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NOVEL ASPECTS OF THE FERRIER CARBOCYCLIC RING-TRANSFORMATION REACTION*†

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ABSTRACT

The mercury salt-mediated carbocyclic ring-transformation reaction of the 3-azido (**4**), 3-benzamido (**8**), and 3-trifluoroacetamido (**11**) derivatives of methyl 4-*O*-benzoyl-2,3,6-trideoxy-β-D-*erythro*-hex-5-enopyranoside, methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy-α-D-*threo*-hex-5-enopyranoside (**16**), and its 3-*O*-benzoyl-β- (**14**) and 3-deoxy-α- (**18**) analogues has been investigated. The resulting cyclohexanone derivatives **20–23**, together with all of the "Ferrier-ketones", have the newly generated HO-5 and the 3-substituent *trans*. The role of the mercury atom in exerting stereocontrol has been substantiated through the formation of the C-5 diastereoisomeric cyclohexanones **24a** and **24b** in the Ferrier-reaction of **18**, which has no 3-substituent.

INTRODUCTION

Interest in the conversion of carbohydrates into carbocyclic compounds has been stimulated by the discovery of new pseudodisaccharide aminocyclitol antibiotics[1–4].

The method introduced by Ferrier[5], involving the mercury salt-mediated ring-transformation of 6-deoxyhex-5-enopyranosides into deoxyinososes, has provided a route of wide practical utilization in the fields of aminocyclitol[6–10] and pseudo-sugar[11,12] chemistry. This procedure has led to the preparation[13] of the B–A ring system of the antibiotic β-rhodomycin, and has been extended[14] to thioglycoside analogues of hex-5-enopyranosides.

In contrast to approaches which use neutral C-5 methylene mono-[8,10,15,20] and

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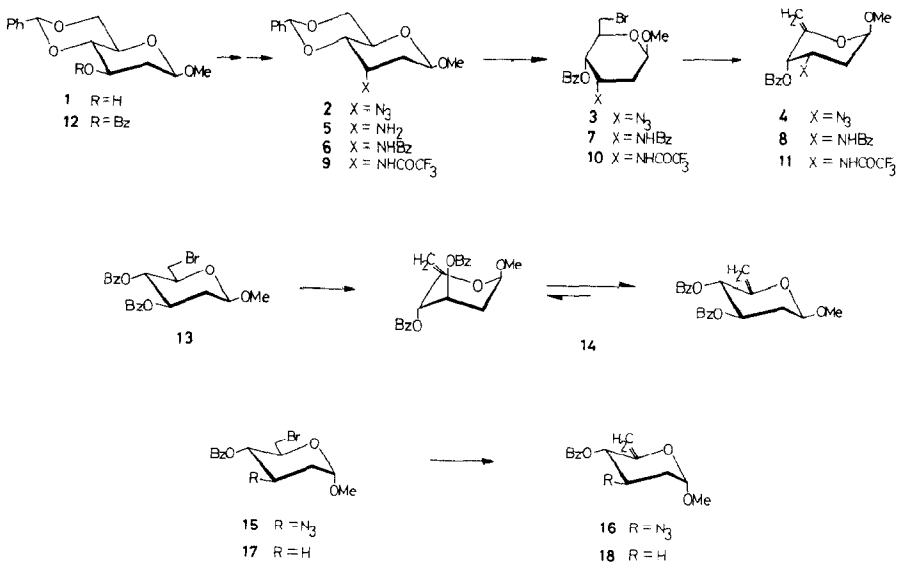
di-saccharides[6,7], our synthesis strategy[9,21,22] involves the ring-transformation of functionalized azido- and amino-deoxyhex-5-enopyranosides already carrying one of the nitrogen functions of the desired diaminocyclitol molecules. Other workers have also utilized azido-[23] and amino-deoxyhex-5-enopyranosides[10–12] to obtain the respective substituted cyclohexanones. We now report the preparation of novel nitrogen-containing deoxyinosose derivatives, and also on stereochemical aspects of the Ferrier carbocyclic ring-transformation reaction.

RESULTS AND DISCUSSION

The C-5 exomethylene sugars, methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy-β-D-*erythro*-hex-5-enopyranoside (**4**), the corresponding 3-benzamido- (**8**) and 3-trifluoroacetamido (**11**) analogues, methyl 3,4-di-*O*-benzoyl-2,6-dideoxy-β-D-*threo*-hex-5-enopyranoside (**14**), methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy-α-D-*threo*-hex-5-enopyranoside (**16**), and methyl 4-*O*-benzoyl-2,3,6-trideoxy-α-D-*glycero*-hex-5-enopyranoside (**18**), used for the ring-transformation reactions, were prepared according to standard procedures. The starting material for the β-D-hex-5-enopyranosides (**4, 8, 11,** and **14**) was methyl 4,6-*O*-benzylidene-2-deoxy-β-D-*arabino*-hexopyranoside (**1**), a key-intermediate in the syntheses of D-ristosamine[24,25] and its various derivatives[26,27]. Compound **16** was obtained by using the published procedures[28,29] and the 3-deoxy analogue **18** of **16** was synthesized from the 6-bromo compound **17**[30].

Acetal ring-cleavage[30] of the 4,6-*O*-benzylidene derivatives **2**[25], **6, 9,** and **12**[26] gave the respective 6-bromo-6-deoxy-β-D-*ribo*- (**3**[25], **7**, and **10**) and -β-D-*arabino*-hexopyranosides (**13**)[26]. The bromo sugars **15**[29] and **17**[30] were obtained in a similar



manner from methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside[28] and methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hexopyranoside[30], respectively. Whereas the 3-azido-6-bromo derivatives both in the β-D-*ribo* (**3**) and α-D-*arabino* (**15**) series, as well as the 6-bromo-3,4-dibenzoate (**13**), are present (in chloroform solution) in the usual $^4C_1$(D) conformer[25], the corresponding 3-acylamino-β-D-ribo derivatives (**7** and **10**) adopt the $^1C_4$(D) chair form ($J_{2a,3}$ 13.0 and 13.2 Hz) (see Table I).

The glycosides **3, 7, 10, 13, 15,** and **17** were readily dehydrobrominated with silver fluoride in pyridine to obtain, respectively, the C-5 exocyclic methylene sugars with β-D-*erythro* (**4**[25], **8**[26], **11**), β-D-*threo* (**14**), α-D-*threo* (**16**)[29], and α-D-*glycero* (**18**) configurations.

The ^{1}H-n.m.r. data (Table I) for the above methyl hex-5-enopyranosides showed that, for the β-D-*erythro* derivatives **4, 8,** and **11**, the $^3J_{H,H}$ values were small except that of $J_{2a,3}$ (11.8–13.5 Hz), indicating an antiperiplanar arrangement of H-2*a* and H-3, and thus a $^1C_4$(D) chair conformation. This assignment is further substantiated by the long-range couplings $^4J_{2e,4e}$ (0.9–1.2 Hz), indicative of an undistorted geometry of the $^1C_4$(D) conformation in three different solvents.

In contrast, the 3-azido-α-D-*threo*- derivative **16** adopts the $^4C_1$(D) conformation ($J_{2a,3}$ 12.0, $J_{3,4}$ 9.9 Hz) and, for methyl 3,4-di-*O*-benzoyl-2,6-dideoxy-β-D-*threo*-hex-5-enopyranoside (**14**), the decreased values of $J_{2a,3}$ and $J_{3,4}$ (each 7.5 Hz) show a $^1C_4$(D) $\rightleftharpoons$ $^4C_1$(D) conformational equilibrium apparently shifted towards the $^4C_1$(D) chair form. In the spectra of the *threo*-hex-5-enopyranosides **14** and **16**, long-range couplings ($^4J_{4,6}$ and $^4J_{4,6'}$) were detected (Table I).

Treatment of methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy-β-D-*erythro*-hex-5-enopyranoside (**4**) with an equimolar amount of mercuric chloride in refluxing aqueous acetone[5] gave 78% of crystalline 2-benzoyloxy-5-hydroxycyclohex-2-enone (**19**) instead of the expected 3-azidocyclohexanone. The ^{1}H- and ^{13}C-n.m.r. data (Tables II and III) for **19** accorded with the structure. Thus, the resonance for H-3 was a triplet with chemical shift (δ 6.74) characteristic of protons attached to unsaturated carbons. The intermediate values (5.0 Hz) for $J_{3,4}$ and $J_{3,4'}$ indicated a greatly distorted chair conformation and, thus, the steric orientation of HO-5 could not be determined. The resonance of C-1 of **19** at δ 190.3 is characteristic of the ketone carbonyl of a conjugated enone, and those of C-2 and C-3 at δ 128.9 and 132.8, respectively, are characteristic of unsaturated carbons. Compound **19** was converted into the oxime **25** and the 2,4-dinitrophenylhydrazone **26**.

The cyclohex-2-enone derivative **19** is produced in a β-elimination process, accompanying the ring-closure reaction[9,19,20,31] and, apparently, being favoured by the *trans* relationship of N_3-3 and H-4 in **4**. A similar elimination involving the loss of BzO-3 of methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-α-D-*ribo*-hex-5-enopyranoside has been reported[18]. Neither the 3-acylamino-β-D-*erythro*-hex-5-enopyranosides **8** and **11**, nor the 3,4-di-*O*-benzoyl-β- (**14**) and 3-azido-α-D-*threo* (**16**) derivatives gave elimination products. Thus, the Ferrier reaction of these compounds gave high yields of (2*S*,3*S*,5*S*)-3-benzamido-2-benzoyloxy-5-hydroxycyclohexanone (**20**),

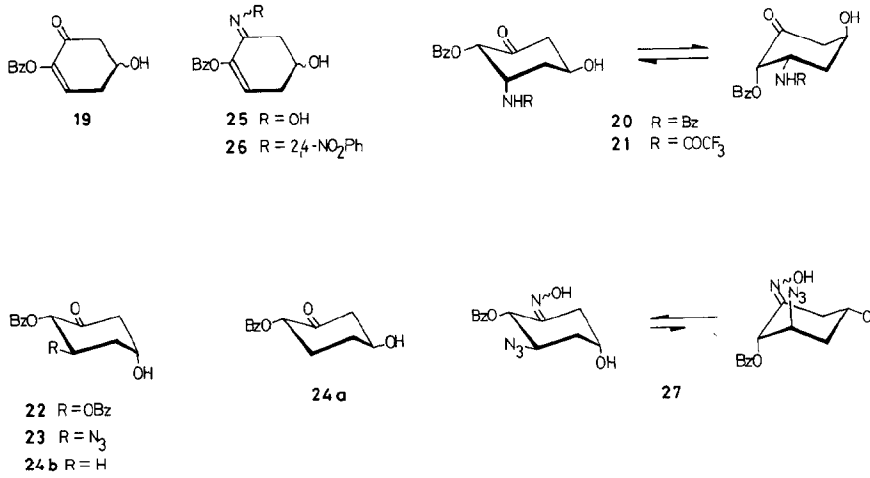
TABLE I

200-MHz ^{1}H-N.M.R. DATA FOR COMPOUNDS **4, 6, 7, 8, 10, 11, 14, 16,** AND **18**

Compound	*Solvent*	*Chemical shifts (δ)*									
		H-1	*H-2e*	*H-2a*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*OCH_3*	*Others*
4	$CDCl_3$	5.03	2.09	2.42	3.88	5.77		4.88	4.90	3.42	
	CD_3OD	5.07	2.09	2.41	4.07	5.79		4.79	4.80	3.45	
6	$CDCl_3$ (100 MHz)	4.65	2.65	1.70	⟵		3.51–3.85		⟶	3.40	PhC*H* 5.60 NH 6.65
7	$CDCl_3$	4.86	2.15	2.20	4.81	5.60	4.30	3.65	3.70	3.51	NH 7.60
8	$(CD_3)_2CO$	5.19	2.09	2.71	4.38	5.93		4.87	4.90	3.50	
	CD_3OD	5.10	1.96	2.53	4.80	5.96		~4.90[a]	~4.90[a]	3.52	
10	$CDCl_3$	4.89	2.12	2.22	4.74	5.50	4.27	3.67	3.74	3.52	NH 7.65
11	$CDCl_3$	5.03	2.10	2.29	4.80	5.71		4.85	4.85	3.49	
	CD_3OD	5.10	1.93	2.50	4.59	5.81		4.78	4.78	3.50	
14	$CDCl_3$	4.88	2.60	2.10	5.37	5.89		4.83	4.69	3.50	
16	CD_3OD	4.95	2.28	1.95	4.14	5.46		4.69	4.50	3.43	
18	$CDCl_3$	4.82		1.95–2.25[c]		5.55		4.65	4.67	3.51	

Compound	*Solvent*	*Coupling constants (Hz)*								
		$J_{1,2e}$	$J_{1,2a}$	$J_{2e,3}$	$J_{2a,3}$	$J_{2e,2a}$	$^4J_{3e,4e}$	$J_{3,4}$	$J_{6,6'}$	*Others*
4	$CDCl_3$	3.0	3.4	4.8	11.8	13.2	1.0	3.5	[b]	
	CD_3OD	2.3	3.5	4.5	12.0	13.2	0.9	3.2	[b]	
6	$CDCl_3$ (100 MHz)	4.0	10.0							$J_{3,NH}$ 6.0
7	$CDCl_3$	3.3	3.3	4.6	13.0	13.1	1.0	3.4	10.5	$J_{5,6}$ 7.5, $J_{5,6'}$ 6.5, $J_{3,NH}$ ~8
8	$(CD_3)_2CO$	1.4	3.5	4.5	13.4	13.4	1.2	3.0	[b]	
	CD_3OD	1.4	3.5	4.5	13.5	13.5	~1	3.3	[b]	
10	$CDCl_3$	3.4	3.4	4.7	13.2	13.2	~1	3.2	10.7	$J_{5,6}$ 7.4, $J_{5,6'}$ 6.6, $J_{3,NH}$ ~8
11	$CDCl_3$	1.5	3.3	4.9	12.9	12.9	1.0	3.3	[b]	
	CD_3OD	1.5	3.5	4.6	13.2	13.2	1.2	3.1	[b]	
14	$CDCl_3$	3.6	5.6	4.9	7.5	14.1		7.5	1.8	$^4J_{4,6} \approx {}^4J_{4,6'} = 1.4$
16	CD_3OD	3.5	1.7	4.9	12.0	13.4		9.9	1.8	$^4J_{4,6} \approx {}^4J_{4,6'} = 1.7$
18	$CDCl_3$	2.4	5.2						~1	$J_{3a,4}$ 8.0, $J_{3e,4}$ 6.0

[a]Partly shielded by the HDO signal. [b]$\delta_6 \approx \delta_{6'}$. [c]Including both protons at C-3.



(2*S*,3*S*,5*S*)-2-benzoyloxy-5-hydroxy-3-trifluoroacetamidocyclohexanone (**21**), (2*S*,-3*R*,5*R*)-2,3-dibenzoyloxy-5-hydroxycyclohexanone (**22**), and (2*S*,3*R*,5*R*)-3-azido-2-benzoyloxy-5-hydroxycyclohexanone (**23**), respectively. Compound **23** was converted into the oxime **27**. The composition of these functionalized cyclohexanones was substantiated by the molecular ions and some common characteristic fragments in the mass spectra *(vide infra)*.

In the ^{13}C-n.m.r. spectra (Table III) of **20–23**, the resonance of C-1 appeared 10 p.p.m. higher (~200 p.p.m.) than that of C-1 of **19**, indicating that the ketone carbonyl group is linked to saturated carbons, as also proved by the ^{13}C-chemical shift data for the skeleton carbons. In addition, the i.r. band for azide at 2100 cm^{-1} for **23** demonstrated that no azide-elimination had occurred with **16** in which N_3-3 and H-4 are *cis*.

A crucial question in the structure elucidation of the cyclohexanones produced in the Ferrier reaction is associated with the determination of the configuration of the newly generated asymmetric center (C-5). By application of the well-known method[32] for averaging of the ^{1}H-n.m.r. J values, it was established that **22** and **23** adopt an almost undistorted $^2C_5$ conformation with a (5*R*)-configuration ($J_{2,3}$ 10.5 and 7.8 Hz, $J_{3,4'}$ 11.5 and 9.0 Hz, respectively). Likewise the $^3J_{H,H}$ values for **20** and **21** accorded only with those calculated[32] for a 1:1 $^2C_5(5S) \rightleftharpoons {}^5C_2(5S)$ equilibrium, and thus the configuration of these compounds at C-5 is *S* (see data in Table II).

The present and previous results accord with the finding of the Lukacs group[11,18] of an apparent relationship between the stereochemistry at C-5 of the cyclohexanone derivatives produced in the Ferrier reaction and the conformation of the starting hex-5-enopyranosides. Thus, the exo-methylene sugars in the $^1C_4$(D) conformation provide cyclohexanones with HO-5 directed upward, whereas those with the $^4C_1$(D) conformation give ketones with HO-5 oriented downward. With a single exception[8], the "Ferrier-ketones" so far prepared have the 3-substituent *trans*

TABLE II

200-MHz ^{1}H-N.M.R. DATA FOR COMPOUNDS **19–23** AND **27**

Compound	*Solvent*	*Chemical shifts (δ)*							
		H-2	*H-3*	*H-4*	*H-4'*	*H-5*	*H-6*	*H-6'*	*Others*
19	$(CD_3)_2CO$		6.74	2.98–2.55		4.40	2.98–2.55		OH 4.75
20	C_5D_5N	6.36	5.82	2.90	2.60	4.91	3.23	3.02	NH 9.16
21	$(CD_3)_2CO$	5.63	4.96	2.55	2.29	4.55	2.94	2.60	
	$CDCl_3$	5.58	4.99	2.91	2.63	4.52	2.54	2.25	OH 4.30, NH 2.80
22	$CDCl_3$	5.77	5.96	~2.7	~2.2	4.55	2.80	2.80	OH 4.50
23	$(CD_3)_2CO$	5.57	4.42	2.43	2.18	4.70	2.58	2.95	OH 4.45
27	$CDCl_3$	5.45	4.27	2.26	1.90	~4.27	3.09	2.57	OH 4.50 and 1.75

Compound	*Solvent*	*Coupling constants (Hz)*									
		$J_{2,3}$	$J_{3,4}$	$J_{3,4'}$	$J_{4,4'}$	$J_{4,5}$	$J_{4',5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	*Others*
19	$(CD_3)_2CO$		5.0	5.0	[a]	[a]	[a]	[a]	[a]	[a]	
20	C_5D_5N	4.0	7.4	4.4	14.0	3.8	7.8	4.5	7.5	13.5	$^4J_{4,6}$ 1.2 $^4J_{2,6'}$ 1.1
21	$(CD_3)_2CO$	4.4	8.1	3.9	13.7	3.7	7.6	4.1	7.4	13.8	$^4J_{4,6}$ 1.6, $^4J_{2,6'}$ 1.3, $^4J_{4',6'}$ <1
	$CDCl_3$	4.5	7.5	4.3	14.6	3.8	8.2	4.5	7.8	14.3	$^4J_{4,6}$ ~1.7, $^4J_{2,6'}$ ~1.2, $^4J_{4',6'}$ <1
22	$CDCl_3$	10.5	4.9	11.5	13.5	~4.5	2.3	[a]	[a]	[a]	
23	$(CD_3)_2CO$	10.7	4.5	11.0	14.0	5.0	2.0	3.0	4.0	14.0	$^4J_{4,6}$ 2.5
27	$CDCl_3$	7.8	4.2	9.0	13.2	6.1	3.0	5.8	3.4	14.6	$^4J_{4,6}$ 1.7, $^4J_{4',6'}$ <1

[a]Values could not be determined because of severe overlap and/or spectral degeneracy.

TABLE III

^{13}C-N.M.R. DATA FOR COMPOUNDS **19–23** AND **27**

Compound	*Solvent*	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*Ester C=O*
19	$CDCl_3$	190.3	128.9	132.8	33.7	66.4	46.9	166.0
20	Pyridine-d_5	201.6	81.0	48.3	38.5	65.7	49.6	166.5
21	$CDCl_3$–acetone-d_6 (9:1)	199.7	76.2	47.2	34.9	65.0	48.0	165.5
22	$CDCl_3$	199.3	79.5	71.0	36.5	65.3	47.1	165.70 165.90
23	Acetone-d_6	200.2	81.5	60.7	37.0	65.9	47.5	165.7
27	$CDCl_3$	151.9	73.8	59.6	35.9	65.0	31.1	165.2

to HO-5. This high stereoselectivity of the ring-closure reaction can be explained as follows.

The mercury atom, as a transition element attached to C-6[9,19], may develop co-ordination with the lone pair-bearing substituent *Y* (*Y* = N or O) at C-3 with the formation of an intermediary six-membered ring (*A*) (see Fig. 1), and thus direct the approach of the C-6 nucleophile towards C-1 from the same side as the 3-substituent is located. The subtended angle (α) between the direction of the approach of the nucleophile and the C-1=O bond is maintained during the reaction (Baldwin's "6-exo-trig" mode of ring closure[33]) and thus represents the angle across C-6–C-5–O-5 in the product. Due to the lesser steric crowding on the opposite side of the ring, HO-5 (to be generated *via* protonation) will be *trans* to the 3-substituent. This mechanism involves an optimal steric arrangement in the transition state, represented by a double-boat conformational system (*B* in Fig. 1).

Proof for the stereocontrol exerted by the mercury atom has been obtained from the carbocyclization of methyl 4-*O*-benzoyl-2,3,6-trideoxy-α-D-*glycero*-hex-5-enopyranoside (**18**). Since there is no 3-substituent, co-ordination with the mercury atom cannot occur, so that the nucleophilic attack of C-6 on C-1 of the ring-opened sugar occurs from both directions and gives a 4:3 mixture of (2*S*,5*S*)- (**24a**) and (2*S*,5*R*)-2-benzoyloxy-5-hydroxycyclohexanone (**24b**). Although this mixture of diastereoisomers could not be fractionated by chromatography, the signal of H-5 of the newly generated chiral center of both **24a** and **24b** could be distinguished readily

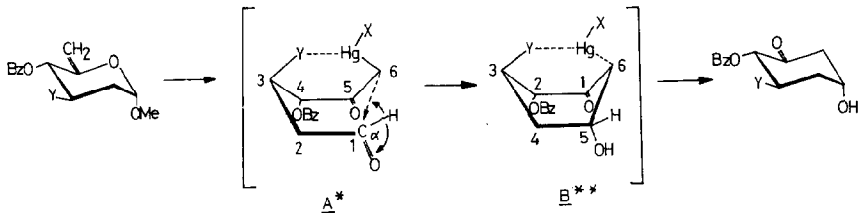


Fig. 1. Stereochemical mechanism of the Ferrier carbocyclic ring-transformation reaction: *carbohydrate numbering of the carbon atoms; **cyclitol numbering of the carbon atoms.

TABLE IV

MAIN IONS (m/z) IN THE E.I.-MASS SPECTRA OF COMPOUNDS **19–24** AND **27**[a]

Compound	M^+	$[M - 18]^+$	$[M - 28]^+$	$[M - 122]^+$	$[PhCOOH]^+$	*Base peak*	*Other peaks*
19	232(5)	214(0.3)	[b]	[b]	[b]	105	
20	353(0.1)	335(1)	325(0.05)	231(1)	122(20)	105	$[M - 122 - 18]^+$
21	345(1)	327(1)	[b]	223(6)	122(5)	105	$[M - 122 - 18]^+$
22	354(0.02)	336(0.2)	326(0.6)	232(3.7)	122(62.1)	105	$[M - 122 - 18]^+$ $[M - 122 - 28]^+$ $[M - HN_3]^+$
23	275(0.1)	[b]	247(0.8)	153(0.4)	122(5)	105	$[M - 28 - 18]^+$ $[M - 28 - 43]^+$
24a,b	234(1.1)	216(0.2)	206(0.2)	112(8.9)	122(3.2)	105	$[M - 28 - 18]^+$ $[M - 122 - 18]^+$ $[M - 122 - 28]^+$
27	290(0.01)	[b]	262(0.02)	168(2)	122(97)	105	$[M - 122 - 18]^+$ m/z 93, 66

[a]Relative abundances are in brackets. [b]These fragment ions are not detectable in the mass spectra.

and assigned at 4.02 and 4.55 p.p.m., respectively. According to the half-width of these two signals and also to the $J_{2,3}$ values ($J_{2,3a}$ 8, $J_{2,3e}$ 6 Hz for each cyclohexanone), the diastereoisomers **24a** and **24b** exist in the $^2C_5$ conformers.

The e.i.-mass spectra (70 eV; ion-source temperature, 200°) of cyclohexanones **19–24** and **27** (Table IV) contained weak peaks for M^+. In general, the consecutive loss of H_2O, CO, and benzoic acid from M^+ was observed. For the azidocyclohexanones **23** and **27**, the loss of HN_3 from M^+ is characteristic.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. I.r. spectra were recorded with a Perkin–Elmer 283 B instrument. ^{1}H- (200 MHz) and ^{13}C-n.m.r. spectra (50.3 MHz) were recorded with a Bruker WP 200 SY spectrometer (internal Me_4Si). Mass spectra were recorded with AEI-MS 902 and VG-7035 instruments. T.l.c. and column chromatography were performed on Kieselgel 60 F_{254} (Merck) and Silica Gel 60 (Merck), using *A*, 3:1 light petroleum–chloroform; *B*, dichloromethane; *C*, chloroform; *D*, 100:1 chloroform–methanol; *E*, 98:2 chloroform–methanol. Evaporations were carried out under diminished pressure at 35–40°.

*Methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-β-*D*-ribo-hexopyranoside* (**5**). — A mixture of **2** (3.0 g, 10.3 mmol) and 5% Pd/$CaCO_3$ (500 mg) in methanol (20 mL) was hydrogenated at atmospheric pressure for 4 h, then filtered, and concentrated. The residue crystallized on treatment with 1:1 ether–light petroleum, to give extremely hygroscopic **5** (2.6 g, 95%), m.p. 97–99°, $[\alpha]_D^{25}$ −23.5° (*c* 0.9, ethanol).

Anal. Calc. for $C_{14}H_{19}NO_4$ (265.30): C, 63.38; H, 7.22; N, 5.28. Found: C, 63.29; H, 7.20; N, 5.35.

*Methyl 3-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-β-*D*-ribo-hexopyranoside* (**6**). — Conventional benzoylation of **5** with benzoyl chloride and pyridine, with recrystallization of the product from ethanol–water, afforded **6** (7.2 g, 93%), m.p. 166–167°, $[\alpha]_D^{25}$ −58.5° (*c* 0.6, chloroform).

Anal. Calc. for $C_{21}H_{23}NO_5$ (369.40): N, 3.79. Found: N, 3.83.

*Methyl 3-benzamido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-β-*D*-ribo-hexopyranoside* (**7**). — A mixture of **6** (2.2 g, 6 mmol), *N*-bromosuccinimide (1.3 g, 7.1 mmol), barium carbonate (1.7 g), and dry carbon tetrachloride (60 mL) was boiled under reflux for 4 h and then concentrated. A solution of the residue in ether (50 mL) was filtered, washed with aqueous 10% sodium hydrogencarbonate (2 × 5 mL) and water, dried (Na_2SO_4), and concentrated. The product was recrystallized from ethanol–water to give **7** (2.1 g, 78%), m.p. 130–132°, $[\alpha]_D^{25}$ −109.5° (*c* 0.6, chloroform); lit.[26] m.p. 131.5–132.5°, $[\alpha]_D^{25}$ −110° (chloroform).

*Methyl 4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-3-trifluoroacetamido-β-*D*-ribo-hexopyranoside* (**10**). — To a solution of **5** (2 g, 7.55 mmol) in ether (20 mL) were

added pyridine (2.6 mL) and trifluoroacetic anhydride (4.6 g, 22 mmol) successively at −40° with stirring, which was continued for 3 h at 0°. The precipitate was collected and washed with ether (2 × 5 mL), and the combined filtrate and washings were washed with aqueous 10% sodium hydrogencarbonate and water, then dried (Na_2SO_4), and concentrated to afford methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-trifluoroacetamido-β-D-*ribo*-hexopyranoside (**9**) as a homogeneous pale-yellow foam (2.7 g, 100%) which was used directly for the acetal-opening reaction[30].

A mixture of the crude **9** (2.5 g, 7.0 mmol), *N*-bromosuccinimide (2.0 g, 7.5 mmol), dry barium carbonate (2.0 g), and carbon tetrachloride (40 mL) was boiled under reflux for 4 h, then cooled, filtered, washed with aqueous 10% $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated. Trituration of the residue with cold methanol gave **10** (2.75 g, 90%), m.p. 168–170°, $[\alpha]_D^{25}$ −106° (*c* 0.8, chloroform).

Anal. Calc. for $C_{16}H_{17}BrF_3NO_5$ (440.22): C, 43.65; H, 3.89; N, 3.18. Found: C, 43.78; H, 3.77; N, 3.15.

*Methyl 4-O-benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-β-D-*erythro-*hex-5-enopyranoside* (**11**). — A mixture of **10** (880 mg, 2 mmol) and dry silver fluoride (800 mg, 3 mmol) in pyridine (8 mL) was stirred in the dark for 24 h at room temperature, then poured into ether (30 mL), and filtered. The filtrate was decolourized with Celite and concentrated, and the residual dark syrup was subjected to flash column chromatography (solvent *C*) to give **11** (580 mg, 81%), m.p. 161–163°, $[\alpha]_D^{25}$ −118° (*c* 0.6, chloroform).

Anal. Calc. for $C_{16}H_{16}F_3NO_5$ (359.30): C, 53.48; H, 4.48; N, 3.90. Found: C, 53.61; H, 4.42; N, 3.85.

*Methyl 3,4-di-O-benzoyl-2,6-dideoxy-β-D-*threo-*hex-5-enopyranoside* (**14**). — Treatment of **13**[26] (4.0 g, 8.9 mmol) with silver fluoride (6.0 g, 47.3 mmol) in pyridine (15 mL) as described above for **11**, with column chromatography (solvent *B*) of the product, gave **14** (2.9 g, 88.7%), isolated as a syrup, $[\alpha]_D^{25}$ −130° (*c* 0.6, chloroform). Mass spectrum: *m/z*: 336 (8%) [M − MeOH]$^+$.

Anal. Calc. for $C_{21}H_{20}O_6$ (368.37): C, 68.46; H, 5.47. Found: C, 68.65; H, 5.51.

*Methyl 4-O-benzoyl-2,3,6-trideoxy-α-D-*glycero-*hex-5-enopyranoside* (**18**). — A mixture of **17**[30] (2.0 g, 6.1 mmol) and dry silver fluoride (2.2 g, 17.3 mmol) in pyridine (20 mL) was stirred in the dark for 48 h, then poured into ether (100 mL), filtered, and concentrated. Toluene was evaporated from the residue which was then subjected to flash column chromatography (solvent *B*) to give **18** (1.1 g, 73%), m.p. 65–67°, $[\alpha]_D^{23}$ +17° (*c* 2, chloroform). Mass spectrum: *m/z*: 248 (2%) M$^+$.

Anal. Calc. for $C_{14}H_{17}BrO_4$ (329.22): C, 51.10; H, 4.52. Found: C, 51.00; H, 5.10.

2-Benzoyloxy-5-hydroxycyclohex-2-enone (**19**). — To a solution of **4** (0.50 g, 1.7 mmol) in 2:1 acetone–water (15 mL) was added mercuric chloride (0.50 g, 1.8 mmol) and the mixture was boiled for 2.5 h under reflux. Most of the acetone was then distilled off and the residue was extracted with chloroform (3 × 5 mL). The combined extracts were washed with water (2 × 3 mL), dried (Na_2SO_4), and con-

centrated. Column chromatography (solvent *C*) of the residue afforded **19** (312 mg, 78%), m.p. 124–125°, $[\alpha]_D^{25}$ +28° (*c* 0.7, chloroform); ν_{max}^{KBr} 3470 (OH), 3100 (=CH), 1740 (C=O ester), 1690 (C=O ketone), and 1610 (C=C) cm^{-1}.

Anal. Calc. for $C_{13}H_{12}O_4$ (232.23): C, 67.23; H, 5.21. Found: C, 67.15; H, 5.19.

(2S,3S,5S)-3-Benzamido-2-benzoyloxy-5-hydroxycyclohexanone (**20**). — To a solution of **8** (366 mg, 1 mmol) in 2:1 acetone–water (10 mL) was added $HgCl_2$ (340 mg, 1.2 mmol), and the mixture was boiled for 3 h under reflux. Most of the acetone was then distilled off and the residue was extracted with chloroform (3 × 5 mL). The combined extracts were washed with water (2 × 3 mL), dried (Na_2SO_4), and concentrated. The residue was crystallized from ethanol to give **20** (286 mg, 81%), m.p. 212–214° (dec.), $[\alpha]_D^{25}$ −102° (*c* 0.5, pyridine).

Anal. Calc. for $C_{20}H_{19}NO_5$ (353.36): C, 67.98; H, 5.42; N, 3.96. Found: C, 67.88; H, 5.39; N, 3.90.

(2S,3S,5S)-2-Benzoyloxy-5-hydroxy-3-trifluoroacetamidocyclohexanone (**21**). — A mixture of **11** (560 mg, 1.6 mmol) and $HgCl_2$ (550 mg, 2.0 mmol) in 2:1 acetone–water (15 mL) was boiled for 3 h under reflux when t.l.c. (solvent *D*) indicated that all of **11** had reacted. Most of the acetone was then distilled off and the residue was extracted with chloroform (3 × 10 mL). The combined extracts were washed with water (3 × 3 mL), dried (Na_2SO_4), and concentrated to give **21** (0.46 g, 86%), m.p. 182–183° (sealed capillary tube), $[\alpha]_D^{25}$ −84° (*c* 0.5, acetone).

Anal. Calc. for $C_{15}H_{14}F_3NO_5$ (345.27): C, 52.18; H, 4.08; N, 4.06. Found: C, 52.32; H, 4.11; N, 4.16.

(2S,3R,5R)-2,3-Dibenzoyloxy-5-hydroxycyclohexanone (**22**). — A mixture of **14** (820 mg, 2.3 mmol) and mercuric chloride (760 mg, 2.8 mmol) in 2:1 acetone–water (12 mL) was boiled for 4 h under reflux. Most of the acetone was then distilled off and the residue was extracted with chloroform (3 × 5 mL). The combined extracts were washed with water (3 × 3 mL), dried (Na_2SO_4), and concentrated. The crystalline residue was washed with dry ether to afford **22** (650 mg, 82.4%), m.p. 158–160°, $[\alpha]_D^{25}$ −99° (*c* 0.7, chloroform).

Anal. Calc. for $C_{20}H_{18}O_6$ (354.34): C, 67.78; H, 5.12. Found: C, 67.57; H, 5.06.

(2S,3R,5R)-3-Azido-2-benzoyloxy-5-hydroxycyclohexanone (**23**). — A mixture of **16** (1.87 g, 6.45 mmol) and mercuric chloride (2.20 g, 8.1 mmol) in 2:1 acetone–water (40 mL) was boiled for 4 h under reflux. T.l.c. (solvent *D*) then showed that all of **16** had reacted. Most of the acetone was then distilled off and the residue was extracted with chloroform (3 × 10 mL). The combined extracts were washed with water (2 × 5 mL), dried (Na_2SO_4), and concentrated, and the residue was crystallized from chloroform–light petroleum to afford **23** (1.46 g, 82%), m.p. 182–183°, $[\alpha]_D^{25}$ −127° (*c* 0.35, chloroform); ν_{max}^{KBr} 3840 (OH), 2110 (C–N azide), 1735 (C=O ester), and 1710 (C=O ketone) cm^{-1}.

Anal. Calc. for $C_{13}H_{13}N_3O_4$ (275.25): C, 56.72; H, 4.76; N, 15.27. Found: C, 56.86; H, 4.75; N, 15.33.

Ferrier reaction of **18**. — A mixture of **18** (200 mg, 0.8 mmol) and mercuric chloride (220 mg, 0.8 mmol) in 2:1 acetone–water (18 mL) was stirred for 2 h at room temperature when t.l.c. (solvent *D*) indicated that all of **18** had reacted. Most of the acetone was then distilled off, the residue was diluted with water and extracted with chloroform, and the extract was washed with water (2 × 2 mL), dried (Na_2SO_4), and concentrated. The residual syrupy mixture of (2*S*,5*S*)-2-benzoyloxy-5-hydroxycyclohexanone (**24a**) and its (2*S*,5*R*) stereoisomer (**24b**) was purified by column chromatography (solvent *E*) to obtain a mixture (85 mg, 43%), but no separation of the diastereoisomers. The ^{1}H-n.m.r. spectrum showed a 4:3 mixture of **24a** and **24b**. Mass spectrum: *m/z*: 234 (1.1%) M^+; see also Table IV.

^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 7.4–8.2 (Ph), 5.3–5.5 (H-2), 1.8–3.0 (H-3,3′,4,4′,6,6′), 4.02 (H-5 of **24a**), 4.55 (H-5 of **24b**), 1.6 (HO-5 of **24a**), 1.75 (HO-5 of **24b**); $J_{3a,4}$ 8, $J_{3e,4}$ 6 Hz.

2-Benzoyloxy-5-hydroxycyclohex-2-enone oxime (**25**). — To a solution of **19** (244 mg) in pyridine (5 mL) was added a solution of hydroxylamine hydrochloride (75 mg) in methanol (5 mL), and the mixture was heated at 50°. T.l.c. (solvent *E*) revealed a considerable amount of **19** even after 15 h. The mixture was then concentrated to dryness and preparative t.l.c. (solvent *E*) of the residue gave **25** (67 mg, 26%), m.p. 174–176°.

Anal. Calc. for $C_{13}H_{13}NO_4$ (247.26): N, 5.67. Found: N, 5.78.

2-Benzoyloxy-5-hydroxycyclohex-2-enone 2,4-dinitrophenylhydrazone (**26**). — To a solution of **19** (226 mg) in 50% aqueous methanol (10 mL) was added a 2-mL aliquot of a solution of 2,4-dinitrophenylhydrazine (2.5 g) and conc. sulfuric acid (15 mL) in water (20 mL) and ethanol (100 mL). The precipitate which separated upon gentle heating was collected, washed with water, and recrystallized from ethanol–water to give **26** (100 mg), m.p. 197–200°, $[\alpha]_{589}^{25}$ +56°, $[\alpha]_{546}^{25}$ +75° (*c* 0.5, chloroform). Mass spectrum: *m/z*: 412 (12%) M^+, 105 (100%) Bz^+, 77 (48%) Ph^+, 57 (8%) $C_4H_9^+$.

Anal. Calc. for $C_{19}H_{16}N_4O_7$ (412.35): N, 13.58. Found: C, 13.12.

(2S,3R,5R)-3-Azido-2-benzoyloxy-5-hydroxycyclohexanone oxime (**27**). — To a solution of **23** (690 mg, 20 mmol) in pyridine (5 mL) was added a hot solution of hydroxylamine hydrochloride (200 mg, 29 mmol) in methanol (8 mL), and the mixture was stirred for 4 h at room temperature. Most of the solvent was then distilled off under reduced pressure, the residue was diluted with water and extracted with chloroform (3 × 5 mL), and the combined extracts were dried (Na_2SO_4) and concentrated. Flash column chromatography (solvent *D*) of the residue gave **27** (560 mg, 77%), m.p. 121°, $[\alpha]_D^{25}$ −144° (*c* 0.6, chloroform).

Anal. Calc. for $C_{13}H_{14}N_4O_4$ (290.27): C, 53.78; H, 4.86. Found: C, 53.69; H, 4.83.

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