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TOTAL SYNTHESIS OF ACARBOSE AND ADIPOSIN-2*

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ABSTRACT

The first total synthesis is described of the α-D-glucosidase inhibitor acarbose (**1a**). 1,6-Anhydro-4′-*O*-(3,4-anhydro-6-deoxy-α-D-galactopyranosyl)-β-maltose (**21**), prepared from 1,6-β-maltotriose (**3a**), and (+)-4,7:5,6-di-*O*-isopropylidene-valienamine (**28**) gave two pseudo-tetrasaccharide derivatives separable as the per-*O*-acetyl derivatives (**29** and **31**) by chromatography, and their structures were established on the basis of ^{1}H-n.m.r. spectroscopy. On acetolysis followed by acetylation, **29** afforded the peracetate (**1b**), which was *O*-deacetylated to give **1a**. Likewise, adiposin-2 (**2a**), the 6″-hydroxy analogue of **1a**, isolated from fermentation broth of *Streptomyces calvus* TM-521, was synthesised.

INTRODUCTION

Acarbose[2] (**1a**), a pseudo-tetrasaccharide produced by *Actinomycetales* strains, is a potent inhibitor of intestinal α-D-glucosidases and saccharases *in vitro*[3], which may find use as an oral antidiabetic agent. Adiposin-2 (**2a**), the 6″-hydroxy analogue of **1a**, is one of the homologues of adiposin[4], an α-D-glucosidase inhibitor produced by *Streptomyces calvus*. There has been considerable interest in the chemistry and biochemistry of this class of inhibitor[5], and there have been extensive studies of synthesis[6–11] in order to elucidate the structure–activity relationship and mechanism of action of enzymes.

We now report the first total synthesis of **1a** and **2a** in an extension of previous work on the synthesis of amylostatin[9] (XG) and adiposin-1[8], showing its applicability to higher homologues.

RESULTS AND DISCUSSION

The protected anhydro derivatives **21** and **23**, needed as synthons for **1a** and

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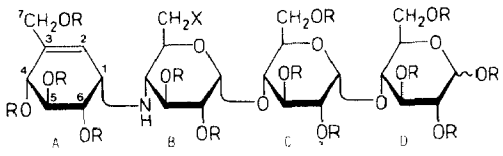
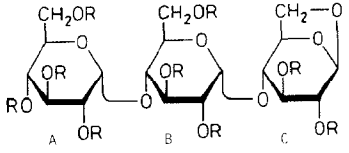


1a R = H; X = H
1b R = Ac; X = H
2a R = H; X = OH
2b R = Ac; X = OAc



3a R = H
3b R = Ac

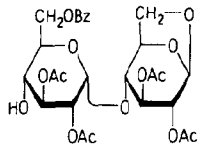
2a, respectively, were obtained from 1,6-anhydromaltotriose[12] (**3a**) which was prepared as follows.

Condensation of 2,3,2′,3′-tetra-*O*-acetyl-1,6-anhydro-6′-*O*-benzoyl-β-maltose[3] (**4**) with 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose[13] (**5**) in dichloromethane in the presence of trimethylsilyl trifluoromethanesulfonate and molecular sieve type 4A for 24 h at room temperature gave, after chromatography, the trisaccharide derivatives **7** and **11**, and 43% of **4** was recovered. Hydrogenolysis (Pd/C) of **7** and **11** gave the respective penta-acetates **8** (20%) and **12** (22%). Use of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose[14] (**6**) as a glycosyl donor under similar conditions did not improve the yields of products. Thus, the resulting mixture of **9** and **13** was hydrogenolysed to give the tetra-acetates **10** (22%) and **13** (10%). *O*-Deacylation of **8** or **10** with methanolic sodium methoxide followed by acetylation afforded 1,6-anhydro-β-maltotriose nona-acetate[12] (**3b**). The corresponding β-anomer **15** was obtained similarly from **12** or **14**.

In the ^{1}H-n.m.r. spectra (400 MHz, $CDCl_3$; Table I) the doublets due to H-1″ of **3b** and **15** appeared at δ 5.42 (*J* 3.9 Hz) and 5.15 (*J* 9.3 Hz), respectively, indicative of the structures assigned.

Alternatively, **3b** was readily accessible from maltotriose by a four-step sequence[12,15].

Treatment of **3a** with 1.3 equiv. of α,α-dimethoxytoluene in *N,N*-dimethylformamide in the presence of *p*-toluenesulfonic acid at 60° gave, after acetylation followed by chromatography, 58% of the 4″,6″-*O*-benzylidene derivative[7] **16**. The diol **17**, obtained in 75% yield by *O*-debenzylidenation of **16** with aqueous 80% acetic acid at 50°, was treated with 4 equiv. of methanesulfonyl chloride in pyridine at room temperature. The resulting dimesylate was treated with an excess of sodium iodide in boiling acetonitrile to give the 6″-iodide, which was hydrogenolysed (Raney nickel) to give 95% of the crystalline 6″-deoxy derivative **18**, the



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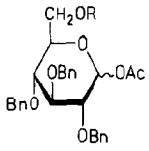
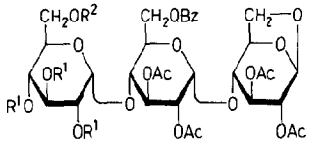
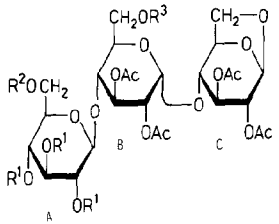


5 R = Ac
6 R = Bn



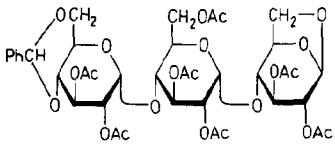
7 R^1 = Bn; R^2 = Ac
8 R^1 = H; R^2 = Ac
9 R^1 = R^2 = Bn
10 R^1 = R^2 = H



11 R^1 = Bn; R^2 = Ac; R^3 = Bz
12 R^1 = H; R^2 = Ac; R^3 = Bz
13 R^1 = R^2 = Bn; R^3 = Bz
14 R^1 = R^2 = H; R^3 = Bz
15 R^1 = R^2 = R^3 = Ac

^{1}H-n.m.r. spectrum of which contained a doublet (δ 1.32, J 5.7 Hz) due to the CHMe group. Selective benzoylation of HO-6″ of **17** was effected by treatment with 1.2 equiv. of benzoyl chloride at room temperature (5 days), and the product was converted into the 4″-mesylate **19** (95% overall yield).

Treatment of **18** with M sodium methoxide in 1:1 chloroform–methanol at 50°



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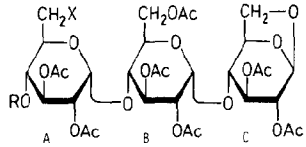
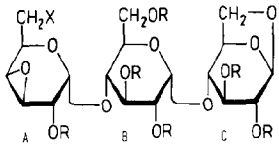
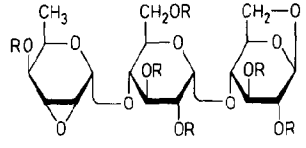


17 R = H; X = OH
18 R = Ms; X = H
19 R = Ms; X = OBz



20 R = Ac; X = H
21 R = X = H
22 R = Ac; X = OAc
23 R = H; X = OH



24 R = Ac
25 R = H

TABLE I

^{1}H-N.M.R. DATA[a]

Proton		*Chemical shifts (p.p.m.)*		J	*Coupling constants*	
		3b	**15**		**3b**	**15**
	1	5.42 d	5.15 d	1,2	3.9	9.3
	2	4.88 dd	4.94 dd	2,3	10.7	7.8
	3	5.37 dd	4.55 dd	3,4	9.8	9.3
A	4	5.08 t	5.08 dd	4,5	9.8	9.8
	5	[b]	2.66 ddd	5,6a	3.2	4.2
	6a	4.25 dd	4.38 dd	5,6b	2.4	2.2
	6b	4.06 dd	4.06 dd	6gem	12.7	12.5
	1	5.19 d	5.19 d	1,2	3.4	3.9
	2	4.72 dd	4.77 dd	2,3	10.3	10.3
	3	5.57 dd	5.51 dd	3,4	9.1	9.5
B	4	3.98 t	1.74 t	4,5	9.1	9.5
	5	4.39 dt	4.34 ddd	5,6a	2.7	~0
	6a	4.51 dd	4.56 d	5,6b	3.9	4.9
	6b	4.22 dd	4.10 dd	6gem	12.7	12.2
	1	5.50 s	5.45 s	1,2	0	0
	2	4.60 s	4.57 s	2,3	0	0
	3	4.84 s	4.80 s	3,4	0	0
C	4	3.48 s	3.43 s	4,5	0	0
	5	4.78 d	4.72 d	5,6a	0	0
	6a	3.99 d	3.96 d	5,6b	5.9	5.9
	6b	3.81 dd	3.77 dd	6gem	7.3	7.3
	Ac	2.21	2.19			
		2.14	2.11			
		2.10(2)	2.095			
		2.05(2)	2.09			
		2.03	2.07			
		2.01	2.04			
		2.00	2.03			
			2.01			
			1.99			

[a]See formulas for designation of the sugar moieties. [b]Overlapped with the resonance of H-4 of B and that of H-6 of C (at 4.00–3.97 p.p.m.).

gave rise to a mixture of epoxides which was acetylated. Column chromatography then gave the epoxide **20** (65%) together with the epoxide **24** (~10%) formed by epoxide-group migration. The ^{1}H-n.m.r. spectrum (Table II) of **20** contained signals at δ 3.28 (d, J 3.9 Hz) and 3.18 (dd, J 2 Hz) due to the epoxide protons H-3″ and H-4″, respectively. The signals of the epoxide protons of **24** appeared at δ 3.38 and 3.22 (2 t, J 2.9 Hz). Crude **20** was *O*-deacetylated with methanolic sodium methoxide at 0° to give, quantitatively, the epoxide **21** slightly contaminated with its isomer **25**. In contrast, treatment of **19** with methanolic sodium methoxide

TABLE II

^{1}H-N.M.R. DATA[a]

Proton		*Chemical shifts (p.p.m.)*			
		18	**19**	**20**	**22**
A	1	5.33 d	5.42 d	5.09 d	5.14 d
	2	4.81 dd	4.87 dd	4.83 d	4.85 d
	3	5.40 dd	5.50 dd	3.28 d	3.32 s
	4	4.39 t	4.91 t	3.18 dd	(2H)
	5	3.88 dq	4.13 dt	4.20 qd	4.36
	6a		4.64 dd		
	6b		4.46 dd		4.26
	CH_3	1.32 d		1.31 d	
B	1	5.18 d	5.19 d	5.18 d	5.18 d
	2	4.72 dd	4.70 dd	4.74 dd	4.74 dd
	3	5.57 dd	5.57 dd	5.53 t	5.52 t
	4	4.02 t	4.01 dd	3.89 t	3.88 t
	5	4.40 dt	4.40 dt	4.30 ddd	4.19 ddd
	6a	4.52 dd	4.53 dd	4.51 dd	4.56 dd
	6b	4.19 dd	4.20 dd	4.20 dd	4.15 dd
C	1	5.50 s	5.49 s	5.47 s	5.48 s
	2	4.60 s	4.60 s	4.57 s	4.57 s
	3	4.84 s	4.83 s	4.81 s	4.81 s
	4	3.48 s	3.48 s	3.44 s	3.44 s
	5	4.77 d	4.77 d	4.73 d	4.73 d
	6a	3.99 d	3.99 d	3.97 d	3.97 d
	6b	3.81 dd	3.81 dd	3.78 dd	3.78 dd
	Ac	2.21	2.21	2.19	2.19
		2.13	2.16	2.13	2.13
		2.10	2.10	2.11	2.12
		2.07	2.095	2.095	2.10
		2.05	2.05	2.05	2.095
		2.04	2.04	2.04	2.05
		2.01	2.00		2.045
		Ms 3.30	Ms 3.05		
			Bz		
			o- 8.08 d		
			p- 7.59 t		
			m- 7.46 t		

J		*Coupling constants (Hz)*			
		18	**19**	**20**	**22**
A	1,2	3.9	3.9	3.7	2.9
	2,3	10.7	10.7	0	0
	3,4	9.8	9.7	3.9	0
	4,5	9.8	9.7	2	0
	5,6a	5.7	2	6.8	
	5,6b		2.9		
	6gem		12.7		

TABLE II *(continued)*

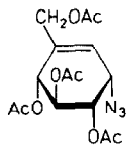
	1,2	3.9	3.9	3.7	3.9
	2,3	10.3	10.3	9.9	9.8
	3,4	9	9.5	9.9	9.8
B	4,5	9	9.5	9.9	9.8
	5,6a	2.4	2.4	2	1.9
	5,6b	3.4	3.7	4.4	4.9
	6gem	12.2	12.2	12.2	12.2
	1,2	0	0	0	0
	2,3	0	0	0	0
	3,4	0	0	0	0
C	4,5	0	0	0	0
	5,6a	0	0	0	0
	5,6b	5.5	5.9	5.9	5.9
	6gem	7.3	7.3	7.7	7.8

[a]See formulas for designation of the sugar moieties.

followed by acetylation gave the 3,4-epoxide **22** (76%) selectively. In the ^{1}H-n.m.r. spectrum, the resonance of the epoxide protons of **22** appeared at δ 3.32 (s, 2 H). *O*-Deacetylation of **22** gave **23**.

The amine synthone (+)-4,7:5,6-di-*O*-isopropylidenevalienamine (**28**, 61%) was derived from (1*S*)-(1,3,6/2)-4-acetoxymethyl-1,2,3-tri-*O*-acetyl-6-azido-4-cyclohexene-1,2,3-triol[16] (**26**) by the sequence: *O*-deacetylation followed by isopropylidenation (→ **27**) and reduction with hydrogen sulfide (→ **28**).

The condensation of **21** with a slight excess of **28** was carried out in 1:1 *N*,*N*-dimethylformamide–2-propanol in a sealed tube for 70 h at 120°. The products were *O*-deisopropylidenated and then acetylated to give, after chromatography, the pseudo-tetrasaccharide derivatives **29** (19%) and **31** (30%). In the ^{1}H-n.m.r.



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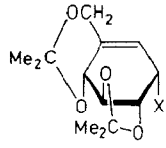
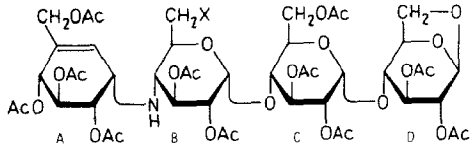
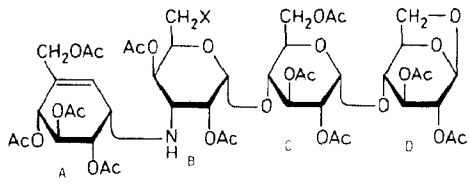


27 X = N_3
28 X = NH_2



29 X = H
30 X = OAc



31 X = H
32 X = OAc

TABLE III

^{1}H-N.M.R. DATA[a]

Proton		*Chemical shifts (p.p.m.)*					
		29	**30**	**31**	**32**	**1b**	**2b**
	1	3.72 t	3.69 t	3.51 t	3.58 t	3.72 t	3.70 t
	2	5.96 d	5.96 d	6.05 d	6.08 d	5.96 d	5.96 d
	4	5.60 d	5.59 d	5.72 d	5.69 d	5.61 d	5.59 d
A	5	5.57 dd	5.55 dd	5.56 dd	5.56 dd	5.56 dd	5.54 dd
	6	4.93 dd	4.97 dd	4.92 dd	5.00 dd	4.93 dd	4.91 dd
	7a	4.66 d	4.63 d	4.71 d	4.69 d	4.66 d	4.63 d
	7b	4.38 d	4.35 d	4.42 d	4.43 d	4.38 d	4.35 d
	1	5.26 d	5.32 d	5.29 d	5.33 d	5.25 d	5.31 d
	2	4.80 dd	4.84 t	4.96 dd	4.99 t	4.77 dd	4.81 dd
	3	5.12 t	5.18 q	2.98 q	3.04 q	5.12 dd	5.20 t
B	4	2.39 t	2.81 q	[b]	4.71 d	2.38 t	2.81 t
	5	3.57 dq	3.68 dt	4.33 q	4.45 t	3.51 dq	3.61 bd
	6a		4.35 dd		4.15 dd		3.92 d
	6b		4.24 dd		4.11 dd		
	CH_3	1.21 d		1.13 d		1.21 d	
	1	5.17 d	5.18 d	5.15 d	5.16 d	5.31 d	5.31 d
	2	4.73 dd	4.71 dd	4.80 dd	4.80 dd	4.75 dd	4.73 dd
	3	5.54 t	5.53 dd	5.55 dd	5.56 t	5.52 t	5.52 t
C	4	3.98 t	3.95 t	4.15 t	4.07 t	3.95 t	4.33 t
	5	4.36 bdt	4.37 bdt	4.24 bdt	4.25 dt	3.90 dt	4.19 dt
	6a	4.53 dd	4.52 dd	4.86 dd	4.89 d	4.49 dd	4.49 dd
	6b	4.21 dd	4.19 dd	4.29 dd	4.2 dd	4.17 dd	4.19 dd
	1	5.50 s	5.50 s	5.42 s	5.43 s	6.24 d	6.24 d
	2	4.59 s	4.60 s	4.50 s	4.51 s	4.96 dd	4.96 dd
	3	4.84 s	4.83 s	4.69 s	4.83 s	5.39 dd	5.39 m
D	4	3.48 s	3.48 s	3.41 s	3.43 s	4.05 t	4.04 t
	5	4.78 d	4.78 d	4.80 d	4.82 d	4.14 dt	4.13 dt
	6a	3.99 d	4.00 d	3.96 d	3.97 d	4.48 dd	4.46 dd
	6b	3.81 dd	3.82 dd	3.77 dd	3.78 dd	4.28 dd	4.29 dd
	Ac	2.19	2.19	2.39	2.37	2.24	2.24
		2.13	2.15	2.15	2.13	2.19	2.18
		2.11	2.12(2)	2.13	2.12	2.16	2.17
		2.10	2.10	2.12	2.10	2.12	2.11(2)
		2.06	2.07	2.09(2)	2.095	2.08	2.06
		2.05	2.06	2.07	2.09	2.04(3)	2.05(2)
		2.04	2.04(2)	2.06	2.07(2)	2.02(3)	2.045
		2.03	2.03	1.99	2.06	2.01	2.03
		2.02	2.02	1.98	2.00	1.99	2.02
		2.01	1.99	1.97	1.99		2.005
		1.99		NH 3.18 d	1.97		2.00
					NH 3.07 d		1.99

TABLE III *(continued)*

J		*Coupling constants (Hz)*					
		29	**30**	**31**	**32**	**1b**	**2b**
	1,2	4.7	4.9	4.9	4.9	4.4	4.7
	4,5	6.8	6.9	7.3	7.5	6.8	6.6
A	5,6	9.8	10.3	10.7	10.6	10.5	9.8
	6,1	4.7	4.9	4.9	4.9	4.7	4.7
	7gem	13.4	12.7	12.7	13.2	12.9	13.2
	1,2	4.1	3.9	3.9	4.2	3.9	3.9
	2,3	10.3	10.7	3.9	4.2	10	10.3
	3,4	10.3	10.7	3.9	4.2	10	10.3
B	4,5	10.3	10.7	~0	~0	10	10.3
	5,6a	5.9	3.9	6.4	6.8	6.3	5.4
	5,6b		4.2		5.8		
	6gem		12.5		10.7		0
	1,2	3.7	3.9	3.6	3.9	3.9	3.9
	2,3	9.9	10.2	10.3	10.4	10.3	9.8
	3,4	9.9	9.5	9.5	10.4	9.3	9.8
C	4,5	9.9	9.5	9.5	10.4	9.3	9.8
	5,6a	2.2	2.4	1.7	0	1.5	0
	5,6b	3.9	3.4	2.2	3.9	2.7	3.4
	6gem	12.3	12	12.5	10.8	12	12
	1,2	0	0	0	0	3.7	3.5
	2,3	0	0	0	0	10.1	9.8
	3,4	0	0	0	0	8.8	9.3
D	4,5	0	0	0	0	8.8	9.3
	5,6a	0	0	0	0	2.4	2.9
	5,6b	6.2	5.7	6.5	5.9	3.2	3.4
	6gem	7.2	7.8	7.3	7.7	12.3	12.2
	NH	0	10.7	3.9	4.2	0	0

[a]See formulas for designation of the sugar moieties A–D. [b]Overlapped with the signal of H-2 of D (at 4.50 p.p.m.).

spectra (Table III) of **29** and **31**, the signals for C*H*–NH–C*H* at δ 2.39 (t, J 10.3 Hz) and 2.98 (q, J 3.9 Hz) were consistent with the structures proposed.

Likewise, condensation of **23** and **28** and subsequent removal of protecting groups gave **30** (30%) and **32** (21%), the ^{1}H-n.m.r. spectra of which contained signals at δ 2.81 (q, J 10.7 Hz) and 3.04 (q, J 4.2 Hz) attributable to H-4″ and H-3″, respectively. Acetolysis of **29** with acetic anhydride–acetic acid–conc. sulfuric acid (70:30:1) at room temperature gave 96% of the acetylated derivative (**1b**) of acarbose (**1a**), the ^{1}H-n.m.r. spectrum (Table III) of which supported the structure proposed. *O*-Deacetylation of **1b** followed by purification on Dowex 50W-X2 (H^+) resin gave 59% of **1a**, which was identical to an authentic sample[2]. Likewise, **30** was converted into the acetylated derivatives (**2b**) of adiposin-2 (**2a**), the ^{1}H-n.m.r.

spectrum of which accorded with the structure proposed. *O*-Deacetylation of **2b** gave **2a**, which was identified by comparison of the ^{1}H-n.m.r. spectral data[4] with those reported for an authentic sample.

Condensation of the anhydro compound **23** with the amino **28** gave products of the diaxial and diequatorial opening of the epoxide in the ratio 1:1.6, in contrast to the reaction of **21** and **28** which gave mainly the diaxial product. Therefore, HO-6″ may be involved in stabilising the transition state that leads to diequatorial products.

EXPERIMENTAL

General methods. — Melting points were determined with a MEL-TEMP capillary melting-point apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-4 polarimeter. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Jeol JNM GX-400 FT (400 MHz) instrument, and the data are listed in Tables I–III. T.l.c. was performed on Silica Gel 60 GF (Merck) with detection by charring with sulfuric acid. Column chromatography was conducted on Wakogel C-200 (200 mesh) or C-300 (300 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated at <50° under diminished pressure.

*2,3,2′,3′,6″-Penta-*O*-acetyl-1,6-anhydro-6′-*O*-benzoyl-β-maltotriose* (**8**) *and 2,3,2′,3′-tetra-*O*-acetyl-4-*O*-(6-*O*-acetyl-β-*D*-glucopyranosyl)-1,6-anhydro-6′-*O*-benzoyl-β-maltose* (**12**). — A suspension of 2,3,2′,3′-tetra-*O*-acetyl-1,6-anhydro-6′-*O*-benzoyl-β-maltose[8] (**4**; 0.20 g, 0.34 mmol), 1,6-di-*O*-acetyl-tri-*O*-benzyl-D-glucopyranose (**5**; 0.36 g, 0.67 mmol), trimethylsilyl trifluoromethanesulfonate ($Me_3SiSO_3CF_3$; 0.17 mL, 0.81 mmol), powdered molecular sieve 4A (0.15 g), and dichloromethane (15 mL) was stirred for 24 h at room temperature, then filtered, washed successively with saturated aqueous $NaHCO_3$ and water, dried, and concentrated. Column chromatography (C-300, 30 g) of the residue (0.60 g) with 1:6 2-butanone–toluene gave **7** (80 mg) and **11** (51 mg) as amorphous powders, together with **4** (87 mg, 43%).

A solution of **7** (80 mg) in 1:9 ethanol–ethyl acetate (10 mL) was hydrogenolysed (3.4 kg/cm^2 of initial hydrogen pressure) in the presence of 10% Pd/C (60 mg) for 3 h at room temperature, then filtered, and concentrated. Column chromatography (C-300, 3 g) of the syrupy residue (60 mg) with 1:5 ethanol–toluene gave **8** (29 mg, 20% based on **4** consumed) as an amorphous powder, $[\alpha]_D^{21}$ +45° (*c* 1.4, chloroform).

Anal. Calc. for $C_{35}H_{44}O_{21}$: C, 52.50; H, 5.54. Found: C, 52.01; H, 5.48.

Similarly, **11** (51 mg) gave **12** (33 mg, 22% based on **4** consumed), $[\alpha]_D^{21}$ +3.9° (*c* 1.6, chloroform).

Anal. Calc. for $C_{35}H_{44}O_{21} \cdot H_2O$: C, 51.34; H, 5.66. Found: C, 51.68; H, 5.44.

*2,3,2′,3′-Tetra-*O*-acetyl-1,6-anhydro-6′-*O*-benzoyl-β-maltotriose* (**10**) *and 2,3,2′,3′-tetra-*O*-acetyl-1,6-anhydro-6′-*O*-benzoyl-4-*O*-β-D-glucopyranosyl-β-mal-*

tose (**14**). — Compound **4** (0.20 g, 0.34 mmol) and 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**6**; 0.39 g, 0.67 mmol) was treated with $Me_3SiSO_3CF_3$ (0.17 mL, 0.81 mmol) in the presence of molecular sieve 4A (0.15 g) in dichloromethane (15 mL) for 4 h at room temperature. The mixture was processed as described in the preparation of **7** and **11**, to give a mixture (62 mg, 16%) of **9** and **13** as an amorphous powder, and **4** (115 mg, 58%). The mixture was hydrogenolysed as described in the preparation of **8**. Column chromatography (C-300, 2.3 g) of the syrupy products (46 mg) with 1:6 ethanol–toluene gave, first, **14** (24 mg, 59%) as an amorphous powder, $[\alpha]_D^{22}$ +17° (*c* 1.2, chloroform).

Anal. Calc. for $C_{33}H_{42}O_{20}$: C, 52.24; H, 5.58. Found: C, 52.02; H, 5.47.

Eluted second was **10** (10 mg, 26%), isolated as a hygroscopic amorphous powder, $[\alpha]_D^{22}$ +42° (*c* 0.5, chloroform).

Anal. Calc. for $C_{33}H_{42}O_{20} \cdot 0.5\ H_2O$: C, 51.63; H, 5.64. Found: C, 51.41; H, 5.55.

1,6-Anhydro-β-maltotriose nona-acetate (**3b**). — A solution of **8** (25 mg, 0.031 mmol) in methanol (1 mL) containing methanolic M sodium methoxide (0.1 mL) was kept for 1 h at room temperature, then neutralised with acetic acid, and concentrated, and the residue was treated with pyridine and acetic anhydride (each 1 mL) overnight at room temperature. Column chromatography (C-300, 1 g) of the product with 1:1 ethyl acetate–toluene gave **3b** (27 mg) as an amorphous powder, $[\alpha]_D^{20}$ +73° (*c* 0.3, chloroform); lit.[12] $[\alpha]_D^{15}$ +82.4° (chloroform).

Anal. Calc. for $C_{36}H_{48}O_{24}$: C, 50.00; H, 5.60. Found: C, 50.06; H, 5.45.

Similarly, **10** (8.0 mg, 0.011 mmol) gave **3b** (10 mg).

1,6-Anhydro-β-maltotriose (**3a**). — Compound **3b** was *O*-deacetylated conventionally to give **3a**, m.p. 250–252°, $[\alpha]_D^{21}$ +122° (*c* 1, water); lit.[12] m.p. 254–254.5°, $[\alpha]_D^{15}$ +130.2° (water). Compound **3a** was prepared also from maltotriose[12].

1,6-Anhydro-4-O-β-D-glucopyranosyl-β-maltose nona-acetate (**15**). — Compound **12** (30 mg, 0.037 mmol) was treated with methanolic M sodium methoxide (0.2 mL) in methanol for 1 h at room temperature and processed, as described in the preparation of **3b**, to give **15** (32 mg) as an amorphous powder, $[\alpha]_D^{20}$ −3.2° (*c* 0.8, chloroform).

Anal. Calc. for $C_{36}H_{48}O_{24}$: C, 50.00; H, 5.60. Found: C, 50.54; H, 5.56.

Similarly, **14** (16 mg, 0.021 mmol) gave **15** (18 mg).

2,3,2′,3′,6′,2″,3″-Hepta-O-acetyl-1,6-anhydro-4″,6″-O-benzylidene-β-maltotriose (**16**). — A mixture of **3a** (0.87 g, 1.8 mmol), α,α-dimethoxytoluene (0.32 mL, 2.3 mmol), toluene-*p*-sulfonic acid monohydrate (0.1 g), and *N,N*-dimethylformamide (10 mL) was heated at 20 mmHg and 60° for 2 h, then neutralised with $NaHCO_3$, and concentrated, and the residue was acetylated in the usual manner. Column chromatography (C-200, 60 g) of the syrupy product (1.24 g) with 1:1 ethyl acetate–toluene gave **16** (0.90 g, 58%) as an amorphous powder, $[\alpha]_D^{25}$ +57° (*c* 1, chloroform).

Anal. Calc. for $C_{39}H_{48}O_{22}$: C, 53.92; H, 5.57. Found: C, 54.15; H, 5.68.

2,3,2′,3′,6′,2″,3″-Hepta-O-acetyl-1,6-anhydro-β-maltotriose (**17**). — A

mixture of **16** (0.90 g, 1.04 mmol) and aqueous 80% acetic acid (20 mL) was stirred for 3 h at 50° and then concentrated. Column chromatography (C-200, 23 g) of the product with 1:10 ethanol–toluene gave **17** (0.61 g, 75%) as an amorphous powder, $[\alpha]_D^{27}$ +70° (*c* 1, chloroform).

Anal. Calc. for $C_{39}H_{48}O_{22}$: C, 49.23; H, 5.68. Found: C, 49.36; H, 5.53.

2,3,2',3',6',2'',3''-Hepta-O-acetyl-1,6-anhydro-6''-deoxy-4''-O-methanesulfonyl-β-maltotriose (**18**). — Compound **17** (0.50 g, 0.64 mmol) was treated with methanesulfonyl chloride (0.20 mL, 2.6 mmol) in pyridine (10 mL) for 4 h at room temperature. The mixture was diluted with ethyl acetate (50 mL), washed successively with saturated aqueous $NaHCO_3$ and water, dried, and concentrated. A solution of the resulting dimesylate (0.59 g) and sodium iodide (0.57 g, 3.8 mmol in acetonitrile (25 mL) was heated at reflux for 4 h and then concentrated. A solution of the residue in ethyl acetate (50 mL) was washed with saturated aqueous sodium thiosulfate and water, then dried. Evaporation of the solvent gave a crude iodide (0.61 g), which was hydrogenolysed in ethyl acetate (15 mL) in the presence of Raney nickel T-4 and pyridine (1.5 mL) in a Parr apparatus (3.4 kg/cm^2 of initial hydrogen pressure) for 10 days at room temperature. The mixture was filtered and concentrated to give **18** (0.51 g, 95%) as thin needles, m.p. 205° (from AcOEt–EtOH), $[\alpha]_D^{25}$ +73° (*c* 1.2, chloroform).

Anal. Calc. for $C_{33}H_{46}O_{23}S$: C, 47.06; H, 5.50. Found: C, 46.76; H, 5.29.

2,3,2',3',6',2'',3''-Hepta-O-acetyl-1,6-anhydro-6''-O-benzoyl-4''-O-methanesulfonyl-β-maltotriose (**19**). — Compound **17** (0.56 g, 0.72 mmol) was treated with benzoyl chloride (0.1 mL, 0.86 mmol) in pyridine (25 mL) for 5 days at room temperature. Methanesulfonyl chloride (0.12 mL, 1.4 mmol) was then added to the ice-cooled mixture, which was stirred for 20 h at room temperature and then processed in the usual manner. Column chromatography (C-300, 23 g) of the product with 3:4 ethyl acetate–toluene gave **19** (0.65 g, 95%) as a hygroscopic amorphous powder, $[\alpha]_D^{26}$ +68° (*c* 1.1, chloroform).

Anal. Calc. for $C_{40}H_{50}O_{25}S \cdot 0.5\ H_2O$: C, 49.43; H, 5.29. Found: C, 49.21; H, 5.11.

2,3,2',3',6'-Penta-O-acetyl-4'-O-(2-O-acetyl-3,4-anhydro-6-deoxy-α-D-galactopyranosyl)- (**20**) *and -4'-O-(4-O-acetyl-2,3-anhydro-6-deoxy-α-D-gulopyranosyl)-1,6-anhydro-β-maltose* (**24**). — Compound **18** (384 mg, 0.46 mmol) was treated with methanolic M sodium methoxide (1.1 mL) in 1:1 dichloromethane–methanol (14 mL) for 1 h at 50°. The solution was neutralised with acetic acid and concentrated, and the residue was acetylated in the usual manner. Column chromatography (C-300, 17 g) of the products with 1:1 ethyl acetate–toluene gave **20** (209 mg, 64%) contaminated with ~10% of **24**, isolated as an amorphous powder.

Anal. Calc. for $C_{30}H_{40}O_{19}$: C, 51.14; H, 5.72. Found: C, 50.90; H, 5.56.

1,6-Anhydro-4'-O-(3,4-anhydro-6-deoxy-α-D-galactopyranosyl)- (**21**) *and -4'-O-(2,3-anhydro-6-deoxy-α-D-gulopyranosyl)-β-maltose* (**25**). — A mixture of crude **20** (172 mg, 0.24 mmol), methanolic 0.2M sodium methoxide (3.5 mL), and dichloromethane (3.5 mL) was stirred for 45 min at 0°, and then neutralised with

Amberlite IRA-120B (H^+) resin. The mixture was concentrated to give a mixture of **21** and **25** (113 mg, ~100%) as an amorphous powder.

2,3,2',3',6'-Penta-O-acetyl-1,6-anhydro-4'-O-(2,6-di-O-acetyl-3,4-anhydro-α-D-galactopyranosyl)-β-maltose (**22**). — Compound **19** (395 mg, 0.41 mmol) was treated with methanolic 0.5M sodium methoxide (8 mL) in dichloromethane (8 mL) for 45 min at room temperature. The mixture was processed as described in the preparation of **20**, to give **22** (238 mg, 76%) as an amorphous powder, $[\alpha]_D^{22}$ +28° (*c* 0.8, chloroform).

Anal. Calc. for $C_{32}H_{42}O_{21}$: C, 51.40; H, 5.21. Found: C, 49.97; H, 5.21.

1,6-Anhydro-4'-O-(3,4-anhydro-α-D-galactopyranosyl)-β-maltose (**23**). — Treatment of **22** (241 mg, 0.32 mmol) with methanolic 0.2M sodium methoxide (3.5 mL) in dichloromethane (3.5 mL), as in the preparation of **21** and **25**, gave **23** (139 mg, 94%) as an amorphous powder, $[\alpha]_D^{22}$ +50° (*c* 1, methanol).

(+)-4,7:5,6-Di-O-isopropylidenevalienamine (**28**). — (1*S*)-(1,3,6/2)-4-Acetoxymethyl-1,2,3-tri-*O*-acetyl-6-azido-4-cyclohexene-1,2,3-triol[16] (**26**; 273 mg, 0.74 mmol) was treated with methanolic M sodium methoxide (1 mL) in methanol (5 mL) for 6 h at room temperature. The solution was neutralised with Amberlite IRA-120B (H^+) resin, then concentrated. The residue was treated with 2,2-dimethoxypropane (1.7 mL) in the presence of toluene-*p*-sulfonic acid monohydrate in *N,N*-dimethylformamide (5 mL) to give **27** (141 mg, 68%) as a syrup, $[\alpha]_D^{22}$ +91° (*c* 2.7, chloroform). The structure was confirmed by comparison of the ^{1}H-n.m.r. spectrum with that of the racemate.

Anal. Calc. for $C_{13}H_{19}N_3O_4$: C, 55.51; H, 6.81; N, 14.94. Found: C, 55.32; H, 6.73; N, 14.82.

Compound **27** (103 mg, 0.37 mmol) was stirred for 6 h at room temperature in 1:1 pyridine–water (2 mL) saturated with hydrogen sulfide. The solution was then concentrated. Column chromatography (C-300, 1 g) of the residue with toluene → 1:5 ethanol–toluene gave **28** (89 mg, ~95%) as a crude syrup, $[\alpha]_D^{22}$ +65° (*c* 1.2, chloroform), the structure of which was confirmed by comparison of the ^{1}H-n.m.r. spectrum with that of the racemate.

2,3,2',3',6',2'',3''-Hepta-O-acetyl-1,6-anhydro-4'',6''-dideoxy-4''-[(1S)-(1,4,6/5)-4,5,6-triacetoxy-3-acetoxymethyl-2-cyclohexenylamino]-β-maltotriose (**29**) *and 2,3,2',3'-tetra-O-acetyl-1,6-anhydro-4'-{2,4-di-O-acetyl-3,6-dideoxy-3-[(1S)-(1,4,6/5)-4,5,6-triacetoxy-3-acetoxymethyl-2-cyclohexenylamino]-α-D-gulopyranosyl}-β-maltose* (**31**). — A mixture of **21** (79 mg, 0.17 mmol), **28** (54 mg, 0.21 mmol), 2-propanol (0.4 mL), and *N,N*-dimethylformamide (0.4 mL) was heated in a sealed tube for 70 h at 120°, then concentrated. The residue was treated with aqueous 70% acetic acid (4 mL) for 2 h at 55°, and the product was acetylated in the usual manner. Column chromatography (C-300, 11 g) of the products (211 mg) with 1:1 ethyl acetate–toluene gave, first, **31** (56 mg, 30% based on **21**) as an amorphous powder, $[\alpha]_D^{20}$ +58° (*c* 1.9, chloroform).

Anal. Calc. for $C_{48}H_{63}NO_{28}$: C, 51.79; H, 5.83; N, 1.64. Found: C, 51.35; H, 5.74; N, 1.64.

Eluted second was **29** (36 mg, 19% based on **21**), isolated as an amorphous powder, $[\alpha]_D^{24}$ +65° (*c* 1.6, chloroform).

Anal. Found: C, 51.84; H, 5.84; N, 1.52.

*2,3,2',3',6',2'',3'',6''-Octa-*O*-acetyl-1,6-anhydro-4''-deoxy-4''-[(1S)-(1,4,6/5)-4,5,6-triacetoxy-3-acetoxymethyl-2-cyclohexenylamino]-β-maltotriose* (**30**) *and 2,3,2',3',6'-penta-*O*-acetyl-1,6-anhydro-4'-*O*-{2,4,6-tri-*O*-acetyl-3-deoxy-3-[(1S)-(1,4,6/5)-4,5,6-triacetoxy-3-acetoxymethyl-2-cyclohexenylamino]-α-*D*-gulopyranosyl}-β-maltose* (**32**). — A mixture of **23** (50 mg, 0.11 mmol), **28** (32 mg, 0.13 mmol), 2-propanol (0.25 mL), and *N,N*-dimethylformamide (0.25 mL) was heated in a sealed tube for 67 h at 120°, and concentrated. The mixture was processed as in the preparation **29** and **31**, and column chromatography (C-300, 6.6 g) with 4:3 ethyl acetate–toluene gave, first, **32** (25 mg, 21% based on **23**) as an amorphous powder, $[\alpha]_D^{21}$ +39° (*c* 0.9, chloroform).

Anal. Calc. for $C_{49}H_{65}NO_{30}$: C, 51.26; H, 5.71; N, 1.22. Found: C, 51.55; H, 5.82; N, 1.50.

Eluted second was **30** (40 mg, 33% based on **23**), isolated as an amorphous powder, $[\alpha]_D^{24}$ +70° (*c* 1.8, chloroform).

Anal. Found: C, 51.13; H, 5.60; N, 1.41.

*1,2,3,6,2',3',6',2'',3''-Nona-*O*-acetyl-4''-6''-dideoxy-4''-[(1S)-(1,4,6/5)-4,5,6-triacetoxy-3-acetoxymethyl-2-cyclohexenylamino]-α-maltotriose* (**1b**). — Compound **29** (27 mg, 0.025 mmol) was treated with acetic anhydride–acetic acid–conc. sulfuric acid (70:30:1, 2 mL) for 2.5 h at room temperature. The solution was poured into ice–water (20 mL) and extracted with ethyl acetate (50 mL), and the extract was washed with saturated aqueous $NaHCO_3$ and water, dried, and concentrated to give **1b** (28 mg, 96%) as an amorphous powder, $[\alpha]_D^{21}$ +87° (*c* 1.4, chloroform).

Anal. Calc. for $C_{51}H_{69}NO_{31}$: C, 51.39; H, 5.83; N, 1.17. Found: C, 51.49; H, 5.93; N, 1.54.

4'',6''-Dideoxy-4''-[(1S)-(1,4,6/5)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenylamino]maltotriose (acarbose) (**1a**). — Compound **1b** (25 mg, 0.021 mmol) was stirred with methanolic M sodium methoxide (0.3 mL) in methanol (1 mL) for 2 h at room temperature. The mixture was eluted from a column of Dowex 50W-X2 (H^+) resin (1 mL) with water → 3% NH_4OH to give **1a** (7.8 mg, 59%), isolated as an amorphous powder, $[\alpha]_D^{18}$ +165° (*c* 0.4, water); lit.[2] $[\alpha]_D^{20}$ +171.3° (water). The ^{1}H-n.m.r. spectrum (400 MHz, D_2O) was identical to that reported[2].

*1,2,3,6,2',3',6',2'',3'',6''-Deca-*O*-acetyl-4''-deoxy-4''-[(1S)-(1,4,6/5)-4,5,6-triacetoxy-3-acetoxymethyl-2-cyclohexenylamino]-α-maltotriose* (**2b**). — Likewise, **30** (29 mg, 0.025 mmol) was converted into **2b** (33 mg, ~100%), isolated as an amorphous powder, $[\alpha]_D^{21}$ +102° (*c* 1.6, chloroform).

Anal. Calc. for $C_{53}H_{71}NO_{33}$: C, 50.92; H, 5.72; N, 1.12. Found: C, 51.32; H, 5.90; N, 1.70.

4''-Deoxy-4''-[(1S)-(1,4,6/5)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenylamino]maltotriose (adiposin-2) (**2a**). — Similarly, **2b** (29 mg, 0.023 mmol) was converted into **2a** (12 mg, 78%), isolated as an amorphous powder, $[\alpha]_D^{18}$ +154° (*c*

0.6, water); lit.[4] $[\alpha]_D^{22}$ +163° (*c* 1, water). The ^{1}H-n.m.r. spectral data (400 MHz, D_2O) accorded with those reported[4] for an authentic sample.

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REFERENCES

1 Part VI: S. OGAWA, N. IKEDA, H. TAKEDA, AND Y. NAKAGAWA, *Carbohydr. Res.*, 175 (1988) 294–301.
2 D. D. SCHMIDT, W. FROMMER, B. JUNGE, L. MÜLLER, W. WINGENDER, E. TRUSCHEIT, AND D. SCHAFER, *Naturwissenschaften*, 64 (1977) 535–536; B. JUNGE, F. R. HEIKER, J. JURZ, L. MÜLLER, D. D. SCHMIDT, AND C. WUNSCHE, *Carbohydr. Res.*, 128 (1984) 235–268.
3 W. PLUS, U. KEMP, H. P. KLAUSE, G. THOMAS, AND F. HOFFMEISTER, *Naturwissenschaften*, 64 (1977) 535–536; K. FUKUHARA, H. MURAI, AND S. MURAO, *Agric. Biol. Chem.*, 46 (1982) 2021–2030.
4 S. NAMIKI, K. KANGOURI, T. NAGATA, H. HARA, K. SUGITA, AND S. OMURA, *J. Antibiot.*, 35 (1982) 1234–1236.
5 E. TRUSCHEIT, W. FROMMER, B. JUNGE, L. MÜLLER, D. D. SCHMIDT, AND W. WINGENDER, *Angew. Chem. Int. Ed. Engl.*, 20 (1981) 744–761, and references therein.
6 N. SAKAIRI AND H. KUZUHARA, *Tetrahedron Lett.*, 23 (1982) 5327–5330.
7 H. KUZUHARA, M. HAYASHIDA, AND N. SAKAIRI, *Int. Symp. Chem. Nat. Prod. (IUPAC), 15th, Hague, Netherlands*, August 1986, Abstr. PC-25.
8 S. OGAWA, Y. IWASAWA, T. TOYOKUNI, AND T. SUAMI, *Chem. Lett.*, (1983) 337–340; *Carbohydr. Res.*, 141 (1985) 29–40.
9 S. OGAWA AND H. SUGIZAKI, *Carbohydr. Res.*, 156 (1986) 264–272.
10 H. PAULSEN AND W. ROBEN, *Justus Liebigs Ann. Chem.*, (1985) 974–994, and references therein.
11 A. KOHNAND AND R. R. SCHMIDT, *Justus Liebigs Ann. Chem.*, (1985) 775–784, and references therein.
12 K. TAKEO, K. MINE, AND T. KUGE, *Carbohydr. Res.*, 48 (1976) 197–208.
13 G. ZEMPLÉN, Z. CSÜRÖS, AND S. J. ANGYAL, *Ber.*, 70 (1937) 1848–1856; S. A. HOLICK, S.-H. L. CHIU, AND L. ANDERSON, *Carbohydr. Res.*, 50 (1976) 215–225.
14 M. CHMIELEWSKI AND J. N. BEMILLER, *Carbohydr. Res.*, 96 (1981) 73–78.
15 H. KUZUHARA AND N. SAKAIRI, *Yuki Gosei Kagaku Kyokai Shi*, 46 (1988) 37–48.
16 S. OGAWA, Y. SHIBATA, T. NOSE, AND T. SUAMI, *Bull. Chem. Soc. Jpn.*, 58 (1985) 3387–3388.