J_{5,6}$ 6.0 Hz, H-6), 3.4–4.4 (m, H-2 and H-5), 1.46 (s, Bu), 6.16 (broad d, NH), 6.40 and 7.63 (each d, *J* 15.6 Hz, alkenic), 7.13 and 7.64 (each d, *J* 8.4 Hz, aromatic), and 7.99 (s, CO_2H).

Anal. Calc. for $C_{20}H_{26}N_4O_7$: C, 55.29; H, 6.03; N, 12.90. Found: C, 55.35; H, 6.11; N, 12.73.

(*b*) *From* tert-*butyl ester* **46**. Compound **46** (124 mg, 0.25 mmol) was dissolved in 90% CF_3CO_2H (1 mL) and the solution was kept for 1.5 h at room temperature. The residue obtained by evaporation of the mixture was dissolved in Et_3N (2 mL) and water (1 mL). To the solution was added di-*tert*-butyl dicarbonate (110 mg, 0.50 mmol), the mixture was kept for 4 h at room temperature, and then extracted with EtOAc after acidification with M HCl. The extract was washed with water, dried, evaporated, and the residue purified on a column of silica gel with 7:3 hexane–Me_2CO to give **24** (59 mg, 54%).

General methods for amide formation. — (*a*) *DCC method.* A mixed solution for the carboxylic acid (0.10 mmol), **47** (0.23 mmol) and DCC (0.20 mmol) in CH_2Cl_2 (2 mL) was kept at room temperature. The residue obtained by evaporation of the solvent was fractionated on a column of silica gel with (*A*) 1:1 PhMe–EtOAc or (*B*) 1:1 hexane–Me_2CO to give the amide.

(*b*) *EEDQ method.* To a solution of the acid (0.10 mmol), EEDQ (0.21 mmol), and DMAP (3 mg) in dry CH_2Cl_2 (1 mL) was added **47** (0.20 mmol), and the mixture was kept at room temperature for the period given in Table III. Similar treatment to that just described gave the amide.

(*c*) *MTT method.* To a solution of the acid (0.18 mmol), EEDQ (0.36 mmol) and DMAP (18 mg) in CH_2Cl_2 was added mercaptothiazoline-2-thione (0.37 mmol), and the mixture was kept for 20 h at room temperature. The residue ob-

tained by evaporation of solvent was fractionated on a column of silica gel, using the yellow color as a marker, with 9:1 PhMe–EtOAc to give the acylthiazolines in 59–83% yields.

A mixed solution of the acylthiazoline and **47** in CH_2Cl_2 was kept at room temperature for the time-period given in Table III. Similar treatment as already described above gave the amide.

(*d*) *CDI method.* A mixed solution of the acid (0.10 mmol) and CDI (0.17 mmol) in THF (1 mL) was kept for 2 h at room temperature. To this solution was added a solution of **47** in THF (1 mL), and the mixture was kept for 20 h at the same temperature. Treatment as before gave the amide.

N^1-p-*(3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-*D*-galactopyranosyloxy)cinnamoyl*-N^2,N^3-*di*-tert-*butoxycarbonylspermidine* (**33**). — Compound **33** was prepared from **21** and **47** by four different methods; the CDI method gave the best result. The solvent system *A* was used for purification. Compound **33** was a syrup, $[\alpha]_D$ +110.5° (*c* 1.0, $CHCl_3$); ν_{max}^{NaCl} 3330 (NH), 2110 (azido), 1750 (ester), 1680 (broad, urethane and amide), and 1605 cm^{-1} (phenyl); ^{1}H-n.m.r.: δ 5.70 (d, $J_{1,2}$ 3.4 Hz, H-1), 3.86 (dt, $J_{2,3}$ 10.0 Hz, H-2), 5.61 (dd, $J_{3,4}$ 2.0 Hz, H-3), 5.55 (d, $J_{4,5}$ 0 Hz, H-4), 4.0–4.4 (m, H-5, H-6, and H-6'), 0.8–1.9 (broad m, 6 H, CH_2), 1.46 and 1.50 (each s, Bu), 1.96, 2.12 and 2.19 (each s, Ac), 3.0–3.5 (m, 8 H, NCH_2), 4.60 (broad s, NH), 6.40 and 7.63 (each d, *J* 15.6 Hz, alkenic), 7.12 and 7.50 (each d, *J* 8.4 Hz, aromatic).

Anal. Calc. for $C_{38}H_{56}N_6O_{14}$: C, 55.60; H, 6.88; N, 10.24. Found: C, 55.79; C, 7.22; N, 10.14.

N^1-p-*(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-*D*-galactopyranosyloxy)cinnamoyl*-N^2,N^3-*di*-tert-*butoxycarbonylspermidine* (**34**). — Compound **34** was prepared by the EEDQ and CDI methods, the latter gave the better result. Solvent system *B* was used for purification. Compound **34** was a syrup, $[\alpha]_D$ +113° (*c* 1.2, $CHCl_3$); ν_{max}^{NaCl} 3300 (broad, NH) 1740 (ester), 1690 (sh, urethane) and 1660 (amide), and 1605 cm^{-1} (phenyl), ^{1}H-n.m.r.: δ 5.62 (d, $J_{1,2}$ 3.6 Hz, H-1), 5.37 (dd, $J_{2,3}$ 11.6 Hz, $J_{3,4}$ 3.2 Hz, H-3), 5.42 (broad s, H-4), 3.8–4.4 (m, H-2, H-5, H-6, and H-6'), 0.8–0.9 (broad m, 6 H, CH_2), 1.44 and 1.48 (each s, Bu), 1.90 (s, NAc), 1.98, 2.03 and 2.17 (each s, OAc), 2.9–3.6 (m, 8 H, NCH_2), 4.70 and 4.79 (each broad d, NH), 6.27 (d, *J* 8.4 Hz, NHAc), 6.34 and 7.50 (each d, *J* 15.2 Hz, alkenic), 6.97 and 7.37 (each d, *J* 8.4 Hz, aromatic).

Anal. Calc. for $C_{40}H_{60}N_4O_{14}$: C, 58.52; H, 7.37; N, 6.83. Found: C, 58.32; H, 7.07; N, 6.40.

N^1-p-*(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyloxy)cinnamoyl*-N^2,N^3-*di*-tert-*butoxycarbonylspermidine* (**35**). — Compound **35** was prepared by the EEDQ and MTT methods; the latter gave the better result. Solvent system *B* was used for purification. Compound **35** had m.p. 137–139°, $[\alpha]_D$ −6.2° (*c* 2.0, $CDCl_3$); ν_{max}^{KBr} 3300 (broad, NH), 1740 (ester), 1660 (broad, urethane and amide), and 1605 cm^{-1} (phenyl), ^{1}H-n.m.r.: δ 5.34 (d, $J_{1,2}$ 8.2 Hz, H-1), 3.93 (m, H-2), 5.45 (t, $J_{2,3} = J_{3,4}$ 9.4 Hz, H-3), 5.13 (t, $J_{4,5}$ 9.4 Hz, H-4), 4.0–4.5 (m, H-5, H-6, and

H-6'), 0.8–1.9 (broad m, 6 H, CH_2), 1.44 and 1.48 (each s, Bu), 1.95 (s, NAc), 2.06 (s, 9 H, OAc), 3.0–3.5 (m, 8 H, NCH_2), 4.66 (broad s, NH), 6.42 (d, NHAc), 6.34 and 7.50 (each d, *J* 15.6 Hz, alkenic), 6.94 and 7.38 (each d, *J* 8.4 Hz, aromatic), and 7.38 (d, NH).

Anal. calc. for $C_{40}H_{60}N_4O_{14}$: C, 58.52; H, 7.37; N, 6.83. Found: C, 58.53; H, 7.89; N, 6.32.

N^1-p-[*4-Azido-2-(*tert-*butoxycarbonyl)amino-2,4,6-trideoxy-α-*D-*glucopyranosyloxy*]*cinnamoyl*-N^2,N^3-*di*-tert-*butoxycarbonylspermidine* (**36**). — (*a*) *From* **24**. Compound **36** was prepared by the MTT and CDI methods, the latter method gave **36** and **38** in 38 and 21% yields, respectively. Solvent system *A* was used for fractionation. Compound **36** was a syrup, $[\alpha]_D$ +114° (*c* 1.1, $CHCl_3$); ν_{max}^{NaCl} 3450 and 3340 (broad, OH and NH), 2110 (azido), 1680 (broad, urethane and amide), and 1605 cm^{-1} (phenyl); ^{1}H-n.m.r.: δ 5.46 (d, $J_{1,2}$ 2 Hz, H-1), 3.90 (dd, H-2), 4.56 (m, H-3), 3.64 (m, H-5), 1.26 (d, $J_{5,6}$ 6 Hz, H-6), 1.3–2.0 (broad m, 6 H, CH_2), 1.45 (s, 18 H, Bu), 1.47 (s, 9 H, Bu), 2.9–3.5 (m, 9 H, NCH_2 and H-4), 5.02 (bs, NH), 6.30 and 7.50 (each d, *J* 15.3 Hz, alkenic), 6.95 and 7.39 (each d, *J* 8.4 Hz, aromatic).

Anal. Calc. for $C_{37}H_{59}N_7O_{10}$: C, 58.33; H, 7.81; N, 12.87. Found: C, 58.58; H, 7.73; N, 12.50.

(*b*) *From* **37**. Compound **24e** (1.06 g, 1.32 mmol) was deacetylated with NaOMe in MeOH, and purified on a column of silica gel as already described to give **36** (713 mg, 71%).

N^1-p-[*3-O-Acetyl-4-azido-2-(*tert-*butoxycarbonyl)amino-2,4,6-trideoxy-α-*D-*glucopyranosyloxy*]*cinnamoyl*-N^2,N^3-*di*-tert-*butoxycarbonylspermidine* (**37**). — Compound **24** was conventionally acetylated with Ac_2O–C_5H_5N to give the corresponding 3-acetate (**25**) quantitatively.

Compound **25** was converted into **37** by the CDI method, and solvent system *A* was used for fractionation. Compound **37** was a syrup, $[\alpha]_D$ +128° (*c* 1.4, $CHCl_3$); ν_{max}^{NaCl} 3430 and 3330 (broad, OH and NH), 2110 (azido), 1740 (ester), 1690 (broad, urethane and amide), and 1605 cm^{-1} (phenyl); ^{1}H-n.m.r.: δ 5.47 (d, $J_{1,2}$ 3.8 Hz, H-1), 4.02 (dt, $J_{2,3}$ 10.4 Hz, H-2), 5.30 (t, $J_{3,4}$ 10.4 Hz, H-3), 3.61 (dq, $J_{4,5}$ 10.4 Hz, H-5), 1.36 (d, $J_{5,6}$ 6.4 Hz, H-6), 0.7–1.9 (broad m, 6 H, CH_2), 2.14 (s, OAc), 2.9–3.5 (m, 9 H, NCH_2), 4.70 (broad s, NH), 4.92 (d, *J* 10.2 Hz, NH), 6.32 and 7.51 (each d, *J* 15.8 Hz, alkenic), 6.99 and 7.41 (each d, *J* 8.2 Hz, aromatic).

Anal. Calc. for $C_{39}H_{61}N_7O_{11}$: C, 58.27; H, 7.65; N, 12.20. Found: C, 57.95; H, 7.51; N, 12.46.

tert-*Butyl* p-*(2-acetamido-3,4,6-tri-*O-*acetyl-α-*D-*galactopyranosyloxy)cinnamate* (**40**). — Hydrogenolysis of **4** (1.61 g, 3.0 mmol) in MeOH (30 mL) in the presence of 5% Pd–$BaSO_4$ (0.41 g) and quinoline (0.11 g) afforded the 2-amino derivative **39**, which was conventionally acetylated with $Ac_2OC_5H_5N$ to give **40** (1.27 g, 76%), m.p. 87.5–89.5°, $[\alpha]_D$ +171° (*c* 2.0, $CHCl_3$); ν_{max}^{KBr} 3300 (broad, NH), 1740 (ester), 1700 (urethane), 1650 (amide), 1630 (alkene), and 1600 cm^{-1} (phenyl); ^{1}H-n.m.r.: δ 5.66 (d, $J_{1,2}$ 3.2 Hz, H-1), 4.80 (m, H-2), 5.40 (dd, $J_{2,3}$ 10.0 Hz, $J_{3,4}$ 3.0 Hz, H-3), 5.46 (broad s, $J_{4,5}$ 2.0 Hz, H-4), 4.28 (m, $J_{5,6}$ 4.8 Hz, H-5),

4.0–4.3 (m, H-6 and H-6'), 1 53 (s, Bu), 1 91 (s, NAc), 1.99, 2 05 and 2 20 (each s, OAc), 5 86 (d, *J* 9.2 Hz, NH), 6 27 and 7 53 (each d, *J* 15.6 Hz, alkenic), 7 06 and 7.48 (d, *J* 8 6 Hz, aromatic)

Anal Calc. for $C_{27}H_{35}NO_{11}$: C, 59.01, H, 6.42, N, 2.55. Found. C, 58.73, H, 6 19; N, 2 46

tert-*Butyl* p-[*3,6-di*-O-*benzoyl-2-(*tert-*butoxycarbonyl)-amino-2-deoxy-α*-D-*galactopyranosyloxy*]*cinnamate* (**42**) — Compound **4** (1 04 g, 1 95 mmol) was conventionally deacetylated with NaOMe and hydrogenolyzed in MeOH (20 mL) in the presence of 5% Pd–$BaSO_4$ (260 mg) and quinoline (69 mg) Undissolved materials were filtered off and the residue obtained by evaporation of the filtrate was treated with 2-(*tert*-butoxycarbonylthio)-4,6-dimethylpyrimidine (478 mg, 2 10 mmol), and Et_3N (213 mg, 2.11 mmol) in a mixture of 1,4-dioxane (9 mL) and water (9 mL) for 20 h at room temperature. The solution was evaporated and the residue dissolved in acetone (8 mL) To this solution was added dropwise Et_3N (774 mg, 7 66 mmol) and BzCl (1 06 g, 7 54 mmol) under cooling with ice–water After 3 h the mixture was processed conventionally to give **42** (700 mg, 53%), syrup, $[\alpha]_D$ +175° (*c* 0 6, $CDCl_3$), ν_{max}^{NaCl} 3500 and 3320 (OH and NH), 1705 (broad, ester and urethane), 1630 (alkene), and 1600 cm^{-1} (phenyl), ^{1}H-n m r : δ 5 78 (d, $J_{1,2}$ 3 0 Hz, H-1), 5.53 (dd, $J_{2,3}$ 10 4 Hz, $J_{3,4}$ 2 Hz, H-3), 1 28 and 1 58 (each s, Bu), and 6.18 (d, *J* 16.0 Hz, alkenic).

Anal Calc for $C_{38}H_{43}NO_{11}$: C, 66.17; H, 6 28, N, 2 03 Found· C, 65 87; H, 6 49, N, 2 12

tert-*Butyl* p-[*3,6-di*-O-*benzoyl-2-(*tert-*butoxycarbonyl)amino-2-deoxy-4-methylsulfonyl-α*-D-*galactopyranosyloxy*]*cinnamate* (**43**) — Conventional mesylation of **42** gave **43** in 98% yield, m p 86 5–88 5°, $[\alpha]_D$ +149° (*c* 1 1, $CDCl_3$), ν_{max}^{KBr} 3400 (broad, NH), 1720 (ester and urethane), 1635 (alkene), and 1605 cm^{-1} (phenyl), ^{1}H-n.m.r.. δ 5.71 (d, $J_{1,2}$ 3 0 Hz, H-1), 5.54 (dd, $J_{2,3}$ 10 0 Hz, $J_{3,4}$ 3 0 Hz, H-3), 5 41 (d, H-4), 4 3–5 0 (m, H-2, H-5, H-6, and H-6'), 1 32 and 1.56 (each s, Bu), 3 11 (s, Ms), 6 17 (d, *J* 16 0 Hz, alkenic) and 7 8–8.2 (m, alkenic and aromatic)

Anal Calc. for $C_{39}H_{45}NO_{13}S$· C, 61 01; H, 5 91, N, 1 82; S, 4 18 Found· C, 61 15, H, 5 89, N, 1.87, S, 4.11

tert-*Butyl* p-[*4-azido-3,6-di*-O-*benzoyl-2-(*tert-*butoxycarbonyl)amino-2,4-dideoxy-α*-D-*glucopyranosyloxy*]*cinnamate* (**44**) — A mixture of **43** (720 mg, 1 10 mmol) and NaN_3 (146 mg, 2 25 mmol) in HMPA (11 mL) was heated for 20 h at 80°, and conventional isolation and fractionation of the products on a column of silica gel with 39 1 PhMe–Me_2CO gave **44** (603 mg, 78%), m.p 87–88°, $[\alpha]_D$ +139° (*c* 1 6, $CDCl_3$); ν_{max}^{KBr} 3350 (broad, NH), 2110 (azido), 1725 and 1710 (ester and urethane), 1635 (alkene), and 1605 cm^{-1} (phenyl), ^{1}H-n m.r δ 5 66 (d, $J_{1,2}$ 3.4 Hz, H-1), 4 37 (dt, $J_{2,3} = J_{2,NH}$ 10 2 Hz, H-2), 5 77 (broad t, $J_{3,4}$ 9 4 Hz, H-3), 4 5–4 7 (m, 2 H, H-4 and H-5), 3 8–4.2 (m, 2 H, H-6 and H-6'), 1 20 (s, Bu in Boc), 1 56 (s, Bu), 6.26 (d, *J* 15.6 Hz, alkenic), and 7 05–8.0 (m, aromatic and alkenic)

Anal Calc for $C_{38}H_{42}N_4O_{10}$ C, 63 85, H, 5 92, N, 7.84 Found C, 63 41, H, 5 77, N, 7.66.

tert-*Butyl* p-[*4-azido-2-(*tert-*butoxycarbonyl)amino-2,4-dideoxy-6-*O-*tolylsulfonyl-α-*D-*glucopyranosyloxy]cinnamate* (**45**). — Conventional de-esterification of **44** (603 mg, 0.86 mmol) with NaOMe gave 3,6-diol derivative, which was treated with TsCl (250 mg, 1.31 mmol) in C_5H_5N (9 mL) for 20 h at room temperature. Conventional isolation and purification of the product on a column of silica gel with 9:1 PhMe–Me_2CO gave **45** (425 mg, 76%), m.p. 97–99°, $[\alpha]_D$ +110° (*c* 1.0, $CDCl_3$); ν_{max}^{KBr} 3400 (broad, NH), 2110 (azido), 1700 (ester and urethane), 1630 (alkene) and 1600 cm^{-1} (phenyl); ^{1}H-n.m.r.: δ 5.49 (d, $J_{1,2}$ 2 Hz, H-1), 3.5–4.3 (other ring protons), 1.47 and 1.56 (each s, Bu), 2.47 (s, Me in Ts), 5.07 (broad d, $J_{2,NH}$ 8.6 Hz, NH), 6.28 (d, *J* 15.8 Hz, alkenic), and 6.9–7.9 (m, aromatic and alkenic).

Anal. Calc. for $C_{31}H_{40}N_4O_{10}S$: C, 56.35; H, 6.10; N, 8.48; S, 4.85. Found: C, 56.77; H, 5.96; N, 8.18; S, 4.89.

tert-*Butyl* p-[*4-azido-2-(*tert-*butoxycarbonyl)amino-2,4,6-trideoxy-α-*D-*glucopyranosyloxy]cinnamate* (**46**). — Reduction of **45** (395 mg, 0.61 mmol) with $NaCNBH_3$ (304 mg, 4.60 mmol) in HMPA (6 mL) in the presence of NaI (504 mg, 3.36 mmol) for 20 h at 70–80° gave the product **46**, which was purified twice on a column of silica gel with 4:1 hexane–EtOAc, yield 238 mg (80%). Compound **46** was a syrup, $[\alpha]_D$ +178° (*c* 1.7, $CDCl_3$); ν_{max}^{NaCl} 3420 (broad, OH and NH), 2120 (azido), 1700 (ester and urethane), 1635 (alkene), and 1605 cm^{-1} (phenyl); ^{1}H-n.m.r.: δ 5.53 (broad s, $J_{1,2}$ 1.5 Hz, H-1), 1.29 (d, $J_{5,6}$ 6.0 Hz, H-6), 3.2–4.2 (m, other ring protons), 1.49 and 1.59 (each s, Bu), 5.16 (broad s, NH), 6.28 and 7.54 (each d, *J* 15.8 Hz, alkenic), 7.04 and 7.46 (each d, *J* 8.4 Hz, aromatic).

Anal. Calc. for $C_{24}H_{34}N_4O_7$: C, 58.76; H, 6.98; N, 11.42. Found: C, 58.61; H, 6.81; N, 11.42.

General method for preparation of free glycosyloxycinnamoylspermidines (**48–51**). — Compounds **33, 34, 35,** or **37** (0.5 mmol) were deacetylated conventionally with NaOMe in MeOH. The mixture was acidified with cation-exchange resin IR-120A (H^+) and evaporated to give a residue, which was dissolved in CF_3CO_2H (2 mL). The solution was poured into Et_2O saturated with HCl. The precipitated amorphous solid was filtered and washed with Et_2O to give the free glycocinnamoylspermidines as hydrogen chloride salts in ~50% yield.

N^1-[p-*2-Azido-2-deoxy-α-*D-*galactopyranosyl)oxy]cinnamoylspermidine dihydrochloride* (**48**). — This product was an amorphous and hygroscopic powder, $[\alpha]_D$ +98° (*c* 0.9, H_2O); ^{1}H-n.m.r. data, see Table IV.

Anal. Calc. for $C_{22}H_{36}Cl_2N_6O_6 \cdot 4\,H_2O$: C, 42.38; H, 7.11; N, 13.48. Found: C, 42.69; H, 6.73; N, 12.96.

N^1-[p-*(2-Acetamido-2-deoxy-α-*D-*galactopyranosyl)oxy]cinnamoylspermidine dihydrochloride* (**49**). — This product was an amorphous and hygroscopic powder, $[\alpha]_D$ +73° (*c* 4.1, H_2O); ^{1}H-n.m.r. data, see Table IV.

Anal. Calc. for $C_{24}H_{40}Cl_2N_4O_7 \cdot 4\,H_2O$: C, 45.07; H, 7.57; N, 8.76. Found: C, 44.69; H, 7.29; N, 8.39.

N^1-[p-*(2-Acetamido-2-deoxy-β-*D-*galactopyranosyl)oxy]cinnamoylspermidine dihydrochloride* (**50**). — This product was an amorphous and hygroscopic powder, $[\alpha]_D$ +10° (*c* 1.0, H_2O); ^{1}H-n.m.r. data, see Table IV.

Anal Calc. for $C_{24}H_{40}Cl_2N_4O_7 \cdot 5\ H_2O$ C, 43 84; H, 7 66; N, 8.52, Found: C, 43 82; H, 7 16, N, 8.32

N^1-[p-*(2-Amino-4-azido-2,4,6-trideoxy-α-*D*-glucopyranosyl)oxy]cinnamoylspermidine trihydrochloride* (**51**) — This product was an amorphous and hygroscopic powder, $[\alpha]_D$ +37° (*c* 2.2, H_2O), ^{1}H-n m r data see Table IV

Anal Calc for $C_{22}H_{38}Cl_3N_7O_4$ C, 43 53, Cl, 17 52, H, 6 97, N, 16 15 Found· C, 43 28; Cl, 17 96; H, 6 63; N, 15 76

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