Cleavage of Validoxylamine A Derivatives with *N*-Bromosuccinimide: Preparation of Blocked Synthons Useful for the Construction of Carba-oligosaccharides Composed of Imino Linkages[1]

Seiichiro Ogawa,* Akihiro Nakajima and Yasunobu Miyamoto
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama, 223 Japan

Reaction of validoxylamine A and several of its derivatives with *N*-bromosuccinimide proceeded through cleavage of the imino bonds to give rise to the synthetically useful blocked derivatives of valienamine and validamine, and the cyclohexanone and cyclohexenone derivatives. Some carba-trehalose derivatives were readily prepared by coupling of a pair of these compounds by reductive alkylation with sodium cyanoborohydride.

Validoxylamine A **1** produced valienamine **6** and validamine **10** by microbial degradation with *Pseudomonas denitrificans*,[2] whereas validoxylamine A **1** gave only validamine **10** on hydrogenolysis.[3] Chemical degradation of compound **1** to give valienamine **6** has not been successfully carried out so far.

During the course of synthetic studies[4] on validamycins and carba-oligosaccharides of biological interest, we needed optically active synthons to be utilised for the construction of such carba-oligosaccharides linked by way of imino linkages. We now describe a cleavage of an imino linkage of the easily available compound **1** with *N*-bromosuccinimide (NBS) in aqueous *N*,*N*-dimethylformamide (DMF), conceivably through *N*-bromination, which gives rise to compounds **6**, **10**, and trihydroxy(hydroxymethyl)cyclohexenone **21** and/or -cyclohexanone **23**. The present procedure has also been applied to the degradation of the blocked derivatives **2**–**5** of validoxylamine A **1**, providing the corresponding appropriately blocked synthons. In addition, reductive coupling between these amines and ketones with sodium cyanoborohydride gave some blocked carbadisaccharides, useful for further transformation.

Treatment of compound **1**[5] with NBS (1.5 mol equiv.) in water for 5 h at room temperature, followed by passage through a column of Amberlite CG (NH_4^+) resin with methanol, afforded, after acetylation with acetic anhydride and pyridine, (4*R*,5*R*)-2,4-diacetoxy-5-(acetoxymethyl)cyclohex-2-enone **27** (12%), which is thought to be derived from the initially formed (2*R*,3*S*,4*R*,5*R*)-2,3,4-trihydroxy-5-(hydroxymethyl)cyclohexanone **23** *via* β-elimination during either elution over the basic resin or the acetylation conditions. The basic compounds recovered by elution of the column with aq. ammonia were then acetylated conventionally to give penta-*N*,*O*-acetyl-valienamine[6] **9**, (9%) and -validamine[7,8] **16** (17%).

In order to obtain the useful synthons, degradation of a blocked derivative of validoxylamine A **1**, *viz.* 2′,3′,4,5,6,7-hexa-*O*-benzyl-4′,7′-*O*-benzylidenevalidoxylamine A[5] **2** was carried out. In aq. 80% acetonitrile, compound **2** reacted smoothly with NBS (1.5 mol equiv.) for 1 h at room temperature to afford, after acetylation, *N*-acetyl-4,5,6,7-tetra-*O*-benzylvalienamine[9] **8** (34%) and *N*-acetyl-2,3-di-*O*-benzyl-4,7-*O*-benzylidenevalidamine **12** (21%), the tetra-*O*-benzyl derivative **22** (11%) of the tetraol **21**, and (1*R*,3*R*,6*R*,9*R*,10*S*)-9,10-dibenzyloxy-3-phenyl-2,4-dioxabicyclo[4.4.0]decan-8-one **24** (36%). Similar yields and product proportions were obtained with aq. DMF as the solvent. The reaction was appreciably retarded when aq. dimethyl sulphoxide or hexamethylphosphoramide was used.

An authentic sample of compound **12** was prepared from known (1*R*)-(1,3/2,4,5)-2,3,4-triacetoxy-1-acetoxymethyl-5-azidocyclohexane[8] **17** by the following sequence: *O*-deacylation followed by benzylidenation (⟶ **18**), benzylation (⟶ **20**), reduction (⟶ **11**), and *N*-acetylation (⟶ **12**).

Treatment of octa-*O*-benzylvalidoxylamine A **3**, derived from compound **1**, with NBS under similar conditions gave products which were readily isolated without acetylation to give tetra-*O*-benzyl-valienamine **7** (49%) and -validamine **13** (21%), and compounds **22** (3%) and **25** (57%). The free amines **7** and **13** were characterised as the *N*-acetyl derivatives **8** and **14**, respectively.

Likewise, treatment of 2′,3′,4,5,6,7-hexa-*O*-benzylvalidoxylamine A[5] **4** with NBS (1.2 mol equiv.) for 19 h gave, after acetylation, compound **8** (50%), *N*-acetyl-4,7-di-*O*-acetyl-2,3-di-*O*-benzylvalidamine **15** (15%), and the 4,7-di-*O*-acetyl-2,3-di-*O*-benzyl derivative **26** (69%) of compound **23**.

Next, attempts were made to demonstrate a simple synthesis of the carbadisaccharides by reductive alkylation[10] of the amines and ketones thus prepared.

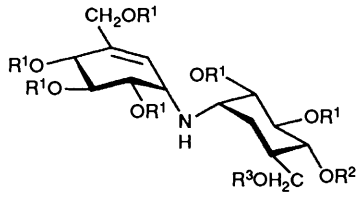
Coupling of equimolar amounts of compounds **7** and **25** with sodium cyanoborohydride (5 mol equiv.) in DMF in the presence of hydrochloric acid for 6 h at 60 °C afforded compound **3** (37%), identical with an authentic sample. Similar results were more easily obtained (yield of **3**, 41%) when substrates **7** and **25** were treated with $NaBH_3CN$ (2 mol equiv.) in methanol for 3 h at reflux temperature.

Coupling of a slightly excess of compound **13** with compound **25** was effected in refluxing methanol for 20 h to give the α,α-trehalose-type carbadisaccharide bis-[(1*S*,2*S*,3*S*,4*R*,5*R*)-2,3,4-tribenzyloxy-5-(benzyloxymethyl)cyclohexyl]amine **28** in 54% yield, the ^1H NMR spectrum ($CDCl_3$; 270 MHz) of which revealed the highly symmetrical nature of the molecule, supporting the assigned structure. Likewise, coupling of compounds **13** and **26** with $NaBH_3CN$ (4 mol equiv.) for 6 h afforded compound **29** (38%).

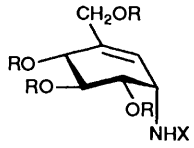
In both cases, no other diastereoisomers could be isolated. The intermediate bulky Schiff bases are likely to be attacked by a hydride anion to give rise to the α-imino linkages exclusively. The carbadisaccharides derived by coupling of these synthons would be of biological interest. The free base obtained from compound **28** has been shown to possess a strong inhibitory activity against trehalase.[11,12]

Experimental

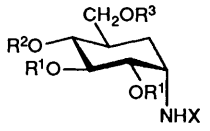
M.p.s were determined on a MEL-TEMP capillary melting point apparatus and are uncorrected. ^1H NMR spectra were measured in deuteriochloroform solution with a JEOL JNM-EX90 (90 MHz) or JNM-GX 270FT (270 MHz) instrument, and *J*-values are given in Hz. IR spectra were measured with a



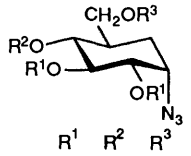
	R^1	R^2	R^3
1	H	H	H
2	Bzl	>—Ph	
3	Bzl	Bzl	Bzl
4	Bzl	H	H
5	Ac	Ac	Ac



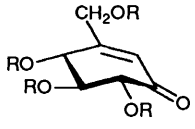
	R	X
6	H	H
7	Bzl	H
8	Bzl	Ac
9	Ac	Ac



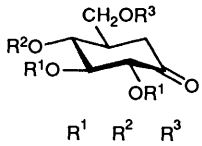
	R^1	R^2	R^3	X
10	H	H	H	H
11	Bzl	>—Ph		H
12	Bzl	>—Ph		Ac
13	Bzl	Bzl	Bzl	H
14	Bzl	Bzl	Bzl	Ac
15	Bzl	Ac	Ac	Ac
16	Ac	Ac	Ac	Ac



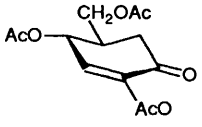
	R^1	R^2	R^3
17	Ac	Ac	Ac
18	H	>—Ph	
19	Ac	>—Ph	
20	Bzl	>—Ph	



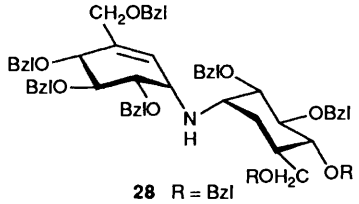
21 R = H
22 R = Bzl



	R^1	R^2	R^3
23	H	H	H
24	Bzl	>—Ph	
25	Bzl	Bzl	Bzl
26	Bzl	Ac	Ac



27



28 R = Bzl
29 R = Ac

Jasco A-202 spectrometer. Optical rotations were measured with a Jasco DIP-4 instrument. TLC was performed on Silica gel 60 F-254 (E. Merck, Darmstadt). The silica gel used for column chromatography was Wakogel C-300 (Wako Co. Osaka, Japan; 300 mesh).

Cleavage of Validoxylamine A **1** *with NBS. Isolation of penta-*N,O*-acetylvalienamine* **9**, *-validamine* **16**, *and* (4R,5R)-2,4-*Diacetoxy*-5-(*acetoxymethyl*)*cyclohex*-2-*enone* **27**.—To a solution of validoxylamine A[5] **1** (109 mg, 0.32 mmol) in DMF–water (4:1, v/v) (2 cm^3) was added NBS (7 mg, 0.49 mmol), and the mixture was stirred for 5 h at room temperature before being evaporated, and the residue was dissolved in a small amount of methanol and charged on top of a column of Amberlite CG-50 (NH_4^+) resin, which was eluted successively with methanol and then with aq. 0.2 mol dm^{-3} ammonia. The first fraction was evaporated and the residue was treated with acetic anhydride (2 cm^3) in pyridine (2 cm^3) overnight at room temperature. The product was eluted from a column of silica gel (5 g) with acetone–hexane (1:7, v/v) as eluent, to give the *enone* **27** (11 mg, 12%) as a syrup (Found: C, 54.8; H, 5.4. $C_{13}H_{10}O_7$ requires C, 54.9; H, 5.7%); $[\alpha]_D^{23}$ +96° (*c* 1.27, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1700 (α,β-unsaturated ketone); δ_H(90 MHz; $CDCl_3$) (*inter alia*) 2.08, 2.13 and 2.22 (each 3 H, s, 3 × Ac), 2.66 (2 H, m, 6-H_2), 3.94–4.32 (2 H, m, 5-CH_2OAc), 5.68 (1 H, dd, $J_{4.5}$ 8.6, $J_{3.4}$ 2.7, 4-H) and 6.47 (1 H, d, 3-H).

The second fraction was evaporated and the residual products were acetylated conventionally and then fractionated on a column of silica gel (3 g) with acetone–toluene (2:7, v/v) as eluent, to give the penta-*N,O*-acetates **9** (12 mg, 9%) and **16** (21 mg, 17%), both of which were identified with authentic samples[6,7] on the basis of their ^1H NMR spectra.

Cleavage of 2′,3′,4,5,6,7-*Hexa*-O-*benzyl*-4,7,-O-*benzylidene-validoxylamine A*[5] **2** *with NBS. Isolation of* N-*Acetyl*-4,5,6,7-*tetra*-O-*benzylvalienamine* **8**, N-*Acetyl*-2,3-*di*-O-*benzyl*-4,7-O-*benzylidenevalidamine* **12**, (4R,5S,6R)-4,5,6-*Tribenzyloxy*-3-(*benzyloxymethyl*)*cyclohex*-2-*enone* **22**, *and* (1R,3R,6R,9R,10S)-9,10-*Dibenzyloxy*-3-*phenyl*-2,4-*dioxabicyclo*[4.4.0]*decan*-8-*one* **24**.—To a solution of the amine **2** (100 mg, 0.10 mmol) in DMF–water (4:1, v/v) was added NBS (27.7 mg, 0.16 mmol) and the mixture was stirred for 17 h at room temperature. The mixture was then diluted with ethyl acetate (25 cm^3), washed with water, and dried (Na_2SO_4). Evaporation of the solvent left products, which were chromatographed on a column of silica gel (5 g) with EtOAc–hexane (1:6, v/v) as eluent to give, first, the *enone* **22** (8.7 mg, 16%) as a syrup (Found: C, 78.7; H, 6.6. $C_{35}H_{34}O_5$ requires C, 78.6; H, 6.4%); $[\alpha]_D^{22}$ −12° (*c* 0.36, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1680 (α,β-unsaturated ketone); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 4.01 (1 H, dd, $J_{4.5}$ 7.5, $J_{5.6}$ 10.3, 5-H), 4.07 (1 H, d, 6-H), 4.08 (1 H, br d, J_{gem} 16, 3-C*H*CHOBzl), 4.26 (1 H, br d, 3-CH*H*OBzl), 4.40 (1 H, br d, 4-H), 4.51–5.15 (8 H, 4 × CH_2Ph), 6.21 (1 H, q, *J* 1.8, 2-H) and 7.18–7.48 (20 H, 4 × Ph).

The second fraction gave the *ketone* **24** (18.6 mg, 40%), isolated as crystals, m.p. 156–157 °C (from EtOH) (Found: C, 75.5; H, 6.1. $C_{28}H_{28}O_5$ requires C, 75.7; H, 6.4%); $[\alpha]_D^{29}$ +57° (*c* 0.6, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (ketone); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.91–2.37 (3 H, m, 6-H, 7-H, 7′-H), 3.68 (1 H, t, $J_{5.5} = J_{5.6}$ = 10.8, 5-H), 3.84 (1 H, t, $J_{1.10} = J_{9.10}$ = 9.2, 10-H), 3.95 (1 H, t, $J_{1.6}$ 9.2, 1-H), 4.09 (1 H, d, 9-H), 4.24 (1 H, dd, $J_{5'.6}$ 4, 5′-H), 4.78 and 4.86 (each 2 H, ABq, CH_2Ph) and 7.25–7.51 (15 H, m, 3 × Ph).

Further elution of the column with methanol gave a mixture (51 mg) of the amines. The mixture was acetylated conventionally and the *N*-acetyl derivatives were chromatographed on a column of silica gel with butan-2-one–toluene (1:4, v/v) as eluent to give compound **8** (22 mg, 36%), $[\alpha]_D^{23}$ +22° (*c* 1, $CHCl_3$); δ_H(90 MHz; $CDCl_3$) (*inter alia*) 1.90 (3 H, s, Ac), 4.34–4.71 (8 H, m, 4 × CH_2Ph), 5.75 (1 H, br d, $J_{5.6}$ 4.5, 6-H), 5.56–5.82 (1 H, m, NH) and 7.05–7.35 (20 H, m, 4 × Ph). This compound was identical with an authentic sample.[9]

The second fraction gave *compound* **12** (9.4 mg, 18%) as crystals, m.p. 159–160 °C (from EtOH) (Found: C, 73.9; H, 6.6; N, 3.2. $C_{30}H_{35}NO_5$ requires C, 73.9; H, 6.8; N, 2.9%); $[\alpha]_D^{26}$ +12° (*c* 1.9, $CHCl_3$); δ_H(90 MHz; $CDCl_3$) 2.06 (3 H, s, Ac), 3.61 (1 H, t, $J_{5,7ax} = J_{7,7}$ = 11.5, 7-H^{ax}), 4.28 (1-H, $J_{5,7eq}$ 4.5, 7-H^{eq}), 4.50–4.77 (1 H, m, 1-H), 4.60–5.17 (4 H, m, 2 × CH_2Ph), 5.76 (1 H, s, PhC*H*), 6.18 (1 H, br d, $J_{1,NH}$ 5.5, NH) and 7.40–7.73 (15 H, m, 3 × Ph).

(1R,3R,6R,8S,9S,10S)-8-*Azido*-9,10-*dihydroxy*-3-*phenyl*-2,4-*dioxabicyclo*[4.4.0]*decane* **18**.—A solution of (1*R*)-(1,3,5/2,4)-2,3,4-tetraacetoxy-1-(acetoxymethyl)-5-azidocyclohexane[8] **17** (2.34 g, 6.31 mmol) in methanol (20 cm^3) was treated with methanolic, 1 mol dm^{-3} sodium methoxide (10 cm^3) for 1 h at 5 °C. After neutralisation with Amberlite IR-120B (H^+) resin, the mixture was evaporated to give the tetraol, which was dissolved in DMF (20 cm^3) and treated with α,α-dimethoxytoluene (1.5 cm^3, 10 mmol) and toluene-*p*-sulphonic acid monohydrate (10 mg) for 8 h at 55 °C. The mixture was neutralised with $NaHCO_3$ and then evaporated. The product was chromatographed on a column of silica gel (30 g) with butan-2-one–toluene (1:4, v/v) as eluent to give the *diol* **18** (885 mg, 48%) as needles, m.p. 184.5–185.5 °C (from EtOH) (Found: C, 58.0; H, 5.9; N, 13.9. $C_{14}H_{17}N_3O_4$ requires C, 57.7; H, 5.9; N, 14.4%); $[\alpha]_D^{28}$ −62° (*c* 0.54, acetone).

The diol **18** (38 mg, 0.13 mmol) was acetylated with acetic anhydride and pyridine in the usual way, and the product was chromatographed on a column of silica gel (1 g) with butan-2-one–toluene (1:5, v/v) as eluent to give the *diacetate* **19** (48 mg, 98%), m.p. 164–165 °C (from EtOH) (Found: C, 57.2; H, 5.6; N, 11.45. $C_{18}H_{21}N_3O_6$ requires C, 57.6; H, 5.6; N, 11.2%); $[\alpha]_D^{28}$ −22° (*c* 1.4, $CHCl_3$); δ_H(90 MHz; $CDCl_3$) (*inter alia*) 2.02 and 2.07 (each 3 H, s, 2 × Ac), 3.56 (1 H, t, $J_{1,6} = J_{1,10}$ = 10.5, 1-H), 3.60 (1 H, t, $J_{5ax,6} = J_{gem}$ = 11, 5-H^{ax}), 4.20 (1 H, t, $J_{7,8} = J_{8,9}$ = 3.8, 8-H), 4.25 (1 H, dd, $J_{5eq,6}$ 4.5, 5-H^{aq}), 5.12 (1 H, dd, $J_{9,10}$ 10.5, 9-H), 5.50 (1 H, s, 3-H), 5.56 (1 H, 10-H) and 7.20–7.48 (6 H, m, Ph).

The diol **18** (761 mg, 2.61 mmol) was dissolved in DMF (15 cm^3) and the solution was treated with 60% sodium hydride (0.42 g, 10 mmol) for 0.5 at 0 °C, and then with benzyl bromide (1.25 cm^3, 10.5 mmol) for 1 h at room temperature. After treatment with methanol, the mixture was diluted with ethyl acetate (100 cm^3) and washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed on a column of silica gel (30 g) with EtOAc–hexane (2:13, v/v) as eluent to give the *bis*(*benzyl ether*) **20** (1.18 g, 95%) as needles, m.p. 109.5–110 °C (from EtOH) (Found: C, 71.2; H, 6.2; N, 8.7. $C_{28}H_{29}N_3O_4$ requires C, 71.3; H, 6.2; N, 8.9%); $[\alpha]_D^{28}$ −29° (*c* 2.6, $CHCl_3$); δ_H(90 MHz; $CDCl_3$) (*inter alia*) 2.00–2.47 (1 H, m, 6-H), 3.55 (1 H, t, $J_{1,6} = J_{1,10}$ = 10, 1-H), 3.59 (1 H, t, $J_{5ax,6} = J_{gem}$ = 11, 5-H^{ax}), 4.08 (1 H, t, $J_{9,10}$ 10, 10-H), 4.23 (1 H, dd, $J_{5eq,6}$ 4.5, 5-H^{eq}), 4.78–5.16 (4 H, m, 2 × CH_2Ph), 5.69 (1 H, s, 3-H) and 7.28–7.57 (15 H, m, 3 × Ph).

(1R,3R,6R,8S,9S,10S)-8-*Amino*-9,10-*dibenzyloxy*-3-*phenyl*-2,4-*dioxabicyclo*[4.4.0]*decane* **11**.—To a solution of the azide **20** (472 mg, 1.0 mmol) in diethyl ether (5 cm^3) was added a suspension of lithium aluminium hydride (114 mg, 3 mmol) in diethyl ether (20 cm^3), and the mixture was stirred for 40 min at room temperature. After treatment with a small amount of water, the mixture was diluted with ethyl acetate (100 cm^3), washed with water, dried (Na_2SO_4), and evaporated. The residue was crystallised from ethanol to give the *amine* **11** (364 mg, 82%) as needles, m.p. 87–88 °C (Found: C, 75.3; H, 6.9; N, 3.2. $C_{28}H_{31}NO_4$ requires C, 75.5; H, 7.0; N, 3.1%); $[\alpha]_D^{28}$ −24° (*c* 1.9, $CHCl_3$); δ_H(90 MHz; $CDCl_3$) (*inter alia*) 1.33 (2 H, br s, NH_2), 3.57 (1 H, t, $J_{5ax,6} = J_{gem}$ = 11, 5-H^{ax}), 4.10 (1 H, t, $J_{1,10} = J_{9,10}$ = 9.5, 10-H), 4.25 (1 H, dd, $J_{5eq,6}$ 4.5, 5-H^{eq}), 4.72–5.18 (4 H, m, 2 × CH_2Ph), 5.70 (1 H, s, 3-H) and 7.31–7.68 (15 H, m, 3 × Ph).

The amine **11** (38 mg, 0.084 mmol) was acetylated in the usual manner and the product was crystallised from ethanol to give the *N*-acetyl derivative **12** (38 mg, 93%), identical in all respects with an authentic sample obtained earlier.

2′,3′,4,4′,5,6,7,7′-*Octa*-O-*benzylvalidoxylamine A* **3**.—A mixture of validoxylamine A **1** (141 mg, 0.42 mmol) in DMF (5 cm^3) was treated with 60% sodium hydride (0.20 g, 5 mmol) for 0.5 h at 0 °C, and then with benzyl bromide (0.60 cm^3, 5 mmol) for 20 h at room temperature. After treatment with methanol, the mixture was diluted with ethyl acetate and washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a column of silica gel (20 g) with EtOAc–hexane (1:9, v/v) as eluent to give the *octakis*(*benzyl ether*) **3** (240 mg, 54%) as a syrup (Found: C, 79.9; H, 6.9; N, 1.2. $C_{70}H_{73}NO_8$ requires C, 79.6; H, 7.0; N, 1.3%); $[\alpha]_D^{23}$ +55° (*c* 1.8, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.35 (1 H, td, $J_{1',6'ax} = J_{5',6'ax}$ = 2.6, J_{gem} 14.0, 6′-H^{ax}), 1.86 (1 H, dt, $J_{1',6'eq} = J_{5',6'eq}$ = 2.8 6′-H^{eq}), 2.32 (1 H, m, 5′-H), 3.22 (1 H, dd, $J_{5',7'}$ 2.2, J_{gem} 10.3, 7′-H^a), 3.34 (1 H, m, 1′-H), 3.39 (1 H, m, 1-H), 3.46 (1 H, t, $J_{3',4'} = J_{4',5'}$ = 9.3, 4′-H), 3.49 (1 H, dd, $J_{1',2'}$ 2.6, $J_{2',3'}$ 9.3, 2′-H), 3.61 (1 H, dd, $J_{1,6}$ 2.8, $J_{5,6}$ 7.3, 6-H), 3.63 (1 H, dd, $J_{5',7'b}$ 6.6, 7′-H^b), 3.87 (1 H, d, J_{gem} 11.9, 7-H^a), 3.93 (1 H, dd, $J_{4,5}$ 4.4, 5-H), 3.95 (1 H, t, 3′-H), 4.04 (1 H, d, 4-H), 4.25 (1 H, 7-H^b) and 5.92 (1 H, d, $J_{1,2}$ 3.1, 2-H).

Cleavage of Octa-O-*benzylvalidoxylamine A* **3** *with NBS. Isolation of* 4,5,6,7-*Tetra*-O-*benzylvalienamine* **7** *and* 2,3,4,7-*Tetra*-O-*benzylvalidamine* **13**, *Compound* **22**, *and* (2R)-(2,4/3,5)-2,3,4-*Tribenzyloxy*-5-(*benzyloxymethyl*)*cyclohexanone* **25**.—(*a*) A mixture of compound **3** (81 mg, 0.076 mmol), NBS (20 mg, 0.12 mmol), and DMF–water (4:1, v/v) (2 cm^3) was stirred for 2 days at room temperature. The mixture was processed in the usual manner and the products were chromatographed on a column of silica gel (3 g) with EtOAc–hexane (1:9, v/v) as eluent, to give, first, *compound* **25** (19.2 mg, 47%) as crystals, m.p. 86–87 °C (from EtOH) (Found: C, 78.6; H, 6.8. $C_{35}H_{36}O_5$ requires C, 78.3; H, 6.8%); $[\alpha]_D^{23}$ +50° (*c* 0.57, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1730 (ketone); δ_H(270 MHz; $CDCl_3$) 1.88 (1 H, m, 5-H), 2.46 (1 H, dd, $J_{5,6}$ 4.2, $J_{6,6}$ 13.7, 6-H), 2.64 (1 H, t, $J_{5,6'}$ 13.7, 6-H′), 3.39 (1 H, dd, $J_{5,7}$ 2.3, $J_{7,7}$ 9.2, 5-C*H*HOBzl), 3.70 (1 H, t, $J_{2,3} = J_{3,4}$ = 9.5, 3-H), 3.77 (1 H, dd, $J_{5,7'}$ 3.7, 5-CH*H*OBzl), 3.91 (1 H, dd, $J_{4,5}$ 10.6, 4-H), 4.13 (1 H, d, 2-H), 4.40–5.00 (8 H, m, 4 × CH_2Ph) and 7.10–7.40 (20 H, m, 4 × Ph).

The second fraction gave compound **22** (4.6 mg, 11%) as a syrup.

Further elution of the column with methanol gave a mixture (41 mg) of the amines **7** and **13**, which was acetylated in the usual manner. The *N*-acetyl derivatives were chromatographed on a column of silica gel (3 g) with acetone–toluene (1:7, v/v) as eluent to give, first, the *acetate* **14** (6 mg, 14%) as a syrup (Found: C, 76.8; H, 7.1; N, 2.4. $C_{37}H_{41}NO_5$ requires C, 76.7; H, 7.1; N, 2.4%); $[\alpha]_D^{23}$ +22° (*c* 2.9, $CHCl_3$); δ_H(90 MHz; $CDCl_3$) (*inter alia*) 1.95 (3 H, s, Ac), 3.30–3.81 (6 H, m, ring protons), 4.38–5.05 (8 H, m, 4 × CH_2Ph), 5.63 (1 H, br d, NH) and 7.15–7.48 (20 H, m, 4 × Ph).

The second fraction gave the acetate **8** (12 mg, 26%), isolated as a syrup, the ^{1}H NMR spectrum of which was identical with that of an authentic sample.[9]

(*b*) Compound **3** was similarly treated with NBS (1.5 mol equiv.) in aq. 80% acetonitrile for 4.5 h at room temperature to give, after conventional processing, compounds **22** (3%) and **25** (57%).

Without *N*-acetylation, the amines were directly fractionated on a column of silica gel with butan-2-one–toluene (1:3, v/v) as

eluent to give, first, the amine **7** (49%), which was identical with an authentic sample[9] in all respects.

Next the *amine* **13** (21%) was obtained as a syrup (Found: C, 78.3; H, 7.4; N, 2.6. $C_{35}H_{39}NO_4$ requires C, 78.2; H, 7.3; N, 2.6%); $[\alpha]_D^{23}$ +43° (*c* 1.5, $CHCl_3$); δ_H(90 MHz; $CDCl_3$) (*inter alia*) 2.20 (1 H, m, 5-H), 3.30–4.07 (6 H, m, 1-, 2-, 3-, 4-H, and CH_2OBzl), 4.37–5.01 (8 H, m, 4 × CH_2Ph) and 7.05–7.48 (20 H, m, 4 × Ph).

*Cleavage of 2′,3′,4,5,6,7-Hexa-*O*-benzylvalidoxylamine A*[5] **4**. *Isolation of Compound* **8**, N-*Acetyl*-4,7-*di*-O-*acetyl*-2,3-*di*-O-*benzylvalidamine* **15** *and* (2R)-(2,4/3,5)-4-*Acetoxy*-5-*acetoxymethyl*-2,3-*benzyloxycyclohexanone* **26**.—Compound **4** was similarly treated with NBS (1.2 mol equiv.) in aq. 80% acetonitrile for 19 h at room temperature. The products were isolated as described in the cleavage of compound **2** to give compound **8** (50%), the N-*acetate* **15** (15%) and the *ketone* **26** (69%).

Compound **15**, m.p. 91–93 °C (from EtOH) (Found: C, 66.9; H, 6.9; N, 2.8. $C_{27}H_{33}NO_7$ requires C, 67.1; H, 6.9; N, 2.9%); $[\alpha]_D^{27}$ +27° (*c* 0.6, $CHCl_3$); δ_H(90 MHz; $CDCl_3$) (*inter alia*) 1.94 and 2.02 (3 and 6 H, s, 3 × Ac), 3.44–3.71 (2 H, m, 2- and 3-H), 3.88 (1 H, dd, $J_{5,7}$ 3.7, J_{gem} 11.4, C*H*HOAc), 4.12 (1 H, dd, $J_{5,7}$ 5.1, CH*H*OAc), 4.33–4.50 (1 H, m, 1-H), 4.50–5.09 (5 H, m, 4-H and 2 × CH_2Ph), 5.70 (1 H, br d, NH) and 7.17–7.48 (10 H, m, 2 × Ph).

Compound **26**, m.p. 103.5–104.5 °C (from EtOH) (Found: C, 68.4; H, 6.4. $C_{25}H_{28}O_7$ requires C, 68.2; H, 6.4%); $[\alpha]_D^{22}$ +38° (*c* 1.0, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1725 (ketone); δ_H(90 MHz; $CDCl_3$) 1.92 and 2.04 (each 3 H, s, 2 × Ac), 2.35 (1 H, t, $J_{5.6ax}$ = $J_{6.6}$ = 10, 6-H^{ax}), 2.51 (1 H, br dd, $J_{5.6eq}$ ~ 1, 6-H^{eq}) 3.65 (1 H, t, $J_{2.3}$ = $J_{3.4}$ = 9.2, 3-H), 3.90 (1 H, dd, $J_{5.7}$ 3.2, J_{gem} 11.2, C*H*COAc), 4.14 (1 H, dd, $J_{5,7}$ 4.8, CH*H*OAc), 4.19 (1 H, d, 2-H), 4.75 and 4.76 (each 2 H, ABq, 2 × CH_2Ph), 5.31 (1 H, dd, $J_{3.4}$ 9.2, $J_{4.5}$ 10.8, 4-H) and 6.9–7.5 (10 H, m, 2 × Ph).

Coupling of Tetra-O-*benzylvalienamine* **7** *and* (2R)-(2,4/3,5)-2,3,4-*Tribenzyloxy*-5-(*benzyloxymethyl*)*cyclohexanone* **25** *with Sodium Cyanoborohydride. Preparation of Octa*-O-*benzylvalidoxylamine A* **3**.—To a solution of compound **7** (51.3 mg, 96 μmmol) in methanol (1 cm^3) was added 1 mol dm^{-3} hydrochloric acid (0.1 cm^3) and the mixture was stirred for 10 min at room temperature and then, after addition of sodium cyanoborohydride (9 mg, 143 μmmol, 1.5 mol equiv.), compound **25** (56.7 mg, 106 μmmol), and powdered anhydrous magnesium sulfate (0.5 g); the mixture was then heated at reflux for 3 h. Concentration of the solvent left a residue which was extracted with ethyl acetate and the extract was washed with water, dried (Na_2SO_4), and evaporated. The product was chromatographed on a column of silica gel (3 g) with EtOAc–toluene (1 : 30, v/v) as eluent, to give compound **3** (42 mg, 41%) as a syrup, identical with an authentic sample obtained before in all respects.

Coupling of Tetra-O-*benzylvalidamine* **13** *and Compound* **25**. *Preparation of Bis*-[(1S)-(1,2,4/3,5)-2,3,4-*Tribenzyloxy*-5-(*benzyloxymethyl*)*cyclohexyl*]*amine* **28**.—Tetra-*O*-benzylvalidamine **13** (11 mg, 21 μmol) and compound **25** (8.6 mg, 16 μmol) was similarly coupled with sodium cyanoborohydride (4.2 mg, 3.2 mol equiv.). The reaction was completed after the mixture was heated at reflux temperature for 25 h. The product was purified to give the blocked *carbadisaccharide* **28** (9.1 mg, 54%) (Found: C, 79.8; H, 7.3; N, 1.3. $C_{70}H_{75}NO_8$ requires C, 79.4; H, 7.1; N, 1.3%); $[\alpha]_D^{24}$ +67° (*c* 0.8, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.37 (2 H, td, $J_{5.6}$ 2.4, $J_{6.6}$ 14.3, 2 × 6-H^a), 1.86 (2 H, $J_{5.6'}$ 2.9, 2 × 6-H^b), 2.23 (2 H, m, 2 × 5-H), 3.12 (2 H, br q, $J_{1.2}$ 3.3, 2 × 1-H), 3.25 (2 H, dd, $J_{5.7}$ 2.6, $J_{7.7}$ 8.8, 2 × C*H*HOBzl), 3.43 (2 H, dd, $J_{1.2}$ 3.7, $J_{2.3}$ 9.5, 2 × 2-H), 3.45 (2 H, t, $J_{3.4}$ = $J_{4.5}$ = 9.7, 2 × 4-H), 3.60 (2 H, dd, $J_{5,7'}$ 4.4, 2 × CH*H*OBzl), 3.86 (2 H, t, $J_{2,3}$ 9.5, 2 × 3-H), 4.38–4.96 (16 H, m, 8 × CH_2Ph) and 7.23–7.29 (40 H, 8 × Ph) (signal for NH not observed).

Coupling of Compound **13** *and* **26**. *Preparation of* [(1S)-(1,2,4/3,5)-4-*Acetoxy*-5-*acetoxymethyl*-2,3-*dibenzyloxycyclohexyl*][(1S)-(1,2,4/3,5)-2,3,4-*tribenzyloxy*-5-(*benzyloxymethyl*)-*cyclohexyl*]*amine* **29**.—Similar coupling of compounds **13** and **26** (1.5 mol equiv.) with $NaBH_3CN$ (4 mol equiv.) in methanol containing hydrochloric acid (1 mol equiv.) for 6 h at reflux temperature gave, after conventional processing, the blocked *carbadisaccharide* **29** (38%) as a syrup (Found: C, 74.6; H, 7.1; N, 1.5. $C_{60}H_{67}NO_{10}$ requires C, 74.9; H, 7.0; N, 1.5%); $[\alpha]_D^{24}$ +56.5° (*c* 1.2, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.17–1.50 (2 H, m, 2 × 6-H^{ax}), 1.86–1.95 (2 H, m, 2 × 6-H^{eq}), 1.94 and 1.96 (each 3 H, s, 2 × Ac), 2.06–2.21 (1 H, m, 5′-H), 2.30–2.45 (1 H, m, 5-H), 3.10–3.15 (2 H, m, 2 × 1-H), 3.33 (1 H, dd, $J_{5',7'}$ 2.8, $J_{7',7'}$ 9, 5′-C*H*HOBzl), 3.43–3.51 (3 H, m, 2-, 2′- and 4′-H), 3.62 (1 H, dd, $J_{5',7',b}$ 4.4, 5′-CH*H*OBzl), 3.68 (1 H, dd, $J_{5,7a}$ 3.7, $J_{7,7}$ 11.4, 5-C*H*HOAc), 3.81 (1 H, t, $J_{2',3'}$ = $J_{3',4'}$ = 9.2, 3′-H), 3.86 (1 H, t, $J_{2.3}$ = $J_{3.4}$ = 9.2, 3-H), 3.98 (1 H, dd, $J_{5,7b}$ 4.8, 5-CH*H*OAc), 4.89 (1 H, dd, $J_{4,5}$ 3.5, 4-H), 4.42–4.99 (12 H, 6 × CH_2Ph) and 7.23–7.33 (30 H, 6 × Ph) (signal for NH not observed).

Acknowledgements

We express sincere thanks to Mr. Hisao Arita and Mr. Eisaku Hata for their elementary analyses.

References

1 Preliminary communications: S. Ogawa, Y. Miyamoto and A. Nakajima, *Chem. Lett.*, 1989, 725.
2 Y. Kameda and S. Horii, *J. Chem. Soc., Chem. Commun.*, 1972, 746.
3 S. Horii, T. Iwasa and Y. Kameda, *J. Antibiot.*, 1971, **24**, 57.
4 Y. Miyamoto and S. Ogawa, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1013.
5 S. Ogawa, T. Nose, T. Ogawa, T. Toyokuni, Y. Iwasawa T. Suami, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2369.
6 S. Ogawa, Y. Shibata, T. Nose and T. Suami, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 3387.
7 S. Ogawa, Y. Shibata, N. Chida and T. Suami, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 494.
8 S. Ogawa, Y. Iwasawa, T. Nose, T. Suami, S. Ohba, M. Ito and Y. Saito, *J. Chem. Soc., Perkin Trans. 1*, 1985, 903.
9 S. Ogawa, Y. Miyamoto and T. Nose, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2675.
10 A. Köhn and R. R. Schmidt, *Liebigs Ann. Chem.*, 1985, 775.
11 N. Asano, M. Takeuchi, Y. Kameda, K. Matsui, Y. Kono, H. Fukase and S. Horii, XIth Japanese Carbohydrate Symposium, July 1988, Gifu, Japan; Abstract B26, p. 111.
12 S. Ogawa, Y. Miyamoto and K. Sato, unpublished results.

Paper 1/03638F
Received 17*th July* 1991
Accepted 27*th August* 1991