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Note

Efficient nitrogen alkylation with carbohydrates

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Abstract

Efficient nitrogen alkylation of various primary and secondary amines, including cyclic, heterocyclic and alkaloid type amines, with a sugar oxetane 3,5-anhydro-1,2-*O*-cyclohexylidene-α-D-xylofuranose is described. As a result, 5-amino-5-deoxy derivatives of xylofuranose were obtained in good yields. © 2003 Elsevier Science Ltd. All rights reserved.

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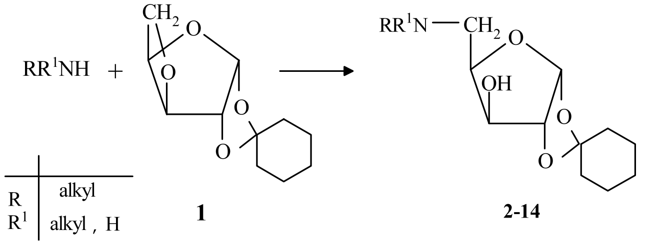
In contrast to numerous synthetic applications of non-carbohydrate oxetane ring opening with a variety of nucleophiles,[1] including amines,[2,3] the opening of the oxetane ring in carbohydrates with an amine has not been studied. In line with the general reactivity of oxetane rings, this reaction would lead to direct one-step nitrogen alkylation of a primary or secondary amines with carbohydrates. According to the reaction scheme proposed for 3,5-anhydro-1,2-*O*-cyclohexylidene-α-D-xylofuranose (**1**), Scheme 1, a prospect of ready alkylation of an amine with a carbohydrate is challenging. In this way, secondary or tertiary amines could be obtained from primary or secondary ones, with defined configuration on all potentially reactive centers in the new alkyl group (i.e., that of a carbohydrate itself). Amino derivatives of xylofuranose in particular are proven enantioselective chiral catalysts for the reaction of aldehydes with diethylzinc compounds.[4]



Scheme 1. N-Alkylation of primary and secondary amines with xylofuranose.

Our previous investigations of the reactivity of the 3,5-anhydro ring in **1** towards several anionic nucleophiles, showed that **1** behaves like non-sugar oxetane system, with pronounced regioselectivity of the process.[5] Further experimental confirmation of this general similarity in reactivity and regioselectivity has now been obtained in reaction of **1** with different primary and secondary amines.

The reaction of 3,5-anhydro-1,2-*O*-cyclohexylidene-D-xylofuranose (**1**) with numerous amines, under the reaction conditions frequently used for oxetane ring opening in non-carbohydrate oxetanes,[2,3,6] gave the N-xylofuranose derivatives of the starting amine in good yield (Scheme 1 and Table 1).

Reiff and co-workers[6] have found that opening of oxetane ring in some simple hydroxymethyl oxetanes is highly dependent on the bulk of the starting amine and advised implementation of high reaction temperatures (up to 250 °C), 10–24 h reaction time, and a catalyst. We have found that alkylation of a variety of amines with oxetane **1** proceeds under relatively milder reaction conditions, shorter reaction time and higher yield (Table 1). Also, in light of our experiments, the structure of the starting amine has little impact on the course of its reaction with **1**: no significant difference in the yield of reaction was observed regardless of whether the starting amine was primary or secondary, simple

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Table 1
N-alkylation of primary and secondary amines with xylofuranose

Entry	Starting amine	Form [a]	Molecular formula [b]	Time (h)	Temperature (°C)	Yield %
2	*n*-Butylamine	n.o.	$C_{32}H_{56}N_2O_{12}$	8	160	78.0
3	*tert*-Butylamine	n.o.	$C_{32}H_{56}N_2O_{12}$	20	140	74.2
4	1-Amino-3-methylbutane	n.o.	$C_{34}H_{60}N_2O_{12}$	8	150	85.8
5	2-Ethylhexylamine	n.o.	$C_{40}H_{72}N_2O_{12}$	6	150	80.2
6	Cyclohexylamine	n.o.	$C_{36}N_{60}N_2O_{12}$	6	150	78.6
7	2,2-Dimethylpropyl amine	n.o.	$C_{34}H_{60}N_2O_{12}$	6	150	74.1
8	Dodecylamine	fb	$C_{23}H_{43}NO_4$	8	160	76.5
9	Morpholine	fb	$C_{15}H_{25}NO_5$	6	150	79.4
10	Piperidine	fb	$C_{16}H_{27}NO_4$	8	100	81.4
11	4-Hydroxypiperidine	fb	$C_{16}H_{27}NO_5$	15	130	81.2
12	Phenethylamine	h	$C_{19}H_{28}ClNO_4$	20	130	74.7
13	Amphetamine	h	$C_{20}H_{30}ClNO_4$	20	160	72.8
14	Demethylmorphine	fb	$C_{27}H_{33}NO_7 \cdot H_2O$	20	140	66.9

[a] n.o., isolated as neutral oxalate of the type B_2A; fb, isolated as free base; h, isolated as hydrochloride.

[b] In the mass spectra, **2**–**14** gave molecular ion for free base irrespective of whether the specimen was free base or its salt.

cyclic or heterocyclic, or when a secondary amino group was a part of the condensed ring system in an alkaloid structure (demethylmorphine). The reactivity of **1** could partly be attributed to the strain relief effect in its system of three condensed rings.

The reaction was found to be highly regiospecific, proceeding via the nucleophilic attack of the amine on the less hindered side of oxetane ring exclusively (i.e., C-5 of xylofuranose).

The results of ^1H and ^{13}C NMR analysis of **2**–**14** were in agreement with the proposed reaction pathway (^1H NMR data of xylofuranose protons in **2**–**14** are tabulated in Table 2, while other significant ^1H NMR signals are given in Section 1; ^{13}C NMR data of **2**–**14** are given in Table 3).

The final outcome of the reaction was an effective N-alkylation of the starting amine by the carbohydrate moiety. Despite of the very different structures of the amines, isolated yields were in the range of 70–85%. The reaction is general, reasonably fast, experimentally simple in using no solvent, thereby facilitating product isolation, high yielding and free from side products. Since the starting anhydro sugar **1** is an easily obtainable compound [5,7], the method of preparation of 5-amino-5-deoxy derivatives of xylofuranose starting from oxetane **1** seems to be superior in its experimental simplicity to the methods described earlier.

1. Experimental

1.1. General methods

Melting points were determined on a Bűchi SMP50 apparatus and are not corrected. The NMR spectra were run on a Bruker AC250E apparatus in $CHCl_3$, D_2O or Me_2SO, using Me_4Si as an internal standard.

Mass spectra were recorded with a Finnigan MAT 311A spectrometer, using EI method, or with a Finnigan MAT 8230BE apparatus, using CI technique; the first number when referring to the mass spectra denotes the m/z value, while the numbers in parenthesis correspond to the relative abundance of the mass peak. Optical rotations were measured with automatic polarimeter Polamet A (Karl Zeiss, Jena). TLC was performed on Silica gel DC Alufolien (E. Merck No. 1.05553), with benzene–EtOAc 4:1 as the mobile phase. Visualization of the spots was achieved by spraying with 50% sulfuric acid and subsequent heating to 150 °C. All organic extracts were dried with anhydrous Na_2SO_4. Organic solutions were concentrated using a rotary evaporator and under diminished pressure.

The reaction of amine with oxetane **1** was performed in a cylindrical stainless steel flask with 10 mL internal volume, closed with a screw cap. General method of synthesis consists of mixing amine, oxetane and catalytic amount of water, followed by heating (see Table 1). The end of reaction was detected by the disappearance of starting oxetane in TLC, whereupon the reaction mixture was dissolved (usually in ether or acetone), and decolourized with active carbon. The unreacted starting amine was removed by evaporation under diminished pressure, where possible.

1.2. 5-Butylamino-1,2-*O*-cyclohexylidene-5-deoxy-α-D-xylofuranose oxalate (2)

A mixture of oxetane **1** (1.0 g, 4.7 mmol), *n*-butylamine (1.72 g, 23.5 mmol) and water (0.3 g) was heated to 160 °C for 8 h in a closed vessel. At this stage, a TLC

Table 2
^{1}H NMR resonancies of xylofuranose protons in **2**–**14**

No.	Chemical shifts (ppm)						Coupling constants (Hz)				
	H-1	H-2	H-3	H-4	H-5$_a$	H-5$_b$	$J_{1,2}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5b}$	$J_{5a,5b}$
2 [a]	6.13 (d)	4.76 (d)	4.38 (d)	4.50 (m)	3.38 (dd)	3.47 (dd)	3.7	2.6	7.3	3.6	13.6
3 [b]	6.07 (d)	4.71 (d)	4.32 (d)	4.41 (dt)	3.24 (dd)	3.42 (dd)	3.7	2.8	8.0	3.2	13.2
4 [b]	6.11 (d)	4.47 (d)	4.36 (d)	4.48 (m)	3.36 (dd)	3.46(dd)	3.7	2.6	7.4	3.5	13.6
5 [b]	6.11 (d)	4.74 (d)	4.37 (d)	4.50 (m)	3.38 (dd)	3.48 (dd)	3.7	2.7	7.0	3.1	13.4
6 [b]	6.09 (d)	4.73 (d)	4.34 (d)	4.45 (m)	3.34 (dd)	3.46 (dd)	3.7	2.7	7.9	3.2	13.5
7 [b]	6.11 (d)	4.74 (d)	4.38 (d)	4.53 (m)	3.40 (dd)	3.52 (dd)	3.7	2.7	7.3	3.1	13.8
8 [a]	5.95 (d)	4.47 (bm)	4.27 (d)	4.19 (m)	2.93 (dd)	3.37 (dd)	3.6	2.7	1.0	3.5	12.9
9 [a]	5.94 (d)	4.47 (d)	4.29 (d)	4.13 (m)	2.85 (dd)	3.09 (dd)	3.7	2.5	2.7	2.9	14.5
10 [a]	5.93 (d)	4.44 (d)	4.27 (d)	4.07 (m)	2.79 (broad dd)	3.02 (dd)	3.6	2.3	2.7	2.6	14.6
11 [a]	5.92 (d)	4.44 (d)	4.25 (d)	4.08 (m)	2.82 (dd)	3.03 (dd)	3.7	2.4	2.9	3.8	14.6
12 [a]	5.83 (d)	4.55 (d)	4.47–4.50 (m)	4.47–4.50 (m)	3.27–3.40 (m)	3.59 (dd)	3.7			2.4	13.4
13 [a]	5.89 (d)	4.45 (d)	4.28 (d)	4.20 (m)	3.03 (dd)	3.29 (dd)	3.7	3.0	1.2	3.7	12.8
14 [c]	5.95 (d)	4.47 (d)	4.05–4.40 group of signals	4.05–4.40 group of signals	0.76–3.69 group of signals	0.76–3.69 group of signals	3.0				

[a] In $CDCl_3$.
[b] In D_2O.
[c] In Me_2SO.

Table 3
^{13}C NMR data for **2–14**

No.	Chemical shifts (ppm)						Other signals
	C-1	C-2	C-3	C-4	C-5	C-1 cd [d]	
2 [a]	106.99	86.95	77.32	78.59	48.79	116.44	15.46, Me; 21.85, 25.80, 26.22, 26.78, 30.05, 37.33 and 38.10, 5× CH$_2$ cd and 2× CH$_2$ butyl; 50.58, CH$_2$–N; 176.20, C=O oxalate
3 [b]	107.04	86.99	77.29	79.04	60.35	116.44	25.84, 26.26, 26.83, 37.39 and 38.13, 5× CH$_2$ cd; 27.43, Me; 43.34, Cq *t*-butyl; 176.19, C=O oxalate
4 [b]	106.96	86.93	77.29	78.54	48.79	116.41	24.05 and 24.08, 2× Me; 25.78, 26.20, 26.76, 37.31 and 38.08, 5× CH$_2$ cd; 28.00, –CH$_2$–*C*H(CH$_3$)$_2$; 36.67, –*C*H$_2$–CH(CH$_3$)$_2$; 49.35, CH$_2$–N; 176.02, C=O oxalate
5 [b]	106.43	86.36	77.01	77.69	48.72	115.95	11.59 and 15.45, 2× Me; 25.26, 25.68, 26.23, 37.58 and 38.09, 5× CH$_2$ cd; 24.37, 25.14, 29.75, 31.66 and 36.81, CH and 4× CH$_2$ from ethylhexyl; 53.47, CH$_2$–N
6 [b]	106.98	86.93	77.25	78.76	45.87	116.39	25.78, 26.21, 26.77, 37.31 and 38.08, 5× CH$_2$ cd; 26.67, 27.18, 31.35 and 31.46, 5× CH$_2$ cyclohexyl; 60.49, CH cyclohexyl; 176.10, C=O oxalate
7 [b]	106.44	86.28	77.15	77.54	49.68	115.91	24.80, Me; 25.27, 25.69, 26.26, 36.82 and 37.58, 5× CH$_2$ cd; 32.06, Cq; 61.66, CH$_2$–N; 175.10, C=O oxalate
8 [a]	104.73	85.64	78.34	76.93	48.55	112.09	14.17, Me; 22.72, 23.63, 23.97, 24.98, 27.16, 29.32, 29.49, 29.58, 29.66, 29.68, 31.95, 35.68 and 36.58, 5× CH$_2$ cd and 10× CH$_2$ dodecyl; 49.67, CH$_2$–N
9 [a]	104.28	85.06	77.87	76.92	57.60	111.99	23.53, 23.86, 24.88, 35.56 and 36.34, 5× CH$_2$ cd; 55.07, CH$_2$–N morpholine; 66.86, CH$_2$–O morpholine
10 [a]	104.28	85.12	77.77	76.88	57.81	111.75	23.47, 23.51, 23.80, 24.84 and 25.98, C-3′, C-4′, C-5′, C-3″, C-4″, C-5″; 35.52 and 36.29, C-2′ and C-6′; 56.02, C-2″ and C-6″
11 [a]	104.46	85.14	77.79	77.00	57.60	112.13	23.69, 24.02 and 25.04, C-3′, C-4′ and C-5′; 34.41 and 34.65, C-3″ and C-5″; 35.72 and 36.48, C-2′ and C-6′; 52.60 and 52.95, C-2″ and C-6″; 66.67, C-4″
12 [a]	104.43	84.69	75.2 and 75.42		46.16	112.95	23.51, 23.87, 24.80, 35.58 and 36.53, 5× CH$_2$ cd; 32.52, *C*H$_2$Ph; 50.87, CH$_2$–N
13 [a]	104.58	85.49	78.15	76.95	45.90	112.02	19.77, Me; 23.50, 23.84, 23.85, 35.61 and 36.50, 5× CH$_2$ cd; 42.95, CH$_2$–amphetamine; 54.26, CH–amphetamine; 126.41,128.31, 129.10, 129.16, 138.20, ArC
14 [c]	104.22	84.76	76.24	77.51		112.08	22.30, 34.48, CH$_2$-10′, CH$_2$-15′; 23.44, 23.77, 24.75, 35.40, 36.16, 5× CH$_2$ cd; 40.53, 59.71, CH-9′, CH-14′: 42.65, C-13′; 46.11 and 55.23, C-5 and CH$_2$-16′; 66.37, CH-6′; 90.91, CH-5′; 124.97, 130.41, 138.19, 145.58, Cq-11′, Cq-12′, Cq-3′,Cq-4′; 117.25 and 119.79, CH-1′ and CH-2′; 124.97, CH-7′; 133.01, CH-8′

[a] In CDCl$_3$.
[b] In D$_2$O.
[c] In Me$_2$SO.
[d] cd = cyclohexylidene.

showed complete disappearance of the starting oxetane. Unreacted *n*-butylamine was removed under diminished pressure, and the reaction mixture dissolved in acetone (50 mL) and decolourized with active carbon. Crude oxalate salt was deposited with oxalic acid dihydrate in acetone (0.30 g in 10 mL) as a creamy crystalline mass. Recrystallization from MeOH–EtOAc gave **2** (1.21 g, 78%), mp 228 °C; ^{1}H NMR ($CDCl_3$): 0.97, t, 3 H, CH_3–butyl; 1.34–1.83, m, 14 H, cyclohexylidene and 2 × CH_2–butyl; 3.15, m, 2 H, CH_2–N; CI MS: 285 (M^+, 51), 242 (19), 153 (62), 140 (28), 86 (100); Anal. Calcd. for $C_{32}H_{56}N_2O_{12}$: C, 58.16; H, 8.54; N, 4.23. Found: C, 58.43; H, 8.47; N, 4.23.

1.3. 5-*tert*-Butylamino-1,2-*O*-cyclohexylidene-5-deoxy-α-D-xylofuranose oxalate (3)

A mixture of oxetane **1** (1.0 g, 4.7 mmol), *tert*-butylamine (1.72 g, 23.5 mmol) and water (0.3 g) was heated to 160 °C for 8 h in a closed vessel. Unreacted *tert*-butylamine was removed under diminished pressure and remaining oil dissolved in acetone (50 mL) and decolourized with active carbon. To the decolourized acetone solution, oxalic acid dihydrate in acetone (0.30 g in 10 mL) was added, whereupon crude oxalate was deposited as white crystalline mass. Recrystallization from MeOH gave **3** (1.15 g, 74.2%), which sublimed in the range 190–240 °C without melting; ^{1}H NMR (D_2O): 1.30–1.76, m, 19 H, 3 × Me and cyclohexylidene; CI MS: 286 ($M^+ + 1$, 100%), 188 (48), 140 (23); Anal. Calcd. for $C_{32}H_{56}N_2O_{12}$: C, 58.16; H, 8.54; Found: C, 58.46; H, 8.72.

1.4. 1,2-*O*-Cyclohexylidene-5-deoxy-5-(3-methylbutylamino)-α-D-xylofuranose oxalate (4)

A mixture of oxetane **1** (1.0 g, 4.7 mmol), 1-amino-3-methylbutane (2.0 g, 23 mmol) and water (0.3 g) was heated to 150 °C for 10 h in a closed vessel. Codistillation of the reaction mixture with benzene (2 × 30 mL) under diminished pressure removed the unreacted 1-amino-3-methylbutane. The remaining mass was dissolved in acetone (100 mL) and decolourized with active carbon. The crude oxalate was deposited with oxalic acid dihydrate in acetone (0.3 g in 10 mL). Recrystallization from MeOH gave **4** (1.39 g, 85.8%), mp 212 °C; ^{1}H NMR (D_2O): 0.95, d, 6 H, 2 × Me, $J_{CH,Me}$ 6.4; 1.35–1.83, m, 13 H, cyclohexylidene and CH_2 and CH alkyl; 3.15, 2 H, CH_2–N; EIMS: 299 (M^+, 5.7), 256 (7.7), 242 (5.0), 140 (14.6), 100 (32.6); Anal. Calcd. for $C_{34}H_{60}N_2O_{12}$: C, 59.28; H, 8.77; N, 4.06. Found: C, 59.60; H, 9.11; N, 3.93

1.5. 1,2-*O*-Cyclohexylidene-5-deoxy-5-(2-ethylhexylamino)-α-D-xylofuranose oxalate (5)

A mixture of oxetane **1** (1.0 g, 4.7 mmol), 2-ethylhexylamine (2.0 g, 15.5 mmol) and water (0.3 g) was heated in a closed vessel to 150 °C for 6 h. Treating the reaction mixture as described in the previous example, gave **5** (1.46 g, 80.2%), crystals from MeOH, mp 204 °C.

^{1}H NMR (D_2O): 0.90, t, 6 H, 2 × Me; 1.26–1.81, 19 H, cyclohexylidene, CH and 4 × CH_2 alkyl, J_{CH,CH_2} 6.7; 3.08, 2 H, CH_2–N; EIMS: 341 (M^+, 10.4), 298 (13.5), 242 (100), 142 (51.0), 140 (47); Anal. Calcd. for $C_{40}H_{72}N_2O_{12}$: C, 62.15; H, 9.38; N, 3.62. Found: C, 62.45; H, 9.56; N, 3.68.

1.6. 5-Cyclohexylamino-1,2-*O*-cyclohexylidene-5-deoxy-α-D-xylofuranose oxalate (6)

A mixture of oxetane **1** (1.0 g, 4.7 mmol), cyclohexylamine (2.0 g, 20.2 mmol) and water (0.3 g) was heated to 150 °C in a closed vessel for 6 h. Treating the reaction mixture as described for **4**, gave **6** as white crystals from MeOH (1.32 g, 78.6%), mp 240 °C; ^{1}H NMR (D_2O): 1.12–2.18, m, 20 H, cyclohexylidene and 5 × CH_2 cyclohexyl; 3.19, m, 1 H, CH cyclohexyl; EIMS: 311 (M^+, 8.5), 267 (15.3), 169 (4.8), 139 (16.2), 111 (100); Anal. Calcd. for $C_{36}H_{60}N_2O_{12}$: C, 60.65; H, 8.48; N, 3.92. Found: C, 60.25; H, 8.09; N, 4.12

1.7. 1,2-*O*-Cyclohexylidene-5-deoxy-5-(2,2-dimethylpropylamino)-α-D-xylofuranose oxalate (7)

A mixture of oxetane **1** (1.0 g, 4.7 mmol), 2,2-dimethylpropylamine (2.0 g, 23 mmol) and water (0.3 g) was heated in a closed vessel to 150 °C for 6 h. After treating the reaction mixture as described for **2** and deposition of oxalate salt with oxalic acid dihydrate in acetone (0.35 g in 10 mL), white crystals were obtained. Recrystallization from MeOH gave **7** (1.20 g, 74.1%), mp 220 °C; ^{1}H NMR (D_2O): 1.05, s, 9 H, 3 × Me; 1.34–1.82, m, 10 H, cyclohexylidene; 3.01, s, 2 H, CH_2–N; EIMS: 299 (M^+, 8.16), 284 (7.1), 256 (18.2), 242 (100), 144 (48.8), 140 (35.2); Anal. Calcd. for $C_{34}H_{60}N_2O_{12}$: C, 59.28; H, 8.77; N, 4.06. Found: C, 59.24; H, 8.91; N, 4.11.

1.8. 1,2-*O*-Cyclohexylidene-5-deoxy-5-dodecylamino-α-D-xylofuranose (8)

A mixture of oxetane **1** (1.0 g, 4.7 mmol), *n*-dodecylamine (1.0 g, 5.4 mmol) and water (0.5 g) was heated in a closed vessel to 160 °C for 8 h. The reaction mixture was dissolved in acetone and decolourized with active carbon. Treating of the decolourized mixture with oxalic acid dihydrate in acetone (0.35 g in 15 mL) formed a white precipitate, which was separated and after drying at room temperature (rt) recrystallized from MeOH. Finely ground crude oxalate salt (1.85 g) was suspended in aq NaOH (2 g in 80 mL) and extracted with $CHCl_3$ (4 × 30 mL). The combined chloroform extracts were dried and evaporated to leave a colourless oil which crystallized on standing. Recrystallization from EtOAc gave **8** (1.43 g, 76.5%), mp 57 °C; $[\alpha]_D^{24}$ + 18.9° (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 0.87, t, 3 H, Me; 1.18–1.31, m, 30 H, cyclohexylidene and 10 × CH_2 dodecyl; 2.57, m, 2 H, CH_2–N; 4.47, broad signal, 3 H, NH, OH, broadening lost on mixing with D_2O; EIMS: 397 (M^+, 8.4), 353 (5.7), 241 (10.8), 197 (80), 139 (30); Anal. Calcd. for $C_{23}H_{43}NO_4$: C, 69.48; H, 10.90; N, 3.52. Found: C, 69.23; H, 11.14; N, 3.62.

1.9. 1,2-*O*-Cyclohexylidene-5-deoxy-5-(tetrahydro-1,4-oxazineamino)-α-D-xylofuranose (9)

A mixture of oxetane **1** (1.0 g, 4.7 mmol), morpholine (1.8 g, 20.7 mmol) and water (0.3 g) was heated in a closed vessel to 150 °C for 6 h. Unreacted morpholine was removed under diminished pressure to leave an oil, which crystallized on standing. The solid mass was dissolved in ether (100 mL), decolourized with active carbon and concentrated to a small volume. On addition of petroleum ether (40–70 °C), **9** crystallized (1.12 g, 79.4%), mp 93 °C; ^{1}H NMR ($CDCl_3$): 1.31–1.74, m, 10 H, cyclohexylidene; 2.47, m, 2 H, CH_2–N; 2.79–2.95, m, 2 H, CH_2–N; 3.67, t, 4 H, 2 × CH_2–O morpholine, *J* 4.6; 7.53, bs, 1 H, OH; EIMS: 299 (M^+, 3.3), 256 (3.1), 140 (3.5), 100 (76.5), 87 (70.5); Anal. Calcd. for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.41; N, 4.67. Found: C, 60.34; H, 8.11; N, 4.30.

1.10. 1,2-*O*-Cyclohexylidene-5-deoxy-5-hexahydropyridineamino-α-D-xylofuranose (10)

A mixture of oxetane **1** (0.5 g, 2.35 mmol), piperidine (0.35 g, 4.1 mmol) and water (0.20 g) was heated in a closed vessel to 100 °C for 8 h. The reaction mixture was dissolved in ether (80 mL) and decolourized with active carbon. After evaporation of ether, the unreacted piperidine was removed by codistillation with benzene (2 × 30 mL) to leave a colourless oil which crystallized on standing. Recrystallization from *iso*-octane gave **10**, (0.57 g, 81.4%), mp 79 °C; $[\alpha]_D^{20}$ + 31.6° (*c* 1.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.26–1.72, m, 17 H, OH, 2 × H-3″, 2 × H-4″, 2 × H-5″ and cyclohexylidene; 2.35, bs, 2 H, H-2″ or H-6″; 2.79, broad dd, 3 H, H-2″ or H-6″ and H-5_a; CI MS: 298 (M^+ + 1, 100), 254 (3), 242 (4), 200 (25); Anal. Calcd. for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15. Found: C, 64.79; H, 9.37.

1.11. 1,2-*O*-Cyclohexylidene-5-deoxy-5-(4-hydroxyhexahydropyridineamino)-α-D-xylofuranose (11)

A mixture of oxetane **1** (0.50 g, 2.35 mmol), 4-hydroxypiperidine (0.30 g, 2.9 mmol) and water (0.15 g) was heated in a closed vessel to 130 °C for 15 h. The reaction mixture was dissolved in acetone (80 mL) and decolourized with active carbon. After evaporation of acetone, unreacted starting amine was removed by codistillation with benzene (2 × 30 mL) to leave an oil (0.65 g), which crystallized on standing. The crude product was dissolved in a minimal amount of hot toluene and *iso*-octane was added until persistent clouding. On cooling, crystallized **11** (0.6 g, 81.2%), mp 109 °C; ^{1}H NMR ($CDCl_3$): 1.31–1.86, m, 16 H, 2 × H-3″, 2 × H-5″ and 2 × OH; 2.15, 2.48, 2.72 and 3.20, 4 m, 4 H, H-2″ and H-6″; CI MS: 314 (M^+ + 1, 100), 296 (5), 216 (8); Anal. Calcd. for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.46. Found: C, 61.17; H, 8.83; N, 4.59.

1.12. 1,2-*O*-Cyclohexylidene-5-deoxy-5-(2-phenylethylamino)-α-D-xylofuranose hydrochloride (12)

A mixture of oxetane **1** (1.00 g, 4.7 mmol), 2-phenylethylamine (0.74 g, 6.1 mmol) and water (0.3 g) was heated in a closed vessel to 130 °C for 20 h. The reaction mixture was dissolved in acetone at rt and decolourized with active carbon. After evaporation of acetone, unreacted 2-phenylethylamine was removed by codistillation with toluene (2 × 15 mL). The remaining yellow oil was dissolved in ether, and the crude hydrochloride was deposited with hydrochloric acid–ether. Recrystallization from isopropyl alcohol–ether gave **12** (1.30 g, 74.7%), mp 251 °C; ^{1}H NMR ($CDCl_3$): 1.26–2.01, m, 13 H, cyclohexylidene, OH and NH_2^+; 3.18, t, 2 H, CH_2–N; 3.27–3.40, m, 3 H, Ph–CH_2 and H-5_a; 7.21–7.38, m, 5 H, ArH; EIMS: 333 (M^+, 10.7), 290 (18.5), 242 (100), 144 (71.2), 105 (55.7); Anal. Calcd. for $C_{19}H_{27}NO_4 \cdot HCl$: C, 61.69; H, 7.63; N, 3.78. Found: C, 61.41; H, 7.50; N, 4.07.

1.13. 1,2-*O*-Cyclohexylidene-5-deoxy-5-(2-phenyl-1-methylethylamino)-α-D-xylofuranose hydrochloride (13)

A mixture of oxetane **1** (1.48 g, 7 mmol), (±) amphetamine (1.0 g, 7.4 mmol) and water (0.3 g) was heated in a closed vessel to 160 °C for 20 h. Diethyl ether (150 mL) was added to the reaction mixture and the insoluble mass was separated. To the ether solution, hydrochloric acid–ether was added as far as formation of insoluble salt could be observed. The crude hydrochloride was separated and air dried. Recrystallization from isopropanol–ether gave **13** (1.95 g, 72.8%), mp 189–191 °C $[\alpha]_D^{20}$ + 6.67° (*c* 1.00, $CHCl_3$); EIMS: 347 (M^+, 8), 304 (25), 255 (100), 157 (58); Anal. Calcd. for $C_{20}H_{29}NO_4 \cdot HCl$: C, 62.57; H, 7.87; N, 3.64. Found: C, 62.55; H, 8.05; N, 3.91.

TLC analysis of the resulting product revealed two close, but separate spots. NMR spectra of the specimen pointed to a mixture of stereoisomers. In order to obtain simpler NMR spectra, the salt mixture was transformed into free bases by suspending in aq NaOH (pH 10) and extracted with $CHCl_3$. Evaporation of the solvent and column separation of isomers with the 4:1:1 benzene–EtOAc–MeOH system provided the less polar isomer as a colourless oil. The ^1H and ^{13}C NMR spectra of the resulting single isomer are tabulated in Tables 2 and 3, with other significant data in ^1H NMR ($CDCl_3$) spectra as follows: 1.06, d, 3 H, Me, J_{CHMe} 6.1; 1.24–1.73, m, 10 H, cyclohexylidene; 2.66, d, 2 H, CH_2–amphetamine, J_{CHCH_2} 6.7; 2.86, m, 1 H, CH–amphetamine; 7.09–7.34, m, 5 H, ArH.

1.14. 1,2-*O*-Cyclohexylidene-5-deoxy-5-((5α,6α)-7,8-didehydro-4,5-epoxy-morphinan-3,6-diolamino)-α-D-xylofuranose hydrate (14)

A mixture of oxetane **1** (2.12 g, 10 mmol), demethylmorphine monohydrate $C_{16}H_{17}NO_3{\cdot}H_2O$ (2.5 g, 8.6 mmol), ethyleneglycol (1 mL) and water (0.5 g) was heated in a closed vessel to 150 °C for 10 h. The cooled reaction mixture was dissolved in acetone, decolourized with active carbon, and the acetone evaporated. The remaining oil was washed with petroleum ether (40–70 °C) in order to remove unreacted oxetane, and again dissolved in acetone. The crude hydrochloride of the N-xylofuranose derivative of demethylmorphine was deposited with hydrochloric acid–ether. The hydrochloride was initially white, but on standing turned yellow and had mp 216–218 °C. The hydrochloride was dissolved in water and the free base deposited with aq ammonia. Recrystallization from 30% aq MeOH gave **14** (2.9 g, 66.9%), mp 152–155 °C; ^1H NMR (Me_2SO): 0.76–3.69, group of signals, 20 H, cyclohexylidene, CH_2-5, CH_2-15′, CH_2-16′, CH_2-10′, H-9′ and H-14′; 4.05–4.40, group of signals, 3 H, H-6′, H-3 and H-4; 4.76, d, 1 H, H-5′; 5.14, bd, 1, H-7′; 5.58, bd, 1 H, H-8′; 5.4–6.25, bs, 3 H, disappears with D_2O; 6.65 and 6.64, 2d, 2 H, H-1′ and H-2′; CI MS: 484 ($M^+ + 1$, 85), 467 (100), 386 (8), 284 (18); Anal. Calcd. for $C_{27}H_{33}NO_7{\cdot}H_2O$: C, 64.65; H, 7.03; N, 2.79. Found: C, 64.92; H, 7.01; N, 3.00.

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