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SUPPLEMENTARY MATERIAL TO

Alkylating ability of carbohydrate oxetanes: Practical synthesis of bolaform skeleton derivatives

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GENERAL METHODS

The melting points were determined on a Büchi MP 50 apparatus and are not corrected. The NMR spectra were recorded on a Bruker AC250E instrument in $CDCl_3$ or D_2O, using Me_4Si as an internal standard. The mass spectra were recorded with a Thermo Finnigan Polaris Q or Finnigan MAT 8230BE spectrometer using the CI technique. TLC was performed on Silica gel DC Alufolien (Merck, Darmstadt), with 4:1 toluene–EtOAc as the mobile phase. The polarity of the mobile phase was augmented by the addition of MeOH or diethylamine when necessary. Visualization of the spots was achieved by spraying with 50 % sulfuric acid, followed by subsequent heating at 150 °C. The organic extracts were dried with anhydrous Na_2SO_4. The solutions were concentrated using a rotary evaporator under diminished pressure. Active carbon was used as decolorizing agent.

The practical way of performing the reaction of diamines with oxetane **1** consists in heating of the appropriate oxetane/amine mixture with occasional stirring in a closed vessel.

SPECIFIC SYNTHESES AND CHARACTERIZATION DATA

*5,5′-(1,2-Ethanediyldiimino)bis[1,2-O-cyclohexylidene-5-deoxy-α-D-xylofuranose] dihydrochloride (**2**)*

A mixture of oxetane **1** (3.2 g, 15 mmol), 1,2-diaminoethane monohydrate (0.35 g, 4.49 mmol) and water (5 drops) was heated in a closed vessel for 12 h at 110 °C. After cooling, the mixture was co-distilled with water to remove the

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unreacted diaminoethane; the crude product was dissolved in chloroform, washed several times with brine and evaporated to leave a red oil. The residue was dissolved in acetone and treated with a concentrated hydrochloric acid in acetone to pH 3. Light yellow precipitate was collected, air-dried and crystallized from 2-propanol–methanol to give pure **2** as the hydrochloride salt.

Yield: 0.81 g, 32.4 %; white crystals; m.p.: 240 °C (decomp.); Anal. Calcd. for $C_{24}H_{40}N_2O_8 \cdot 2HCl$: C, 51.70; H, 7.59; N, 5.02 %. Found: C, 51.56; H, 7.55; N, 5.07 %; CI MS (*m*/*z* (relative abundance, %)): 484 (M^+ for free base, 4), 405 (23), 327 (100), 242 (90), 211 (73).

*5,5′-(1,4-Butnediyldiimino)bis[1,2-*O*-cyclohexylidene-5-deoxy-*α*-D-xylofuranose]dihydrochloride (**3**)*

A mixture of oxetane **1** (4 g, 18 mmol), 1,4-diaminobutane (0.7 g, 8 mmol) and water (5 drops) was heated in a closed vessel for 12 h at 110 °C. The crude reaction mixture was dissolved in 1:1 diethyl ether–ethyl acetate, the solution washed with water, dried, decolorized and the solvent evaporated to oil. The oil was dissolved in MeOH, diluted with water to form a milky emulsion, and then left in the cold for 48 h. The separated solid was collected, air-dried and dissolved in acetone. An addition of aqueous hydrochloric acid in acetone, followed by an addition of a small amount of diethyl ether deposited the crude hydrochloride salt that was collected, air dried and recrystallized from MeOH–diethyl ether to give pure **3** as the hydrochloride salt, white crystals. The melting point determination revealed deterioration of substance without a sharp melting point at temperatures above 220 °C.

Yield: 1.42 g, 30.3 %, white crystals: Anal. Calcd. for $C_{26}H_{44}N_2O_8 \cdot 2HCl$: C, 53.33; H, 7.69; N, 4.78 %. Found: C, 53.22; H, 7.86; N, 4.80 %; CI MS (*m*/*z* (relative abundance, %)): 512 (M^+ for free base, 5), 428 (15), 412 (17), 355 (100).

*5,5′-(1,4-Piperazinediyl)bis[1,2-*O*-cyclohexylidene-5-deoxy-*α*-D-xylofuranose] (**4**)*

A mixture of oxetane **1** (2.12 g, 10 mmol), piperazine (0.5 g, 5 mmol) and water (2 drops) was heated in a closed vessel for 12 h at 130 °C. After cooling, the reaction mixture (a creamy solid) was dissolved in aqueous hydrochloric acid and washed with diethyl ether. The aqueous phase was separated, rendered alkaline (aq. Na_2CO_3) and extracted with chloroform. The extract was washed with water, dried, decolorized and evaporated to a colorless oil, which solidified spontaneously. Crystallization from dichloromethane–isooctane gave pure **4**.

Yield: 1.32 g, 52 % (based on piperazine); white crystals; m.p.: 158 °C; Anal. Calcd. for $C_{26}H_{42}N_2O_8$: C, 61.15; H, 8.29; N, 5.48 %. Found: C, 60.88; H, 8.26; N, 5.51 %; CI MS (*m*/*z* (relative abundance, %)): 510 (M^+, 5), 467 (17), 353 (100), 311 (82), 255 (137).

*5-((2-Aminoethyl)amino)-1,2-*O*-cyclohexylidene-5-deoxy-*α*-D-xylofuranose dioxalate (**5**)*

A mixture of oxetane **1** (2.12 g, 10 mmol), 1,2-diaminoethane monohydrate (3.9 g, 50 mmol), ethylene glycol (4 mL) and tap water (5 drops) was heated in a closed vessel for 12 h at 110 °C. The crude reaction mixture was dissolved in MeOH, diluted with water (30 mL) and concentrated to remove unreacted diaminoethane by distillation under diminished pressure. The residue was extracted with dichloromethane and the combined extracts were decolorized, dried, and evaporated. The remaining mass was dissolved in MeOH and filtered through a short pad of silica. The main fraction was evaporated, dissolved in acetone and treated with solution of oxalic acid dihydrate in acetone (2.88 g, 22.8 mmol). The white precipitate was collected and air-dried. Crystallization from methanol–water gave pure **5**.

Yield: 3.20 g, 73 %; white crystals; m.p.: 205–209 °C. Anal. Calcd. for the dioxalate, salt $C_{13}H_{24}N_2O_4 \cdot 2C_2H_2O_4$: C, 45.13; H, 6.24; N, 6.19 %. Found: C, 44.78; H, 6.45; N, 6.18 %.

*5-((4-Aminobutyl)amino)-1,2-*O*-cyclohexylidene-5-deoxy-*α*-D-xylofuranose dioxalate (**6**)*

A mixture of oxetane **1** (2.12 g, 10 mmol), 1,4-diaminobuthane (4.4 g, 48 mmol), ethylene glycol (4 mL) and water (5 drops) was heated in a closed vessel for 12 h at 110 °C. After cooling to room temperature, the mixture was triturated with dichloromethane, filtered and the organic solution was washed with water, dried, decolorized and evaporated to leave a light yellow oil (2.7 g). The oil was dissolved in acetone and treated with a solution of oxalic acid dihydrate (2.88 g, 22.8 mmol) in acetone to deposit a white precipitate. Recrystallization from MeOH–water gave pure **6**. The melting point determination revealed gas evolution and deterioration of the substance without melting at temperatures above 175 °C.

Yield: 3.46 g, 72 %; white crystals; Anal. Calcd. for $C_{15}H_{28}N_2O_4 \cdot 2C_2H_2O_4$: C, 47.50; H, 6.71; N, 5.83 %. Found: C, 47.71; H, 6.92; N, 5.43 %.

*1,2-*O*-Cyclohexylidene-5-deoxy-5-(1-piperazinyl)-*α*-D-xylofuranose (**7**)*

A mixture of oxetane **1** (2.0 g, 9.4 mmol), piperazine (3.0 g, 34.8 mmol), ethylene glycol (4 mL) and tap water (5 drops) and catalytic amount of lactic acid (one drop) was heated in a closed vessel, with occasional shaking for 12 h at 120 °C. The reaction mixture was then dissolved in chloroform and the organic layer washed several times with aqueous sodium carbonate. The chloroform solution was decolorized, dried and evaporated to leave a yellow oil that showed no presence of the starting oxetane (by TLC), but showed a minor spot for dialkylated piperazine, apart from the main spot corresponding to the monoalkylated piper-

azine. The obtained oil was dissolved in acetone; the resulting solution was decolorized again, and concentrated to a small volume. On addition of *n*-pentane while cooling, pure **7** was obtained.

Yield: 1.75 g, 62 %; white crystals; m.p.: 127–130 °C; Anal. Calcd. for $C_{15}H_{26}N_2O_4$: C, 60.38; H, 8.78; N, 9.39 %. Found: C, 60.06; H, 8.80; N, 9.17 %; CI MS (*m*/*z* (relative abundance, %)): 298 (M^+, 3), 255 (21), 183 (8), 141 (28), 99 (100).

1,2-O-*Cyclohexylidene-5-deoxy-5-(4-methylpiperazin-1-yl)*-α-*D*-*xylofuranose* ***(8)***

A mixture of oxetane **1** (2 g, 9.4 mmol), *N*-methylpiperazine (1.50 g, 15 mmol) and tap water (5 drops) was heated in a closed vessel for 12 h at 110 °C. At this time, complete disappearance of the starting oxetane was found (by TLC). Unreacted *N*-methylpiperazine was removed by co-distillation with toluene under diminished pressure to leave light yellow oil that crystallized on standing. The crude crystals were dissolved in boiling hexane (80 mL), the solution concentrated to a smaller volume (25–30 mL) and left in the cold to give **8**.

Yield: 2.2 g, 73 %; white crystals; m.p.: 101–103 °C; Anal. Calcd. for $C_{16}H_{28}N_2O_4 \cdot 0.5H_2O$: C, 60.16; H, 9.10; N, 8.90 %. Found: C, 59.79; H, 9.09; N, 8.72 %; CI MS (*m*/*z* (relative abundance, %)): 313 (M^++1, 25), 269 (32), 155 (90), 140 (23), 70 (100).

1,2-O-*Cyclohexylidene-5-deoxy-5-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7*H-*purin-7-yl)*-α-*D*-*xylofuranose* ***(9)***

Theophylline, potassium salt. A solution of theophylline (9 g, 50 mmol) and potassium hydroxide pellets (2.8 g, 50 mmol) in water (50 mL) was evaporated to dryness. The remaining white mass was ground to powder and considered as the potassium salt of theophylline.

A mixture of oxetane **1** (1.4 g, 6.6 mmol), potassium salt of theophylline (2 g, 9.2 mmol), ethylene glycol (1.5 mL) and tap water (5 drops) was heated in a closed vessel for 12 h at 160 °C with occasional shaking. After this time, the TLC analysis revealed full disappearance of the starting oxetane and the formation of the product with an R_f value of 0.5 (ethyl acetate). The crude reaction mixture was dissolved in ethyl acetate, washed with brine, dried and decolorized. Evaporation of the solvent left an oil that was chromatographed on a silica gel column with ethyl acetate to give pure **9**.

Yield: 1.4 g, 54 %; colorless viscous oil; CI MS (*m*/z (relative abundance, %)): 392 (M^+, 19), 345 (32), 277 (36), 194 (45), 180 (100).

TABLE S-I. ^{1}H-NMR spectral data for **2**–**9**; cy – cyclohexylidene

Cmpd.	Chemical shifts of xylose protons, ppm						Coupling constants, Hz					Other signals, ppm
	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]	6.18 (*d*)	4.80 (*d*)	4.46 (*d*)	4.60 (*m*)	3.49–3.75 (*m*)		3.5	1.6				1.41–1.91 (*m*, cy); 3.49–3.75 (*m*, N–C**H**$_2$C**H**$_2$–N)
3[a]	6.06 (*d*)	4.69 (*d*)	4.31 (*d*)	4.44 (*m*)	3.32 (*dd*)	3.42 (*dd*)	3.7	2.7	7.3	3.4	13.6	1.31–1.90 (*m*, cy and N–CH$_2$C**H**$_2$C**H**$_2$CH$_2$–N); 3.14 (*m*, N–C**H**$_2$CH$_2$CH$_2$C**H**$_2$–N)
4[b]	5.93 (*d*)	4.46 (*d*)	4.27 (*d*)	4.09 (*m*)	2.82 (*dd*)	3.05 (*dd*)	3.7	2.2	2.4	2.6	14.5	1.12–1.75 (*m*, cy); 2.05–4.0 (*bs*, piperazine); 7.60 (*bs*, OH)
5[a]	6.06 (*d*)	4.68 (*d*)	4.32 (*d*)	4.44 (*m*)	3.33–3.55 (*m*)		3.6	2.8				1.28–1.73 (*m*, cy); 3.33–3.55 (*m*, N–C**H**$_2$C**H**$_2$–N)
6[a]	6.17 (*d*)	4.80 (*d*)	4.42 (*d*)	4.55 (*m*)	3.44 (*dd*)	3.54 (*dd*)	3.5	2.6	7.5	3.5	13.7	1.36–1.94 (*m*, cy and N–CH$_2$C**H**$_2$C**H**$_2$CH$_2$–N); 3.08–3.30 (*m*, N–C**H**$_2$CH$_2$CH$_2$C**H**$_2$–N)
7[b]	5.93 (*d*)	4.45 (*d*)	4.27 (*d*)	4.10 (*m*)	2.32–2.97 (*m*)	3.06 (*dd*)	3.6	2.2		2.7	14.7	1.28–1.75 (*m*, cy); 2.32–2.97 (*m*, piperazine protons, NH)
8[b]	5.89 (*d*)	4.41 (*d*)	4.23 (*d*)	4.07 (*m*)	2.81 (*dd*)	3.03 (*dd*)	3.7	2.5	2.8	2.8	14.5	1.25–1.66 (*m*, cy); 2.19 (*s*, CH$_3$); 2.24–2.65 (*bs*, piperazine); 7.60 (*bs*, OH)
9[c]	5.93 (*d*)	4.54 (*d*)	4.19 (*d*)	4.33 (*td*)	4.38 (*dd*)	4.76 (*dd*)	3.6	2.6	4.8	6.3	13.2	1.23–1.69 (*m*, cy); 3.37 (*s*, N–CH$_3$); 3.56 (s, N–CH$_3$); 7.74 (s, H8 from xanthine)

[a]D_2O; [b]$CDCl_3$; [c]$CDCl_3$+D_2O

8 TABLE S-II. ^{13}C-NMR spectral data for **2**–**9**; cy – cyclohexylidene

Cmpd.	Chemical shifts of xylose carbons, ppm						Other signals, ppm
	C-1	C-2	C-3	C-4	C-5	C-1cy	
2[a]	107.10	87.02	77.47	78.54	49.69	116.61	25.90, 26.31, 26.87, 37.45, 38.23 (cy), 46.36 (–**C**H$_2$–**C**H$_2$–)
3[a]	107.08	87.03	77.43	78.65	49.02	116.55	25.36 (–CH$_2$**C**H$_2$**C**H$_2$CH$_2$–); 25.90, 26.31, 26.86, 37.43, 38.21 (cy), 50.05 (–NHCH$_2$–)
4[b]	104.22	85.01	77.82	76.75	56.85	111.90	23.47, 23.80, 24.83, 35.49, 36.26 (cy), 54.62 (piperazine carbons)
5[a]	107.10	87.01	77.45	78.56	49.65	116.62	25.87, 26.29, 26.84, 37.42, 38.17 (cy), 38.17 & 47.50 (–**C**H$_2$–**C**H$_2$–), 169.17 (carbonyl from oxalate)
6[b]	107.07	87.01	77.41	78.63	49.00	116.54	25.90, 26.30, 26.68, 37.41, 38.19, 25.21, 26.84 (cy & –HN–CH$_2$**C**H$_2$**C**H$_2$CH$_2$–NH–), 41.60 & 50.10 (–HN–**C**H$_2$CH$_2$CH$_2$**C**H$_2$–NH–), 169.05 (carbonyl from oxalate)
7[b]	104.31	85.13	77.87	76.93	57.78	111.94	23.55, 23.88, 24.90, 35.58, 36.36 (cy), 46.03, ((CH$_2$)$_2$NH), 55.94 ((**C**H$_2$)$_2$N–CH$_2$–)
8[b]	104.20	85.02	77.70	76.85	56.92	111.81	23.44, 23.76, 24.80, 35.49, 36.30 (cy), 45.77 (CH$_3$), 54.51 and 54.99 (piperazine carbons)
9[c]	104.15	84.78	73.96	79.96	44.90	112.44	23.35, 23.67, 24.64, 35.32, 36.09 (cy), 28.06 and 29.78 (2×CH$_3$), 106.61, 142.63, 148.95, 151.19 & 155.74 (C-5, C-8, C-4, C-2 and C-6 from xanthine part

9 [a]D$_2$O; [b]CDCl$_3$; [c]CDCl$_3$+D$_2$O