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Note

Preparation of novel polysubstituted chiral cyclohexanone derivatives containing a quaternary carbon by Ferrier reaction

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Abstract

2-*C*- and 3-*C*-[(2′-chloro)pyrid-5′-yl]-hex-5-enopyranosides were synthesized from 4,6-*O*-benzylidene acetals in three steps. By treatment with mercury or palladium salts, the corresponding cyclohexanones could be obtained. The stereochemistry of these reactions was highly dependent on the substitution pattern of the starting material and the nature and concentration of the catalyst.

Keywords: Carbocyclization; (2′-Chloro)pyridyl cyclohexanones

Syntheses of the 7-azabicyclo[2.2.1]heptane alkaloid epibatidine have mostly been performed by intramolecular nucleophilic ring closure of aminocyclohexane derivatives.[1] The mercury salt mediated ring transformation of 6-deoxyhex-5-enopyranosides into 2-deoxyinosose derivatives described by Ferrier[2] provides a route for the preparation of intermediate cyclohexanone derivatives which can be used for the synthesis of hydroxylated and polyhydroxylated analogues of epibatidine. We have previously reported the preparation of new 2-*C*- and 3-*C*-aryl pyranosides,[3] as chiral synthons, as well as 2-*C*- and 3-*C*-(2′-chloro)pyrid-5′-yl pyranosides (**1** and **2**) in connection with epibatidine precursors. This paper describes the preparation of novel (2′-chloro)pyrid-5′-yl-containing polysubstituted optically active cyclohexanone derivatives and discusses the stereochemical aspects of the Ferrier carbocyclic ring-transformation reaction in the presence of a quaternary carbon.[2d]

N-Bromosuccinimide mediated radical 4,6-*O*-benzylidene-acetal ring opening[4] in the presence of a basic nitrogen atom was successfully carried out on both **1** and **2** affording, respectively, **3** (70%) and **4** (92%). After benzoyl cleavage on **3** and **4**, simultaneous dehydrohalogenation and benzylation were attempted on derivatives **5** and **6** by treatment with sodium hydride–benzyl bromide in *N*,*N*′-dimethylformamide;[5] in these conditions, the formation of a mixture of mono- and di-benzylated derivatives **7** and **9**, **8** and **10**, respectively were observed in all cases. Treatment of **5** and **6** in phase transfer conditions (potassium hydroxide, 1.1 equiv benzyl bromide, 0.1 equiv benzyl triethylammonium chloride in

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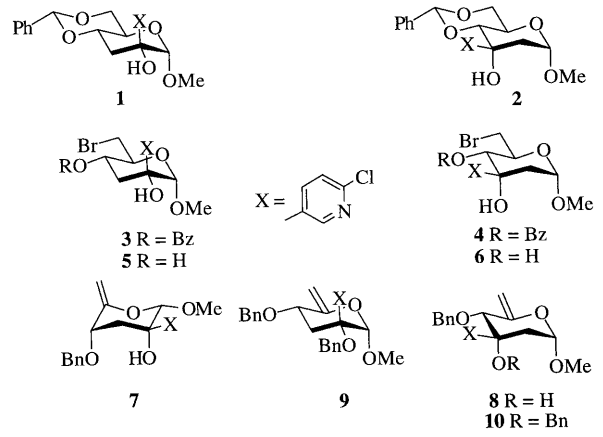


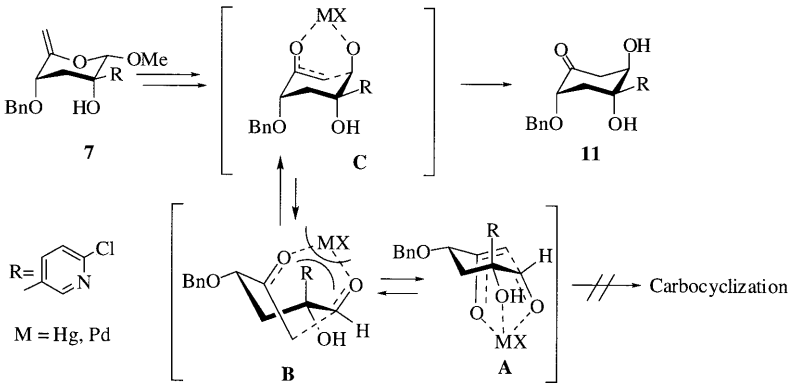
Scheme 1.

dichloromethane)[6] followed by sodium hydride–*N*,*N*′-dimethylformamide dehydrohalogenation at room temperature furnished **7** from **5** (62%) and **8** from **6** (75%). Doubling the amount of benzyl bromide under the conditions described above resulted in the preparation of the 2,4-di-*O*-benzyl- and 3,4-di-*O*-benzyl-hex-5-enopyranosides (**9**) (50%) and (**10** (54%), respectively (Scheme 1).

Conversion of the hex-5-enopyranosides into the carbocyclic products was attempted with various mercury or palladium salts at different concentrations. Both the nature of the metallic salts and the amount used had a crucial influence on the ratio of the epimeric cyclohexanones formed. A clear figure of the reaction conditions and isomer ratios is presented in Table 1. When the unsaturated product **7** was submitted to the reaction with mercury salts, no carbocyclic product could be obtained, regardless of the experimental conditions. Nevertheless, in the presence of 0.15 equiv of palladium chloride[7] in a mixture of (60/40) dioxane–water, a single ketone **11** was isolated with a rather modest yield, (20%, entry 3, Table 1) (Scheme 2). A large fraction of the starting material underwent the well-documented ring opening[8,9] affording an unstable compound. The ^{1}H and ^{13}C NMR spectra of the latter indicated the presence of an aldehyde although the material could not be adequately characterised. The 2,4-di-*O*-benzylated product **9** gave a 1/1 mixture of ketones **12** and **13** when mercury salts in nearly stoichiometric (1.2 equiv) amounts

Table 1
Experimental conditions for carbocyclization reactions

Entry	Starting compound	Reagents (equiv)	Solvent	*t* (h)	*T* (°C)	Products (yield % α, β)	α/β
1	**7**	$HgCl_2$ (1.2 or 0.1)	3/2 acetone–H_2O	3	50 or 25		
2	**7**	$Hg(OCOCF_3)_2$ (1.2 or 0.1)	3/2 acetone–H_2O	3	50 or 25		
3	**7**	$PdCl_2$ (0.15)	3/2 dioxane–H_2O	4	60	**11** (20)	0/1
4	**8**	$HgCl_2$ (1.2)	3/2 acetone–H_2O	4	50	**14**, **15** (86)	1/1
5	**8**	$Hg(OCOCF_3)_2$ (1.2)	3/2 acetone–H_2O	3	25	**14**, **15** (87)	9/1
6	**8**	$Hg(OCOCF_3)_2$ (0.1)	3/2 acetone–H_2O	4	25	**14**, **15** (83)	1/0
7	**9**	$HgCl_2$ (1.2)	3/2 acetone–H_2O	3	25	**12**, **13** (83)	1/ 1
8	**9**	$Hg(OCOCF_3)_2$ (1.2)	3/2 acetone–H_2O	4	25	**12**, **13** (75)	1/ 1
9	**9**	$Hg(OCOCF_3)_2$ (0.1)	3/2 acetone–H_2O	4	25	**12**, **13** (68)	1/ 9
10	**10**	$Hg(OCOCF_3)_2$ (1.2)	3/2 acetone–H_2O	3	25	**16**, **17** (75)	1/ 1
11	**10**	$Hg(OCOCF_3)_2$ (0.1)	3/2 acetone–H_2O	4	25	**16**, **17** (77)	3/7



Scheme 2.

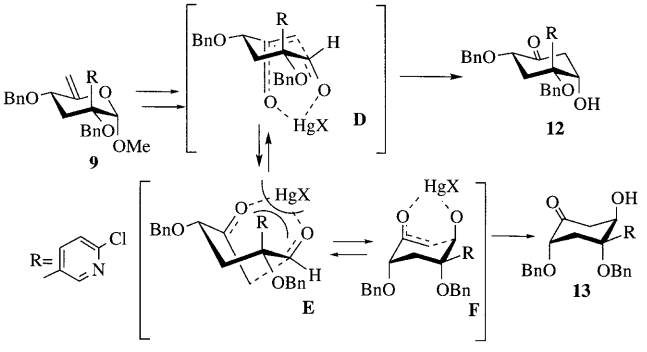
were used (Scheme 3) (entries 7, 8, Table 1). This ratio could be dramatically displaced in favour of β isomer **13** (68%) by reducing the amount of trifluoroacetate to 0.1 equiv (entry 9, Table 1).

When the quaternary centre was at position C-3, as in **8** and **10**, the desired cyclohexanones were obtained in high yield. The ratio of α and β cyclohexanones **14** and **15**, **16** and **17** was also dependent on the nature and concentration of mercuric salts: from **8**, in catalytic conditions, α ketone **14** was the main product, but from **10**, β ketone **17** was always the major one in catalytic conditions (entries 4, 5, 6 10, 11, Table 1) (Scheme 4).

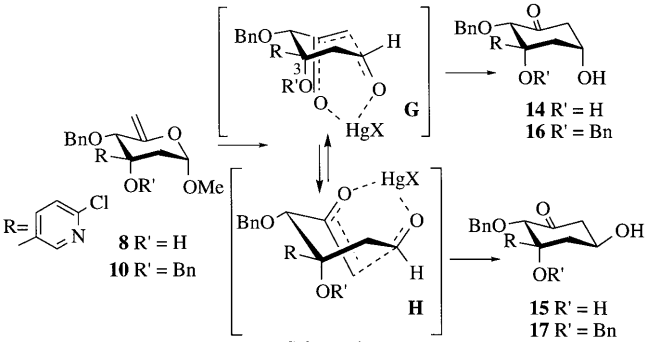
Structural and conformational proofs were straightforward for the derivatives having the quaternary centre at position C-2 in the unsaturated carbohydrates. The resulting carbocyclic products afforded unambiguous large or narrow ABX type proton signals in their NMR spectrum for H-3ax and H-6ax. The aspect of these signals was indicative of the axial or equatorial nature of the substituents at C-2 and C-5; **11**: H-6ax, dd, $J_{5,6ax}$ 3 Hz, J_{gem} 14 Hz; H-3ax, dd, $J_{2,3ax}$ 3Hz, J_{gem} 15 Hz; **12**: H-6ax, dd, $J_{5,6ax}$ 4 Hz, J_{gem} 15 Hz; H-3ax, t, $J_{2,3ax} = J_{gem}$ 15 Hz; **13**: H-6ax, dd, $J_{5,6ax}$ 4 Hz, J_{gem} 14 Hz; H-3ax, dd, $J_{2,3ax}$ 4 Hz, J_{gem} 15 Hz. The chloropyridine substituent is equatorial in both **11** and **13** and axial in **12**.

The ^{1}H NMR spectrum of **14**, **15**, **16**, and **17** did not afford unambiguous evidence about their configurations and conformations. Since these spectra exhibited similar coupling constants for **14** and **16** on the one hand and for **15** and **17** on the other, it appeared necessary and sufficient to determine the structure of one of them, **15**, by X-ray crystallography to elucidate the structure of all of them. The correct absolute configuration of **15** was established as 2-L-(2,3/5)-2-benzyloxy-3-*C*-[(2′-chloro)pyrid-5′-yl]-3,5-dihydroxycyclohexanone by crystallographic studies (see Sections 1.2 and 2).

The molecule **15** shows a folded conformation with the aromatic rings in a tilted T position. The pyridine and phenyl rings are in



Scheme 3.



Scheme 4.

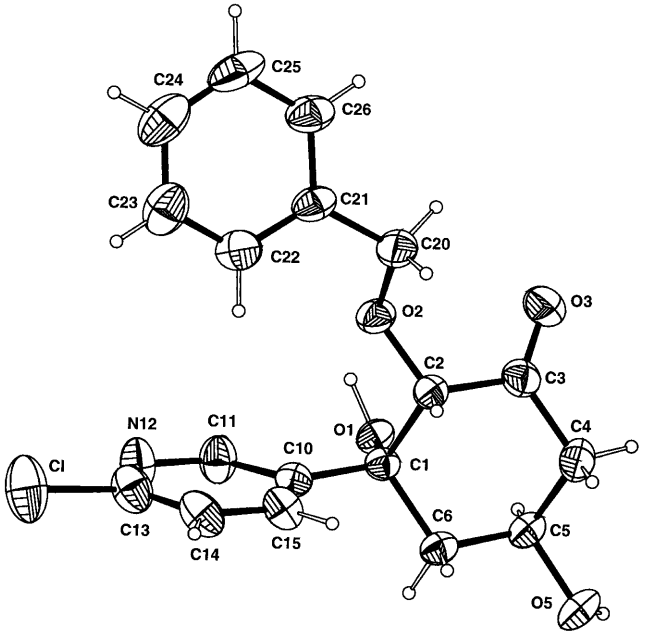


Fig. 1. ORTEP diagram of **15** showing the crystallographic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level; H-atoms are shown as small circles of arbitrary radii.

a nearly perfect T-relationship. Two aromatic moieties are oriented nearly perpendicularly with dihedral angle of 75.3(1)° and the relative disposition of aromatic systems 'edge-to-face'. The relevant centroid distance is short, 5.13 Å (Fig. 1).

Thus seven new chiral (2′-chloropyrid-5′-yl) cyclohexanones were synthesized from 2-*C*- and 3-*C*-(2′-chloropyrid-5′-yl) pyranosides by mercury or palladium salt mediated carbocyclization. The difference in the product distribution might be explained by the interactions in the metal-complexed intermediates suggested by Machado et al.[10,11] When complexation or steric compression were present as in complexes **A** or **B** for **7** (Scheme 2), or **D** and **E** for **9** (Scheme 3) or **G** and **H** for **10** (Scheme 4), formation of β isomers **11**, **13**, and **17**, respectively, was observed and their yield increased in catalytic conditions (Table 1). In the case of **8**, as in most examples described in the literature,[2b] the α ketone was formed in greater amount under catalytic conditions. It seemed that substituents at C-5, C-3 or C-4 are not the only drawing forces which influence the ratio of α and β cyclohexanones.[2d,10,12]

1. Experimental

General methods and equipment.—Flash column chromatography was performed using 35–70 m Silica Gel (60) purchased from S.D.S. Company. TLC was run using DC-Plastikfolien, Silica Gel F_{254} (Schleicher and Schuell), detection by UV light (254 nm) and by heating after H_2SO_4 treatment. ^1H and ^{13}C spectra (Tables 2 and 3) were recorded at 250 and 62.91 MHz and at 300 and 75.49 MHz (Bruker WP 250, WP 300, respectively). Tetramethylsilane was the internal standard ($\delta = 0.00$ ppm), δ were reported in parts per million, and J values in Hertz. ^1H and ^{13}C chemical shifts for benzyl, benzoyl and benzylidene aromatic protons and carbons are not given. Mass spectra (CI) were recorded on AEI MS 9 spectrometer. Melting points were measured on a Reichert apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter.

Crystallographic data collection and refinement of the structure.—The crystal data of **15** and the parameters of data collection are available in supplementary material. A prismatic colourless crystal from EtOH with the dimensions $0.66 \times 0.53 \times 0.25$ mm was chosen for the X-ray diffraction experiment. The unit-cell and intensity data were measured with an Enraf–Nonius CAD-4 diffractometer with graphite monochromated Cu Kα radiation ($\lambda = 1.54178$ Å). The cell constants were obtained by least-squares procedures based upon the 2θ values of 25 reflections measured in the ranges $38.20 < 2\theta < 41.31°$ at ambient temperature. During data collection, three control reflections were measured every 2 h; the crystal was stable, and the check reflections showed only slight decay in intensity of 0.79% during the whole X-ray data collection. A total of 2936 reflections were collected in the range $3.89 < 2\theta < 65.11°$ within $[-7 < h < 7, 0 < k < 18, 0 < l < 19]$. From all reflections, 2467 were considered as observed $[I > 2\sigma(I)]$. The structure was solved by direct methods with the program SHELXS-86[13] and refined by using the SHELXL-93[14] program. The drawing was prepared with ORTEPII.[15]

Table 2
^{1}H NMR chemical shifts (δ in ppm) and coupling constants (J in Hz)

Compound	H-1	H-2 or		H-3 or		H-4 or		H-5	H-6a	H-6b	OH	OCH_3	CH_2Ph system AB	H-3′	H-4′	H-6′
		H-2ax	H-2eq	H-3ax	H-3eq	H-4ax	H-4eq									
3	4.90, *s*			2.38, *t* J_{gem} 12	2.58, *dd* $J_{3eq,4}$ 5	4.80, *dt* $J_{3ax,4} = J_{4,5}$ 12		4.20, *m*	3.62 *dd* J_{gem} 12 $J_{5,6a}$ 10	3.45 *dd* $J_{5,6b}$ 5	3.00, *s*	3.64, *s*		7.50, *d* $J_{3',4'}$ 7	8.10, *dd* $J_{4',6'}$ 2	8.80, *d*
4	5.05, *d* $J_{1,2ax}$ 3	2.38, *m*				5.38, *d* $J_{4,5}$ 10		4.43, *ddd* $J_{5,6a}$ 5 $J_{5,6b}$ 4	3.48, *m*		2.70, *s*	3.56, *s*		7.20, *d* $J_{3',4'}$ 7	7.90, *dd* $J_{4',6'}$ 2	8.60, *d*
5	4.70, *s*			2.20, *m*		3.24, *m*		3.85, *dt* $J_{4,5} = J_{5,6a}$ 10 $J_{5,6b}$ 3	3.73, *t* J_{gem} 10	3.64, *dd*	4.30, *s* 2.75, *s*	3.50, *s*		7.30, *d* $J_{3',4'}$ 7	8.00, *dd* $J_{4',6'}$ 2	8.65, *d*
6	4.90, *t* $J_{1,2ax} = J_{1,2eq}$ 1	2.10, *m*				3.61, *m*		3.85, *m*	3.85, *m*	3.61, *m*	4.45, *s* 2.80, *s*	3.41, *s*		7.15, *d* $J_{3',4'}$ 7	7.85, *dd* $J_{4',6'}$ 2	8.55, *d*
7	5.00, *s*			2.20, *m*		4.00, *t* $J_{3ax,4} = J_{3eq,4}$ 4			4.80, *s*	4.70, *s*	4.65, *s*	3.50, *s*	4.55 J_{gem} 12	7.15, *d* $J_{3',4'}$ 7	7.90, *dd* $J_{4',6'}$ 2	8.40, *d*
8	5.00, *d* $J_{1,2ax}$ 4	2.30, *dd* J_{gem} 15	2.10, *d*			4.00, *d*			5.10, *t* $J_{gem} = J_{5,6a}$ 2	5.02, *s*	4.28, *s*	3.38, *s*	4.38 J_{gem} 12	6.80, *d* $J_{3',4'}$ 7	7.50, *dd* $J_{4',6'}$ 2	8.30, *d*
9	5.20, *s*			2.50, *t* $J_{gem} = J_{3ax,4}$ 10	2.10, *dd* $J_{3eq,4}$ 5	3.45, *t*			4.82, *s*	4.73, *s*		3.58, *s*	4.48 J_{gem} 12 4.12 J_{gem} 12	7.10, *d* $J_{3',4'}$ 7	7.80, *dd* $J_{4',6'}$ 2	8.60, *d*
10	4.68, *dd* $J_{1,2ax}$ 5 $J_{1,2eq}$ 4	2.64, *dd* J_{gem} 15	2.38, *dd*			4.17, *s*			4.95, *s*	4.80, *s*		3.48, *s*	4.48 J_{gem} 12 4.32 J_{gem} 12	7.10, *d* $J_{3',4'}$ 7	7.80, *dd* $J_{4',6'}$ 2	8.50, *d*
11		4.15, *m*		3.05, *dd* J_{gem} 15 $J_{2,3ax}$ 3	2.40, *dd* $J_{2,3eq}$ 2			4.42, *m*	3.71, *dd* $J_{5,6ax}$ 3 J_{gem} 14	2.70, *dd* $J_{5,6eq}$ 2	5.30, *s*		4.68 J_{gem} 12	7.30, *d* $J_{3',4'}$ 7	8.10, *dd* $J_{4',6'}$ 2	8.50, *d*
12		4.20, *m*		2.88, *t* $J_{2,3ax} = J_{gem}$ 15	2.63, *dd* $J_{3eq,5}$ 2			4.20, *m*	2.53, *dd* $J_{5,6ax}$ 4 J_{gem} 15	3.22, *dd* $J_{5,6eq}$ 4			4.66 J_{gem} 12 4.08 J_{gem} 12	7.00, *d* $J_{3',4'}$ 7	7.70, *dd* $J_{4',6'}$ 2	8.40, *d*
13		3.98, *m*		2.98, *dd* $J_{2,3ax}$ 4 J_{gem} 15	2.63, *ddd* $J_{2,3eq}$ 4 $J_{3eq,5}$ 2			4.28, *m*	3.68, *dd* $J_{5,6ax}$ 4 J_{gem} 14	2.45, *dd* $J_{5,6eq}$ 5 $J_{2,6eq}$ 2			4.33 J_{gem} 11 4.53 J_{gem} 12	7.10, *d* $J_{3',4'}$ 7	7.85, *dd* $J_{4',6'}$ 2	8.30, *d*
14		4.45, *s*				2.42, *dd* $J_{4ax,5}$ 3 J_{gem} 14	2.25, *dd* $J_{4eq,5}$ 2	4.50, *m*	2.94, *dd* $J_{5,6ax}$ 4 J_{gem} 14	2.80, *dt* $J_{5,6eq} = J_{4,6eq}$ 2	4.40, *s*		4.50 J_{gem} 12	6.90, *d* $J_{3',4'}$ 7	7.60, *dd* $J_{4',6'}$ 2	8.30, *d*
15	5.30, *dd*	4.25, *s*				2.05, *t* $J_{2,3ax} = J_{gem}$ 14		4.40, *m*						3.50, *s* $J_{3',4'}$ 7	$J_{4',6'}$ 2	
16		4.80, *s*				2.20, *dd* $J_{4ax,5}$ 4 J_{gem} 15	2.48, *dt* $J_{4eq,5} = J_{4eq,6eq}$ 3	4.30, *m*	2.85, *dd* $J_{5,6ax}$ 5 J_{gem} 14	2.98, *dd* $J_{5,6eq}$ 2	4.18, *s*		4.90 J_{gem} 12 4.58 J_{gem} 11	7.20, *d* $J_{3',4'}$ 7	7.50, *dd* $J_{4',6'}$ 2	8.30, *d*
17		4.18, *s*				2.20, *dd* $J_{4ax,5}$ 11 J_{gem} 14	2.48, *ddd* $J_{4eq,5}$ 6 $J_{4eq,6eq}$ 2	3.94, *m*	2.85, *dd* $J_{5,6ax}$ 11 J_{gem} 13	2.98, *dd* $J_{5,6eq}$ 5	1.85, *s*		4.47 J_{gem} 12 4.33 J_{gem} 12	7.00, *d* $J_{3',4'}$ 7	7.40, *dd* $J_{4',6'}$ 2	8.40, *d*

Methyl 4-O-benzoyl-6-bromo-2-C-[(2′-chloro)-pyrid-5′-yl]-3,6-dideoxy-α-D-ribo-hexopyranoside (**3**).—Barium carbonate (0.38 g, 1.98 mmol) and *N*-bromosuccinimide (0.25 g, 1.45 mmol) were added to a solution of 4,6-*O*-benzylidene hexopyranoside (**1**) (0.5 g, 1.32 mmol) in CCl_4 (10 mL). The solution was refluxed for 3 h. The reaction mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (15 mL), washed with aq sodium thiosulfate solution (15 mL), brine (15 mL), and water (15 mL), dried over anhyd magnesium sulfate and concentrated under reduced pressure. Flash chromatography (3/7: EtOAc–heptane) afforded **3** (0.42 g, 70%); $[\alpha]_D$ +46° (*c* 1.0, $CHCl_3$); *m/z* (CI) 456–458–460 $[M+H]^+$, 378–380 $[M-Br]^+$. Anal. Calcd for $C_{19}H_{19}BrClNO_5$: C, 49.97; H, 4.19; N, 3.07. Found: C, 49.67; H, 4.02; N, 3.28.

Methyl 4-O-benzoyl-6-bromo-3-C-[(2′-chloro)-pyrid-5′-yl]-2,6-dideoxy-α-D-ribo-hexopyranoside (**4**).—This compound was obtained (92%) from **2** as described for the preparation of **3** from **1**; $[\alpha]_D$ +2.7° (*c* 1.0, $CHCl_3$); *m/z* (CI) 456–458–460 $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}BrClNO_5$: C, 49.97; H, 4.19; N, 3.07. Found: C, 50.06; H, 4.10; N, 2.89.

Methyl 6-bromo-2-C-[(2′-chloro)-pyrid-5′-yl]-3,6-dideoxy-α-D-ribo-hexopyranoside (**5**).—Sodium (0.06 g, 2.6 mmol) was dissolved in MeOH (35 mL) at rt before the addition of **3** (1.2 g, 2.6 mmol). The reaction mixture was stirred for 2 h at rt, concentrated in vacuo. The residue was dissolved in EtOAc (35 mL), washed with brine (35 mL) and water (35 mL), dried over anhyd magnesium sulfate and concentrated under reduced pressure; **5** (1.15 g, 80%) was obtained analytically pure. $[\alpha]_D$ +65.5° (*c* 1.02, $CHCl_3$); *m/z* (CI) 352–354–356 $[M+H]^+$, 272–274 $[M-HBr]^+$. Anal. Calcd for $C_{12}H_{15}BrClNO_4$: C, 40.88; H, 4.29; N, 3.97. Found: C, 41.16; H, 4.47; N, 3.76.

Methyl 6-bromo-3-C-[(2′-chloro)-pyrid-5′-yl]-2,6-dideoxy-α-D-ribo-hexopyranoside (**6**).—This compound was obtained (80%) from **4** as described for the preparation of **5** from **3**; $[\alpha]_D$ +62.6° (*c* 1.25, $CHCl_3$); *m/z* (CI) 352–354–356 $[M+H]^+$, 272–274 $[M-HBr]^+$. Anal. Calcd for $C_{12}H_{15}BrClNO_4$: C,

Table 3
^{13}C NMR chemical shifts (δ in ppm)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	OMe	COBz	CH_2Ph	C-2′	C-3′	C-4′	C-5′	C-6′
3	100.4	63.6	39.5	68.2	69.6	32.3	55.7	164.9		150.7	123.9	135.5	137.2	148.0
4	98.3	42.1	73.1	67.8	76.6	32.2	55.8	169.0		150.9	123.5	135.6	136.1	147.5
5	100.2	72.0	43.3	65.6	72.3	33.4	55.6			150.7	123.9	137.8	137.1	147.9
6	98.2	41.6	73.0	69.6	72.3	33.9	55.7			148.4	123.8	136.4	137.8	147.4
7	106.6	71.8	40.7	72.5	154.0	101.2	57.4		70.3	147.8	123.9	136.8	137.6	146.7
8	100.0	41.4	74.1	79.1	155.1	99.9	55.8		73.2	147.6	123.4	136.4	137.6	146.5
9	99.1	72.3	39.4	71.1	154.7	95.7	55.5		71.4 65.1	149.2	124.2	136.8	137.6	148.7
10	100.1	37.1	67.5	77.3	154.0	98.7	56.1		71.6 65.2	148.8	124.0	137.2	137.6	148.1
11	207.3	81.1	36.2	73.5	77.1	41.9			72.6	148.9	123.7	137.5	138.8	147.1
12	204.3	80.6	32.9		76.5	44.5			72.6 65.4	150.1	124.4	135.9	138.1	148.8
13	202.3	78.8	31.1		76.9	42.5			72.6 65.4	151.1	124.5	137.9	138.1	148.8
14	206.1	84.3	81.9	42.7	69.4	49.0			72.9	148.8	123.4	136.3	138.5	146.3
15	205.0	83.9	81.8	46.4	66.0	49.7			72.9	148.8	123.9	135.9	138.1	146.6
16	205.1	85.1	87.4	47.1	69.5	50.2			73.4 69.3	151.5	124.7	137.8	139.4	148.7
17	205.1	85.3	81.3		66.4	49.9			73.2 65.8	151.5	124.7	137.8	139.4	148.7

40.88; H, 4.29; N, 3.97. Found: C, 41.15; H, 4.36; N, 3.81.

Methyl 4-O-benzyl-2-C-[(2′-chloro)-pyrid-5′-yl]-3,6-dideoxy-α-D-erythro-hex-5-enopyranoside (**7**).—Pulverised KOH (0.17 g, 3.12 mmol), benzyltriethylammonium chloride (0.03 g, 0.14 mmol) and BnBr (0.18 mL, 1.54 mmol) were added to a solution of **5** (0.5 g, 1.42 mmol) in CH_2Cl_2 (15 mL). The solution was stirred vigorously overnight at rt. MeOH (2 mL) was introduced and the reaction mixture was stirred at rt for 3 h. The mixture was filtered through a Celite® pad and the filtrate concentrated under reduced pressure. The crude residue was dissolved in DMF (20 mL) and NaH (0.15 g, 3.12 mmol, 50% in dispersion) was added at 0 C and the reaction mixture stirred at rt for 3 h. After the addition of MeOH (0.5 mL) and CH_2Cl_2 (20 mL), the reaction mixture was washed with water (20 mL) and the aq layer extracted three times with CH_2Cl_2 (20 mL). The combined organic layers were dried over anhyd magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (1/1: EtOAc–heptane) to afford **7** (0.32 g, 62%); mp 101 °C (AcOEt–heptane); $[\alpha]_D$ + 57.7° (*c* 0.99, $CHCl_3$); *m/z* (CI) 362–364 $[M + H]^+$. Anal. Calcd for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.57; Cl, 10.08; N, 3.87. Found: C, 63.07; H, 5.41; Cl, 9.80; N, 3.72.

Methyl 4-O-benzyl-3-C-[(2′-chloro)-pyrid-5′-yl]-2,6-dideoxy-α-D-erythro-hex-5-enopyranoside (**8**).—This compound was obtained (0.38 g, 75%) from **6** as described for the preparation of **7** from **5**; mp 123 °C (CH_2Cl_2–heptane); $[\alpha]_D$ −7.2° (*c* 1.04, $CHCl_3$); *m/z* (CI) 362–364 $[M + H]^+$. Anal. Calcd for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.57; N, 3.87; Cl, 9.80. Found: C, 63.11; H, 5.45; N, 3.83; Cl, 9.71.

Methyl 2,4-di-O-benzyl-2-C-[(2′-chloro)-pyrid-5′-yl]-3,6-dideoxy-α-D-erythro-hex-5-enopyranoside (**9**).—Following the procedure described above, a mixture of pulverised KOH (0.16 g, 3 mmol), benzyltriethylammonium chloride (0.03 g, 0.14 mmol), BnBr (0.35 mL, 3 mmol) and compound **5** (0.48 g, 1.36 mmol) in CH_2Cl_2 (15 mL) was stirred vigorously overnight at rt. The purification followed the work-up described above for the preparation of **7**. The purified mixture was dissolved in DMF (20 mL) and NaH (0.08 g, 1.6 mmol, 50% in dispersion) was added at 0 °C and the reaction mixture stirred at rt for 3 h. Compound **9** (0.32 g, 50%) was afforded by the same work-up described above for compound **7**; $[\alpha]_D$ +75.7° (*c* 1.03, $CHCl_3$); *m/z* (CI) 452–454 $[M + H]^+$. Anal. Calcd for $C_{26}H_{26}ClNO_4$: C, 69.10; H, 5.80; N, 3.10; Cl, 7.84. Found: C, 69.11; H, 6.07; N, 3.30; Cl, 7.55.

Methyl 3,4-di-O-benzyl-3-C-[(2′-chloro)-pyrid-5′-yl]-2,6-dideoxy-α-D-erythro-hex-5-enopyranoside (**10**).—This compound was obtained (0.33 g, 54%) from **6** as described for the preparation of **9** from **5**. $[\alpha]_D$ +38.6° (*c* 1.28, $CHCl_3$); *m/z* (CI) 452–454 $[M + H]^+$. Anal. Calcd for $C_{26}H_{26}ClNO_4$: C, 69.10; H, 5.80; N, 3.10. Found: C, 69.33; H, 5.84; N, 3.42.

2-L-(2,4/5)-2-Benzyloxy-4-C-[(2′-chloro)-pyrid-5′-yl]-4,5-dihydroxycyclohexanone (**11**).—To a stirred mixture of hexenopyranoside **7** (0.5 g, 1.4 mmol) in 2/3 water–dioxane (10 mL) was added palladium(II) chloride (37 mg, 0.21 mmol). The mixture was heated at 60 °C for 3 h. Dioxane was evaporated under reduced pressure and the aq layer diluted with 10 mL of water; the resulting mixture was extracted three times with EtOAc (10 mL). The combined organic layers were dried over anhyd magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (3/7: EtOAc–heptane) to afford compound **11** (96 mg, 20%). $[\alpha]_D$ −32.7° (*c* 1.02, $CHCl_3$); *m/z* (CI) 348–350 $[M + H]^+$. Anal. Calcd for $C_{18}H_{18}ClNO_4$: C, 62.16; H, 5.22; N, 4.03; Cl, 10.19. Found: C, 61.92; H, 5.32; N, 3.94; Cl, 10.63.

2-L-(2,4,5/0)-2,4-Dibenzyloxy-4-C-[(2′-chloro)-pyrid-5′-yl]-5-hydroxycyclohexanone (**12**) *and 2-L-(2,4/5)-2,4-dibenzyloxy-4-C-[(2′-chloro)-pyrid-5′-yl]-5-hydroxy-cyclohexanone* (**13**)

Method A: with 1.2 equiv mercury(II) chloride. To a stirred mixture of hexenopyranoside (**9**) (0.38 g, 1.05 mmol) in 2/3 water–acetone (10 mL) was added mercury(II) chloride (0.32 g, 1.3 mmol). The mixture was stirred at rt for

3 h. Acetone was evaporated under reduced pressure and the aq layer was diluted with 10 mL of water, the resulting mixture was extracted three times with CH_2Cl_2 (10 mL). The combined organic layers were washed with water, dried over anhyd magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (7/3: EtOAc–heptane). Ketone **12** was eluted first (0.14 g, 41%); $[\alpha]_D$ −3.0° (*c* 1.05, $CHCl_3$); *m/z* (CI) 438–440 $[M+H]^+$. Anal. Calcd for $C_{25}H_{24}ClNO_4$: C, 68.57; H, 5.52; N, 3.20. Found: C, 68.55; H, 5.44; N, 3.55. Ketone **13** was then eluted (0.14 g 41%); $[\alpha]_D$ −36.3° (*c* 1.07, $CHCl_3$); *m/z* (CI) 438–440 $[M+H]^+$. Anal. Calcd for $C_{25}H_{24}ClNO_4$: C, 68.57; H, 5.52; N, 3.20; Cl, 8.10. Found: C, 68.50; H, 5.67; N, 3.34; Cl, 8.02.

Method B: with mercury(II) trifluoroacetate. With mercury(II) trifluoroacetate (1.2 equiv/**9**), instead of mercury(II) chloride, as described above, ketones **12** and **13** were isolated in 37 and 37% yields, respectively.

Method C: catalytic method. With mercury(II) trifluoroacetate (0.1 equiv/**9**), the ketones **12** and **13** were isolated in 7 and 61% yields, respectively.

2-L-(2,3,5/0)-2-benzyloxy-3-C-[(2′-chloro)-pyrid-5′-yl]-3,5-dihydroxy-cyclohexanone (**14**) *and 2-L-(2,3/5)-2-benzyloxy-3-C-[(2′-chloro)-pyrid-5′-yl]-3,5-dihydro-xycyclohexanone* (**15**)

Method A: with mercury(II) chloride. With mercury(II) chloride (1.2 equiv/**8**), as described above, chromatography (7/3: EtOAc–heptane) afforded first ketone **14** (41%); $[\alpha]_D$ −59.3° (*c* 1.24, $CHCl_3$); *m/z* (CI) 348–350 $[M+H]^+$. Anal. Calcd for $C_{18}H_{18}ClNO_4$: C, 62.16; H, 5.22; N, 4.03; Cl, 10.19. Found: C, 62.26; H, 5.05; N, 4.11; Cl, 10.14. Ketone **15** was eluted next (0.16 g, 48%); $[\alpha]_D$ −65.2° (*c* 1.01, $CHCl_3$); *m/z* (CI) 348–350 $[M+H]^+$. Anal. Calcd for $C_{18}H_{18}ClNO_4$: C, 62.16; H, 5.22; N, 4.03; Cl, 10.19. Found: C, 62.18; H, 5.18; N, 3.98; Cl, 10.47.

Method B: with mercury(II) trifluoroacetate. With mercury(II) trifluoroacetate (1.2 equiv/**8**), instead of mercury(II) chloride, the ketones **14** and **15** were isolated in 78 and 9% yields, respectively.

Method C: catalytic method. With mercury(II) trifluoroacetate (0.1 equiv/**8**), only ketone **14** was isolated in 83% yield.

2-L-(2,3,5/0)-2,3-dibenzyloxy-3-C-[(2′-chloro)-pyrid-5′-yl]-5-hydroxycyclohexanone (**16**) *and 2-L-(2,3/5)-2,3-dibenzyloxy-3-C-[(2′-chloro)-pyrid-5′-yl]-5-hydroxy-cyclohexanone* (**17**)

Method A: with mercury(II) trifluoroacetate. With mercury(II) trifluoroacetate (1.2 equiv/**10**), following the same procedure, chromatography (7/3: EtOAc–heptane) afforded first ketone **16** (37%). $[\alpha]_D$ −26.4° (*c* 1.10 in $CHCl_3$); *m/z* (CI) 438–440 $[M+H]^+$, 330–332 $[M+H-PhCH_2OH]^+$. Anal. Calcd for $C_{25}H_{24}ClNO_4$: C, 68.57; H, 5.52; N, 3.20; Cl, 8.10. Found: C, 68.46; H, 5.77; N, 3.06; Cl, 7.66. Ketone **17** was eluted next (37%); $[\alpha]_D$ −38.9° (*c* 1.08, $CHCl_3$); *m/z* (CI) 438–440 $[M+H]^+$, 330–332 $[M+H-PhCH_2OH]^+$. Anal. Calcd for $C_{25}H_{24}ClNO_4$: C, 68.57; H, 5.52; N, 3.20; Cl, 8.10. Found: C, 68.82; H, 5.31; N, 3.14; Cl, 8.38.

Method B: catalytic method. With mercury(II) trifluoroacetate (0.1 equiv/**10**), the ketones **16** and **17** were isolated in 23 and 54% yields, respectively.

2. Supplementary material

Complete crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited at the Cambridge Crystallographic Data Centre with no. 143894 CCDC. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or, www: http://www.ccdc.cam.ac.uk).

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