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SYNTHESIS OF ADIPOSIN-1 AND RELATED COMPOUNDS*

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ABSTRACT

The synthesis is described of adiposin-1 (**2a**), isolated from an α-D-glucosidase inhibitor complex, adiposin, produced by *Streptomyces calvus* TM-521. The synthesis involved the coupling of 1,6-anhydro-4-*O*-(3,4-anhydro-α-D-galactopyranosyl)-β-D-glucopyranose (**13**) with the di-*O*-isopropylidene derivative (**7**) of DL-(1,4,6/5)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexenylamine. All possible diastereoisomers of the secondary amine were isolated by chromatography on silica gel. Their structures were tentatively assigned on the basis of ^{1}H-n.m.r. spectroscopy and optical rotation. Likewise, both the core-structure (**4**) of adiposin and the saturated analog (**22a**) of **2a** were synthesized.

INTRODUCTION

In recent years, several pseudo-oligosaccharidic α-D-glucosidase inhibitors, such as acarbose (**1**) and its homologs[2], amylostatins[3], trestatins[4], etc., have been isolated from cultures of microorganisms, and considerable interest has been stimulated in the biochemistry and chemistry of this class of inhibitors[5]. The characteristic core-structure essential for inhibitory action is composed of a trihydroxy(hydroxymethyl)cyclohexene moiety and a 4-amino-4,6-dideoxy-D-glucopyranose moiety, bonded by way of an imino linkage at the allylic position. A similar structural unit has been found in the validamycin antibiotics[6].

Adiposin-1 (**2a**) was isolated from an inhibitor complex, adiposin, produced by *Streptomyces calvus* TM-521 and was shown to possess α-D-glucoside hydrolase inhibitory activity as well as antibacterial activity[7]. The structure was determined by ^{1}H-n.m.r. spectroscopy[8]. Adiposin is somewhat different from the other analogous inhibitors in its common core-structure, where a 4-amino-4-deoxy-D-glucopyranose residue replaces the 4-amino-4,6-dideoxy-D-glucopyranose residue.

As part of studies elucidating structure–activity relationships of these in-

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*Synthesis of Pseudo-oligosaccharidic Glycosidase Inhibitors, Part I. For a preliminary account of part of this work, see ref. 1.

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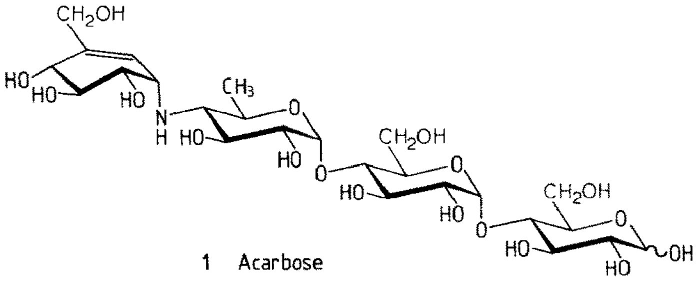
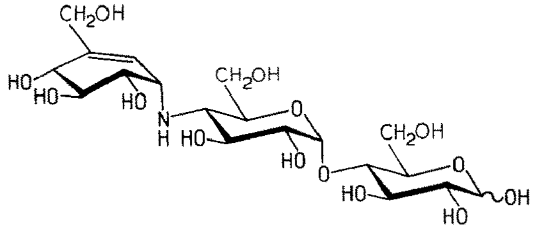


1 Acarbose



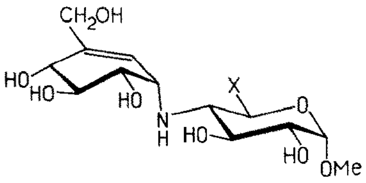
2a Adiposin-1

hibitors, we have synthesized **2a** and several related substances. The present synthesis involves the condensation of a newly prepared disaccharide epoxide with a protected, racemic trihydroxy(hydroxymethyl)cyclohexenylamine.

RESULTS AND DISCUSSION

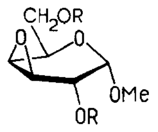
Synthesis of the core-structure of adiposin. — The core-structure of **1** and analogous inhibitors was first described as the methyl glycoside (**3**) or methyl dehydro-oligobiosaminide obtained by methanolysis of oligostatin C (ref. 9).

Attempts were made initially to synthesize the methyl glycoside (**4**) of the core-structure of adiposin, to study its biological properties and also to elucidate the course of the coupling reaction of the sugar epoxide with the amine. We chose methyl 3,4-anhydro-α-D-galactopyranoside (**5**) for coupling with a di-*O*-isopropylidene derivative[10] (**7**) of DL-(1,4,6/5)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexenylamine [di-*O*-(isopropylidene)valienamine]. Compound **5** is readily accessible by the modified procedure of Buchanan[11].

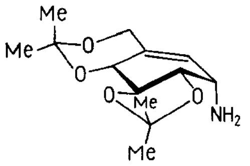


3 Methyl dehydro-oligobiosaminide, X = CH_3

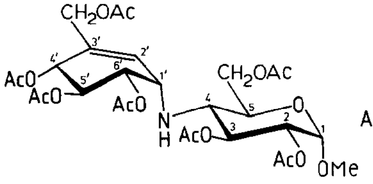
4 Core structure of adiposin, X = CH_2OH



5 R = H
6 R = Ac

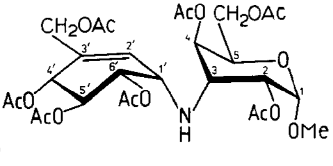


7
racemate



8a

8b diastereomer



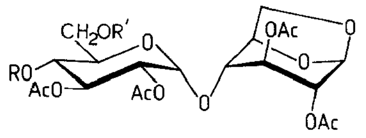
9a

9b diastereomer

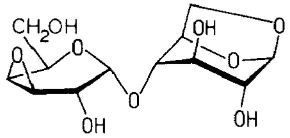
Condensation of **5** with **7** was performed in 2-propanol in a sealed tube for 40 h at 120°. The product was then treated with acetic anhydride in pyridine, and the acetylated products were roughly separated by chromatography on silica gel to give a mixture of the condensation products and recovered **5** as the diacetate **6**. The condensation products were deacetonated with 70% aqueous acetic acid and the products, after acetylation, were separated on a column of silica gel to give first the protected pseudo-disaccharides **8b** (20%) and **9a** (20%). *O*-Deacetylation of the homogeneous fraction containing **8a** and **9b** with methanolic sodium methoxide gave a mixture of methyl glycosides, from which crystalline **4** was isolated in 17% yield by fractional recrystallization. Compound **4** was convertible into **8a**. Acetylation of the other, crude methyl glycoside gave pure **9b** (18%). The elemental analyses and spectral data for the products were consistent with the assigned structures. In particular, the ^{1}H-n.m.r. spectra of **8a** and **8b** showed wide triplets (*J* 10 Hz), attributable to the signals of the axial protons attached to the carbon atoms (C-4) of the sugar bonded to imino groups. Compounds **8a** and **8b** are, therefore, deduced to be diastereoisomers that contain the 4-amino-4-deoxy-D-glucopyranose residue. On the other hand, in the spectra of **9a** and **9b**, the corresponding signals appeared as triplets (*J* 4.5 Hz), attributable to equatorial protons at C-3 of 3-amino-3-deoxy-D-gulopyranose residues. In these secondary amines, the nitrogen atom seems to be hindered by the bulky cyclohexenyl and glycosyl substituents, and does not undergo acetylation under standard conditions[12]. The notable regioselectivity of the cleavage of the epoxide ring was not observed in this case.

Assignments of the absolute configurations were based on optical rotation. As it is known that (1*S*)-penta-*N*,*O*-acetylvalienamine[13] has $[\alpha]_D$ +30.2°, the cyclohexene moiety whose absolute configuration is related to that of the (1*S*)-enantiomer would make a dextrorotatory contribution to the molecular rotation of the pseudo-sugar. Accordingly, comparison of the relative magnitudes of the optical rotations in each set of diastereoisomers permitted tentative assignment of the absolute configurations of **8a** and **8b**, as well as **9a** and **9b**, as shown in the Scheme.

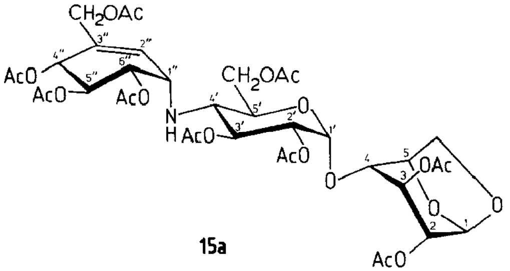
Synthesis of adiposin-1 and related compounds. — The synthesis of **2a** was performed by the method employed for the synthesis of **4**. For this purpose, 1,6-anhydro-4-*O*-(3,4-anhydro-α-D-galactopyranosyl)-β-D-glucopyranose (**13**) was prepared from the known 2,3,2′,3′-tetra-*O*-acetyl-1,6-anhydro-β-maltose[14] (**10**). Selec-



10 R = R′ = H
11 R = H, R′ = Bz
12 R = Ts, R′ = Bz

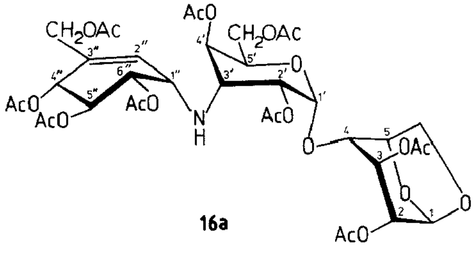


13



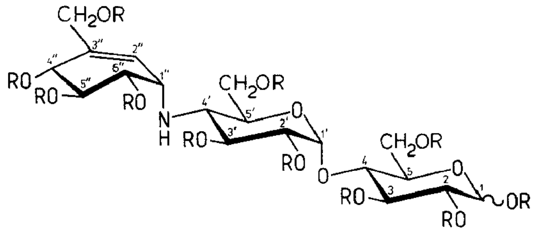
15a

15b diastereomer



16a

16b diastereomer

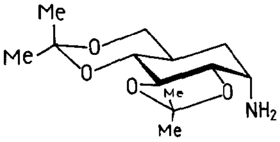


17a R = Ac
2a R = H

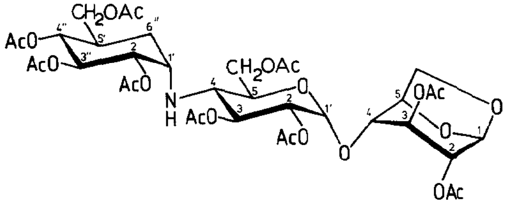
17b diastereomer
2b diastereomer

tive benzoylation gave the 6′-benzoate **11**, which was then converted into the *p*-toluenesulfonate **12**. Treatment of **12** with excess of methanolic sodium methoxide in chloroform gave a single, crystalline, epoxide **13** in an overall yield of 68%. The structure of **13** was determined by the ^{1}H-n.m.r. spectrum of its tetraacetate **14**.

Condensation of **7** with **13** and isolation of the protected pseudo-trisaccharides formed was conducted as described for the preparation of **4**. Chromatography of the products on silica gel gave the pseudo-trisaccharide nonaacetates **15a** (13%), **15b** (14%), **16a** (21%), and **16b** (16%). The structures of **15a,b** and **16a,b** were similarly proposed from their ^{1}H-n.m.r. spectra and specific rotations. Acetolysis

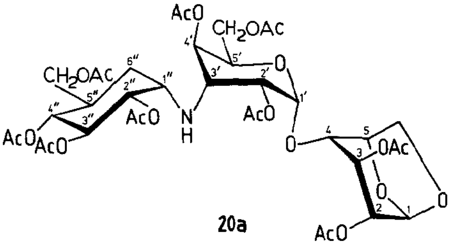


18
racemate



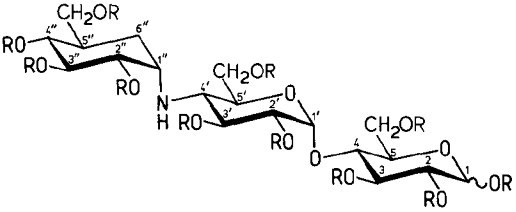
19a

19b diastereomer



20a

20b diastereomer



21a R = Ac
22a R = H

21b diastereomer
22b diastereomer

of **15a** with 30:70:1 (v/v) acetic acid–acetic anhydride–conc. sulfuric acid at room temperature for 2 h gave the undecaacetate **17a** (99%), which was then *O*-deacetylated to the free pseudo-trisaccharide **2a** whose ^{1}H-n.m.r. spectrum (400 MHz, D_2O) was superposable on that reported for an authentic sample[7] of adiposin-1. Similar acetolysis of **15b** gave **17b** (98%), which was assigned as the diastereoisomer of **17a**, judging from its closely similar ^{1}H-n.m.r. spectrum. The tentative assignment of absolute configurations on the basis of optical rotation was thus shown to be feasible in these instances.

Hydrogenation of homologs of acarbose gave a mixture of two diastereoisomers having trihydroxy(hydroxymethyl)cyclohexane (pseudo-hexopyranose) residues with the L-*ido* and D-*gluco* configurations. Both compounds were inactive against α-D-glucosidase, but the compound having the D-*gluco* configuration showed a profound effect on sucrase. The double bond in the branched-chain cyclitol was found to play an important role in this effect[5]. We then became interested in preparing the adiposin-1 analog having a saturated cyclitol moiety with the D-*gluco* configuration.

Condensation of **13** with the di-*O*-isopropylidene derivative[15] (**18**) of DL-(1,2,4/3,5)-2,3,4-trihydroxy-5-(hydroxymethyl)cyclohexylamine [di-*O*-(isopropylidene)validamine] was performed similarly in a mixture of *N*,*N*-dimethylformamide and 2-propanol. Chromatography of the mixture of protected pseudo-trisaccharides on silica gel gave **19b** (25%) and **20a** (26%), together with an inseparable mixture of **19a** and **20b**. The mixture was *O*-deacetylated and the products were separated on a column of Dowex 50W X2 (H^+) resin to give, after acetylation, **19a** (22%) and **20b** (26%). The structures of **19a,b** and **20a,b** were deduced by their ^{1}H-n.m.r. spectra and the optical rotations. Compounds **19a** and **19b** were converted into the respective pseudo-trisaccharide undecaacetates **21a** and **21b** in good

TABLE I

PARTIAL ^{1}H-N M R SPECTRAL DATA FOR COMPOUNDS **21a** AND **21b**[a]

Proton	**21a**		**21b**	
	δ (p.p.m)	J *(Hz)*	*δ (p.p.m)*	J *(Hz)*
H-1	6.24 d	4	6.24 d	4
H-2	4.94 dd	4, 10	4.96 dd	4, 10
H-3	5.48 dd	9.2, 10	5.50 dd	9.2, 10
H-4	4 00 t	9.2, 9.2	3.96 t	9.2, 9.2
H-1′	5.29 d	4	5 31 d	4.2
H-3′	5.23 t	10.4, 10.4	5 17 t	10.4, 10.4
H-4′	2.86[b] t	10 4, 10.4	2.79[b] t	10.4, 10 4
H-5′	3.70 br d	~10 5	3 72 br d	~10.5
H-1″	3.52 m		3.30 m	
H-3″	5.30 t	10, 10	5.34 t	10, 10
H-4″	4 95 t	10, 10	4.95 t	10, 10

[a]Measured at 200 MHz in chloroform-*d* [b]Appears on deuteration.

yields. Their ^{1}H-n.m.r. spectra were consistent with the assigned structures. The free pseudo-trisaccharides **22a** and **22b** were obtained from **21a** and **21b**, respectively.

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi 510 capillary melting-point apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-4 polarimeter. T.l.c. was performed on plates coated with Silica gel G F-254 (E. Merck, Darmstadt, G.F.R.); components were detected by spraying the plates with 10% sulfuric acid, with subsequent heating. ^{1}H-N.m.r. spectra were recorded, unless otherwise stated, at 90 MHz with a Varian EM-390 spectrometer, for solutions in chloroform-*d* with tetramethylsilane as the internal standard. Spectra at 200 MHz were recorded with a Jeol FX-200, and 400 MHz spectra, with a Jeol FX-400 instrument. The silica gel used for column chromatography was Wakogel C-300 (Wako Co., Osaka, Japan; 300 mesh). Organic solutions were dried over anhydrous sodium sulfate and evaporated at temperatures below 50° under diminished pressure.

*Methyl 3,4-anhydro-α-*D*-galactopyranoside* (**5**). — This compound was prepared according essentially to the method of Buchanan[11]; m.p. 117.5–118°, $[\alpha]_D^{21}$ +71° (*c* 1.0, H_2O) [lit.[11] m.p. 118.5–119.5°, $[\alpha]_D$ +67.5° (*c* 1.11, H_2O)]; ^{1}H-n.m.r. data (CD_3OD): δ 4.76 (d, 1 H, *J* 4.4 Hz, H-1), 3.46 (s, 3 H, OMe), and 3.27 (br d, 1 H, *J* 4 Hz), and 3.15 (br d, 1 H, *J* 4 Hz, H-3,4).

Condensation of **5** *with* DL-*di-O-(isopropylidene)valienamine*[10] (**7**). — A mixture of **5** (165 mg, 0.97 mmol) and **7** (200 mg, 0.78 mmol) in 2-propanol (1 mL) was heated in a sealed tube for 40 h at 120° and then evaporated. The residue was treated with acetic anhydride (4 mL) in pyridine (4 mL) at room temperature overnight, the mixture was evaporated, and the residue was chromatographed on a column of silica gel (25 g) with 1:5 butanone–toluene as eluant. The first fraction gave the di-*O*-acetyl derivative (**6**, 66 mg, 27%) of **5** as a syrup, $[\alpha]_D^{23}$ +85° (*c* 1.22, chloroform) (lit.[11] $[\alpha]_D$ +57.4°); ^{1}H-n.m.r. data: δ 4.79 (d, 1 H, *J* 4.2 Hz) and 4.68 (d, 1 H, *J* 4.2 Hz, H-1,2), 3.37 (s, 3 H, OMe), 3.20 (s, 2 H, H-3,4), and 2.10 and 2.03 (s, 6 H, 2 OAc). (*Anal.* Found: C, 50.44; H, 5.93).

The second fraction gave a syrup (95 mg) which was treated with aqueous 70% acetic acid (10 mL) for 2 h at 55° and then evaporated. The residue was acetylated and the product was eluted with chloroform from a short column of alumina to give methyl 2,4,6-tri-*O*-acetyl-3-deoxy-3-[(1*S*)-(1,4,6/5)-4,5,6-triacetoxy-3-acetoxymethyl-2-cyclohexenyl]amino-α-D-glucopyranoside (**9a**, 101 mg, 20% based on **7** used) as a syrup, $[\alpha]_D^{20}$ +75° (*c* 1.41, chloroform): ^{1}H-n.m.r. data: δ 5.98 (d, 1 H, *J* 5 Hz, H-2′), 3.67 (t, 1 H, *J* 5 Hz, H-1′, appears on deuteration), 3.41 (s, 3 H, OMe), and 3.16 (t, 1 H, *J* 4.2 Hz, H-3, appears on deuteration).

The third fraction (292 mg) was similarly treated with aqueous 70% acetic acid and the products were acetylated. Chromatography of the products on silica gel (elution with 1:3 butanone–toluene) gave a homogeneous syrup (220 mg), which was then treated with M methanolic sodium methoxide (4 mL) overnight at room temperature. The mixture was charged onto a column of Dowex 50W X2 (H^+) resin (3 mL) which was washed with methanol and then eluted with aqueous 1% ammonia. The product was crystallized from ethanol to give methyl 4-deoxy-4-[(1*S*)-(1,4,6/5)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl]amino-α-D-glucopyranoside (**4**, 48 mg, 17%) as needles, m.p. 185–186°, $[\alpha]_D^{18}$ +188° (*c* 0.94, H_2O); R_F 0.61 (3:2:2 1-butanol–H_2O–ethanol).

Acetylation of **4** (20 mg) gave the heptaacetate **8a** (100%) as a syrup, $[\alpha]_D^{20}$ +130° (*c* 0.96, chloroform): ^{1}H-n.m.r. data: δ 5.91 (d, 1 H, *J* 5.4 Hz, H-2′), 5.27 (m, 1 H, H-5′), 4.55 (br s, 1 H) and 4.36 (s, 1 H) ($C{=}CCH_2OAc$), 4.36 (dd, 1 H, *J* 3 and 12 Hz) and 4.12 (dd, 1 H, *J* 4.4 and 12 Hz) (CH_2OAc), 3.34 (s, 3 H, OMe), 2.73 (t, 1 H, *J* 10.2 Hz, H-4, appears on deuteration), and 2.08, 2.03, 2.01, and 1.99 (s, 21 H, 7 OAc).

The mother liquor from **4** was evaporated to a syrup (51 mg) that was acetylated to give, after chromatography, the diastereoisomer **9b** (93 mg, 18%) of **9a** as a syrup, $[\alpha]_D^{25}$ +22° (*c* 1.15, chloroform); ^{1}H-n.m.r. data: δ 5.98 (d, 1 H, *J* 5.2 Hz, H-2′), 5.55 (d, 1 H, *J* 6 Hz, H-1), 5.42 (t, 1 H, *J* 7.5 Hz, H-5′), 3.87 (t, 1 H, *J* 5.2 Hz, H-1′, appears on deuteration), 3.37 (s, 3 H, OMe), 3.01 (t, 1 H, *J* 4.4 Hz, appears on deuteration), and 2.10–1.98 (clusters of singlets, 21 H, 7 OAc).

The second fraction gave the diastereoisomer **8b** (99 mg, 20%) of **8a** as a syrup, $[\alpha]_D^{16}$ +44° (*c* 3.47, chloroform); ^{1}H-n.m.r. data: δ 5.80 (d, 1 H, *J* 5.4 Hz, H-2′), 5.18 (t, 1 H, *J* 8.7 Hz, H-5′), 3.30 (s, 3 H, OMe), 2.69 (t, 1 H, *J* 9.5 Hz, H-4), and 2.07–1.97 (clusters of singlets, 21 H, 7 OAc).

Anal. Calc. for $C_{14}H_{25}NO_9$: C, 47.86; H, 7.17; N, 3.99. Found for **4**: C, 47.57; H, 6.99; N, 3.82. Calc. for $C_{28}H_{39}NO_{16}$: C, 52.09; H, 6.09; N, 2.17. Found for **8a**: C, 51.77; H, 5.95; N, 2.06. Found for **8b**: C, 52.13; H, 6.04; N, 2.00. Found for **9a**: C, 52.04; H, 6.03; N, 2.06. Found for **9b**: C, 52.06; H, 6.04; N, 2.07.

2,3,2′,3′-Tetra-O-acetyl-1,6-anhydro-6′-O-benzoyl-β-maltose (**11**). — To a solution of 2,3,2′,3′-tetra-*O*-acetyl-1,6-anhydro-β-maltose[14] (**10**, 188 mg, 0.38 mmol) in dry pyridine (7.5 mL) was added benzoyl chloride (0.06 mL, 0.52 mmol) at −20°, and the mixture was stirred for 20 h at room temperature. The mixture was evaporated, the residue was dissolved in ethyl acetate (10 mL), and the solution was washed with aqueous sodium hydrogencarbonate and water, dried, and evaporated to give **11** (239 mg, 100%) as a syrup, $[\alpha]_D^{18}$ +33° (*c* 1.02, chloroform); ^{1}H-n.m.r. data: δ 5.39 (s, 1 H, H-1), 5.39 (t, 1 H, *J* 9.8 Hz, H-3′), 5.21 (d, 1 H, *J* 3.6 Hz, H-1′), 3.40 (br d, 1 H, H-4), and 2.15, 2.07, and 2.05 (s, 12 H, 4 OAc).

Anal. Calc. for $C_{27}H_{32}O_{15}$: C, 54.36; H, 5.41. Found: C, 54.24; H, 5.33.

*2,3,2′,3′-Tetra-O-acetyl-1,6-anhydro-6′-O-benzoyl-4′-O-*p*-tolylsulfonyl-β-maltose* (**12**). — To a solution of **11** (61 mg, 0.10 mmol) in dry pyridine (1 mL) was added *p*-toluenesulfonyl chloride (171 mg, 0.90 mmol), and the mixture was stirred for 45 h at room temperature. The mixture was poured into ice–water, the aqueous solution was extracted with ethyl acetate, and the extract solution was processed conventionally to give **12** (71 mg, 95%) as a syrup, $[\alpha]_D^{19}$ +47° (*c* 0.96, chloroform); ^{1}H-N.m.r. data: δ 5.62 (t, 1 H, *J* 9.2 Hz, H-3′), 5.34 (s, 1 H, H-1), 5.19 (d, 1 H, *J* 4 Hz, H-1′), 4.17 (dd, 2 H, *J* 4.5 and 12 Hz, C*H*$_2$OBz), 3.81 (d, 1 H, *J* 7.8 Hz, H-6endo), 3.51 (dd, 1 H, *J* 6 and 7.8, H-6exo), 3.36 (s, 1 H, H-4), 2.36 (s, 3 H, tosyl methyl), and 2.09–2.00 (clusters of singlets, 12 H, 4 OAc).

Anal. Calc. for $C_{34}H_{38}SO_{17}$: C, 54.40; H, 5.10; S, 4.27. Found: C, 54.61; H, 5.16; S, 3.99.

*1,6-Anhydro-4-O-(3,4-anhydro-α-*D*-galactopyranosyl)-β-*D*-glucopyranose* (**13**). — To a solution of **12** (861 mg, 1.15 mmol) in chloroform (5 mL) was added methanolic sodium methoxide (5 mL, containing 50 mg of sodium), and the mixture was stirred for 4 h at 5°. The mixture was made neutral with carbon dioxide, evaporated, and the residue was dissolved in water. The aqueous solution was washed with petroleum ether and evaporated, and the residue was chromatographed on silica gel with 3:1 chloroform–methanol to give, after crystallization, **13** (249 mg, 71%) as prisms, m.p. 155–157°, $[\alpha]_D^{20}$ +18° (*c* 0.52, in methanol).

Anal. Calc. for $C_{12}H_{18}O_9 \cdot 0.5\ H_2O$: C, 45.71; H, 6.07. Found: C, 45.55; H, 6.15.

Acetylation of **13** (34 mg) gave the diacetate **14** (53 mg, 100%) as a syrup, $[\alpha]_D^{20}$ +26° (*c* 0.66, chloroform); ^{1}H-n.m.r. data: δ 5.36 (s, 1 H, H-1), 5.14 (d, 1 H, *J* 4.5 Hz, H-1′), 3.92 (dd, 1 H, *J* 0.9 and 7.4 Hz, H-6endo), 3.72 (dd, 1 H, *J* 5.4 and 7.4 Hz, H-6exo), 3.41 (s, 1 H, H-4), and 2.17–2.09 (clusters of singlets, 12 H, 4 OAc).

Anal. Calc. for $C_{20}H_{26}O_{13}$: C, 50.63; H, 5.52. Found: C, 50.25; H, 5.47.

Condensation of **13** *with* **7**. — A mixture of **13** (240 mg, 0.78 mmol), **7** (200 mg, 0.78 mmol), and 2-propanol (1.5 mL) was heated in a sealed tube for 50 h at 120°. The mixture was processed as described for the condensation of **5** with **7**. The products were purified by conversion into the nona-*O*-acetyl derivatives. Chromatography on silica gel gave first *N*-[(1*S*)-(1,4,6/5)-4,5,6-triacetoxy-3-acetoxymethyl-2-cyclohexenyl)-(1→3)-*O*-(2,4,6-tri-*O*-acetyl-3-amino-3-deoxy-α-D-gulopyranosyl)-(1→4)-2,3-di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (**16a**, 141 mg, 21%) as a syrup, $[\alpha]_D^{22}$ +28° (*c* 0.63, chloroform); ^{1}H-n.m.r. data: δ (d, 1 H, *J* 4.7 Hz, H-2″), 3.15 (t, 1 H, *J* 4.2 Hz, H-3′), 2.84 (br s, 1 H, NH), and 2.11–2.02 (clusters of singlets, 27 H, 9 OAc).

The second fraction gave the diastereoisomer **16b** (107 mg, 16%) of **16a** as a syrup, $[\alpha]_D^{22}$ −6° (*c* 1.46, chloroform); ^{1}H-n.m.r. data: δ 6.15 (d, 1 H, *J* 5 Hz, H-2″), 5.22 (d, 1 H, *J* 3.8 Hz, H-1′), 3.47 (br s, 1 H, H-4), 3.07 (t, *J* 4.2 Hz, H-3′), and 2.18–2.03 (clusters of singlets, 27 H, 9 OAc).

The third fraction gave 2,3,2′,3′,6′-penta-*O*-acetyl-1,6-anhydro-4′-deoxy-4′-[(1*S*)-(1,4,6/5)-4,5,6-triacetoxy-3-acetoxymethyl-2-cyclohexenyl]amino-β-maltose (**15a**, 87 mg, 13%) as a syrup, $[\alpha]_D^{22}$ +61° (*c* 0.86, chloroform); ^{1}H-n.m.r. data: δ 5.94 (d, 1 H, *J* 5.3 Hz, H-2″), 5.42 (s, 1 H, H-1), 5.34 (t, 1 H, *J* 10 Hz, H-3′), 5.14 (d, 1 H, *J* 4 Hz, H-1′), 3.41 (br s, 1 H, H-4), 2.76 (t, 1 H, *J* 9.8 Hz, H-4′), and 2.14–2.00 (clusters of singlets, 27 H, 9 OAc).

The fourth fraction gave the diastereoisomer **15b** (94 mg, 14%) of **15a** as a syrup, $[\alpha]_D^{22}$ +8° (c 1.04, chloroform); ^{1}H-n.m.r. data: δ 5.80 (d, 1 H, J 5 Hz, H-2″), 5.13 (d, 1 H, J 3.8 Hz, H-1′), 3.40 (br s, 1 H, H-4), 2.72 (t, 1 H, J 9.8 Hz, H-4′), and 2.14–1.98 (clusters of singlets, 27 H, 9 OAc).

Anal. Calc. for $C_{37}H_{49}NO_{22}$: C, 51.69; H, 5.74; N, 1.63. Found for **15a**: C, 51.88; H, 5.72; N, 1.48. Found for **15b**: C, 51.95; H, 5.72; N, 1.49. Found for **16a**: C, 51.88; H, 5.79; N, 1.41. Found for **16b**: C, 51.51; H, 5.73; N, 1.43.

1,2,3,6,2′,3′,6′-Hepta-O-acetyl-4′-deoxy-4′-[*(1S)-(1,4,6/5)-4,5,6-triacetoxy-3-acetoxymethyl-2-cyclohexenyl*]*amino-α-maltose* (**17a**) *and its diastereoisomer* (**17b**). — A mixture of **15a** (46 mg) and 2.2 mL of a 30:70:1 (v/v) mixture of acetic acid–acetic anhydride–conc. sulfuric acid was stirred for 2 h at room temperature. The mixture was poured into ice–water, the aqueous solution was extracted with ethyl acetate, the extract was washed with aqueous sodium hydrogencarbonate and water, dried, and evaporated to give **17a** (51 mg, 99%) as a syrup, which was shown, by its ^{1}H-n.m.r. spectrum, to contain a trace of the β anomer, $[\alpha]_D^{17}$ +93° (c 0.94, chloroform); ^{1}H-n.m.r. data (200 MHz, $CDCl_3$) see ref. 1.

Compound **15b** (31 mg) was subjected to acetolysis to give **17b** as already described: yield 34 mg (98%) as a syrup, $[\alpha]_D^{17}$ +47° (c 1.38, chloroform); ^{1}H-n.m.r. data (200 MHz, $CDCl_3$) see ref. 1.

Anal. Calc. for $C_{41}H_{55}NO_{25}$: C, 51.20; H, 5.76; N, 1.46. Found for **17a**: C, 50.92; H, 5.72; N, 1.22. Found for **17b**: C, 50.85; H, 5.65; N, 1.22.

*4′-Deoxy-4′-[(1S)-(1,4,6/5)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl]aminomaltose (***2a***, adiposin-1) and its diastereoisomer* (**2b**). — Compound **17a** (33 mg) was treated with M methanolic sodium methoxide (0.3 mL) for 2 h at room temperature and the product was eluted from a column of Dowex 50W X2 (H^+) resin with 1.5% methanolic ammonia to give **2a** (17 mg, 99%) as a syrup, $[\alpha]_D^{22}$ +127° (c 1.0, H_2O) [lit.[7] $[\alpha]_D$ +139° (c 1.0, H_2O)]; R_F 0.45 in 12:8:5 1-butanol–pyridine–H_2O, R_F 0.35 in 3:2:2 1-butanol–ethanol–H_2O (cf. D-glucose, R_F 0.60 and 0.54, respectively). The ^{1}H-n.m.r. spectrum (400 MHz, D_2O) was shown to be superposable on that reported for an authentic sample.

Compound **17b** (54 mg) was similarly O-deacetylated to give **2b** (27 mg, 97%) as a syrup, $[\alpha]_D^{20}$ +26° (c 1.27, H_2O).

Anal. Calc. for $C_{19}H_{33}NO_{14} \cdot 0.5\ H_2O$: C, 44.88; H, 6.74; N, 2.75. Found for **2a**: C, 44.48; H, 6.39; N, 2.74. Found for **2b**: C, 44.88; H, 6.35; N, 2.50.

Condensation of **13** *with* DL-*di-O-(isopropylidene)validamine* (**18**). — A mixture of **13** (52 mg, 0.17 mmol), **18** (44 mg, 0.17 mmol), N,N-dimethylformamide (0.2 mL), and 2-propanol (0.2 mL) was heated in a sealed tube for 60 h at 120°. The condensates were deacetonated and then acetylated as described for the preparation of **8a,b** and **9a,b**, and the products were separated on a column of silica gel to give first N-[(1S)-(1,2,4/3,5)-2,3,4-triacetoxy-5-(acetoxymethyl)cyclohexyl]-(1→3)-O-(2,4,6-tri-O-acetyl-3-amino-3-deoxy-α-D-gulopyranosyl)-(1→4)-2,3-di-O-acetyl-1,6-anhydro-β-D-glucopyranose (**20a**, 38 mg, 26%) as a syrup, $[\alpha]_D^{23}$ +60° (c 1.96, chloroform); ^{1}H-n.m.r. data: δ 5.44 (t, 1 H, J 9.8 Hz, H-3″), 5.29 (s, 1 H, H-1), 5.19

(d, 1 H, *J* 3.5 Hz, H-1′), 2.99 (t, 1 H, *J* 4.4 Hz, H-3′, appears on deuteration), and 2.14–1.96 (clusters of singlets, 27 H, 9 OAc).

The second fraction gave a mixture (72 mg, 49%), which were *O*-deacetylated and then separated by elution from a column of Dowex 50W X2 (H^+) resin with water. The faster-moving fraction gave, after acetylation, the diastereoisomer **20b** (38 mg, 26%) of **20a** as a syrup, $[\alpha]_D^{17}$ −11° (*c* 1.38, chloroform); ^{1}H-n.m.r. data: δ 5.49 (t, 1 H, *J* 9 Hz, H-3″), 5.38 (s, 1 H, H-1), 3.29 (m, 1 H, H-1″), 3.12 (t, 1 H, *J* 4 Hz, H-3′, appears on deuteration), and 2.12–1.95 (clusters of singlets, 27 H, 9 OAc).

The slower-moving fraction gave, after acetylation 2,3,2′,3′,6′-penta-*O*-acetyl-1,6-anhydro-4′-deoxy-4′-[(1*S*)-(1,2,4/3,5)-2,3,4-triacetoxy-5-(acetoxymethyl)cyclohexyl]amino-β-maltose (**19a**, 32 mg, 22%) as a syrup, $[\alpha]_D^{27}$ +69° (*c* 0.62, chloroform); ^{1}H-n.m.r. data: δ 5.42 (s, 1 H, H-1), 5.12 (d, 1 H, *J* 3.8 Hz, H-1′), 3.41 (s, 1 H, H-4), 2.78 (t, 1 H, *J* 10.5 Hz, H-4′, appears on deuteration), 2.15–1.95 (clusters of singlets, 27 H, 9 OAc).

The third fraction gave the diastereoisomer **19b** (37 mg, 25%) of **19a** as a syrup, $[\alpha]_D^{23}$ −4° (*c* 3.12, chloroform); ^{1}H-n.m.r. data: δ 5.41 (s, 1 H, H-1), 5.24 (t, 1 H, *J* 9.6 Hz, H-3′), 5.30 (t, 1 H, *J* 9.8 Hz, H-3″), 5.12 (d, 1 H, *J* 3.8 Hz, H-1′), 4.21 (s, 1 H, H-4), 2.76 (t, 1 H, *J* 10 Hz, H-4′, appears on deuteration), 2.19–1.97 (clusters of singlets, 27 H, 9 OAc).

Anal. Calc. for $C_{37}H_{51}NO_{22}$: C, 51.57; H, 5.97; N, 1.63. Found for **19a**: C, 51.35; H, 5.97; N, 1.51. Found for **19b**: C, 51.28; H, 5.93; N, 1.81. Found for **20a**: C, 51.34; H, 5.90; N, 1.62. Found for **20b**: C, 51.57; H, 5.92; N, 1.53.

*1,2,3,6,2′,3′,6′-Hepta-O-acetyl-4′-deoxy-4′-[(1S)-(1,2,4/3,5)-2,3,4-triacetoxy-5-(acetoxymethyl)-cyclohexyl]amino-α-*maltose (**21a**) *and its diastereoisomer* (**21b**). — Compound **19a** (50 mg) was subjected to acetolysis and the mixture was processed conventionally to give **21a** (51 mg, 91%) as a syrup, $[\alpha]_D^{25}$ +113° (*c* 1.26, chloroform); ^{1}H-n.m.r. data see Table I.

Compound **21b** was obtained similarly from **19b** (59 mg); yield 63 mg (96%) as a syrup, $[\alpha]_D^{25}$ +51° (*c* 1.23, chloroform); ^{1}H-n.m.r. data see Table I.

Anal. Calc. for $C_{41}H_{57}NO_{25}$: C, 51.09; H, 5.96; N, 1.45. Found for **21a**: C, 51.38; H, 5.99; N, 1.36. Found for **21b**: C, 51.07; H, 5.93; N, 1.36.

4′-Deoxy-4′-[(1S)-(1,2,4/3,5)-2,3,4-trihydroxy-5-(hydroxymethyl)-cyclohexyl]aminomaltose (**22a**) *and its diastereoisomer* (**22b**). — Compound **21a** (21 mg) was *O*-deacetylated and purified as described for the preparation of **2a** to give **22a** (11 mg, 100%) as a white powder, $[\alpha]_D^{25}$ +91° (*c* 0.53, H_2O); R_F 0.37 in 12:8:5 1-butanol–pyridine–H_2O.

Compound **22b** was similarly obtained from **21b** (16 mg); yield 8 mg (94%), $[\alpha]_D^{25}$ +33° (*c* 0.41, H_2O); R_F 0.29 in 12:8:5 1-butanol–pyridine–H_2O.

Anal. Calc. for $C_{19}H_{35}NO_{14}$: C, 45.51; H, 7.04; N, 2.79. Found for **22a**: C, 45.55; H, 6.75; N, 2.69. Found for **22b**: C, 45.76; H, 6.82; N, 3.06.

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