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Synthesis of Spiro[pyrido[3,2-*b*][1,4]oxazin-2,2′-pyrans] based upon Methyl D-*arabino*-2-Hexulopyranosonate

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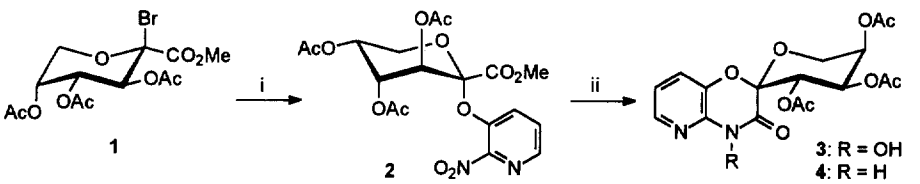
Dedicated to Professor Klaus Burger on the occasion of his 60th birthday

Abstract: The novel glycosyl donor **1**, derived from methyl D-*arabino*-2-hexulopyranosonate, was transformed into glycoside **2**, diastereoselectively. Catalytic hydrogenation of **2** and spontaneous reductive cyclization gave access to the spiro[pyrido[3,2-*b*][1,4]oxazin-2,2′-pyrans] **3** and **4**.

Keywords: Carbohydrate mimetics; Cyclization; Glycosidation; Spiro compounds;

D-*arabino*-2-Hexulosonic acid[1] is an ignored carbohydrate building block though it is used on industrial scale for the production of D-isoascorbic acid.[2] We wish to report on the synthesis of a novel combination of the D-*arabino*-2-hexulosonate unit with the pharmacological[3] and herbicidal active[4,5] 2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one skeleton. This heterocycle-monosaccharide combination resembles some benzoxazinoid acetal glucosides naturally occurring in *Gramineae* species.[6]

Glycosyl donor **1**[7] was obtained on bromination of methyl 2,3,4,5-tetra-*O*-acetyl-β-D-*arabino*-2-hexulopyranosonate[8] with 33% hydrogen bromide in glacial acetic for 2 h at 20°C.



Conditions: (i) 3-hydroxy-2-nitropyridine, K_2CO_3, acetone, reflux; (ii) H_2/Pt-C, MeOH, 20°C.

Scheme 1. Synthesis of spiro acetals **3** and **4**

Nucleophilic substitution of **1** with 3-hydroxy-2-nitropyridine gave neighbouring group assisted diastereoselectively the 2,3-trans glycoside **2**.[9] Catalytic hydrogenation of **2** and spontaneous cyclization of the hydroxylamine intermediate led to the hydroxamic acid **3** accompanied by lactam **4**.[10] Standard deprotection of **3** and **4** with NaOMe/MeOH gave rise to the free heterocyclic spiroacetals.[11]

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By means of ^{1}H NMR, the conformational change from the $^2C_5$ geometry of **1** ($J_{3,4}$=10.0, $J_{4,5}$=3.2 Hz) into $^5C_2$ geometry in **2** ($J_{3,4}$=4.8, $J_{4,5}$=3.6 Hz) and back to $^2C_5$ in **3**, **4** ($J_{3',4'}$=10.4-10.6, $J_{4',5'}$=3.7 Hz) was proven.

In summary, the procedure described here makes use of D-*arabino*-2-hexulopyranosonates as carbohydrate building block for a novel heterocycle-saccharide combination.

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7. **1** (98%) of colourless powder from $CHCl_3$, mp. 78-80°C; $[\alpha]_D^{21}$ -175° ($CHCl_3$, *c* 1); ^{1}H NMR (200 MHz, $CDCl_3$), δ 2.00 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.15, (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.25 (d, 1H, $J_{6a,b}$=13.4, H-6a), 4.33 (d, 1H, $J_{6a,b}$=13.4 Hz, H-6b), 5.13 (dd, 1H, $J_{3,4}$=10.0, $J_{4,5}$=3.2 Hz, H-4), 5.39 (m, 1H, H-5), 5.48 (d, 1H, $J_{3,4}$=10.0 Hz, H-3). See ref.[11] for ^{13}C NMR and EIMS.
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9. Chromatography (toluene/EtOAc 3:1 v:v) on flash Silicagel 60 (Merck) yielded **2** (82%) as yellow crystals mp. 47-49°C; $[\alpha]_D^{28}$ +25° ($CHCl_3$, *c* 1); ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.99 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.97 (dd, 1H, $J_{6a,6b}$=10.2, $J_{5,6}$=8.8 Hz, H-6a), 4.06 (dd, 1H, $J_{5,6b}$=4.4 Hz, H-6b), 5.29 (m, 1H, H-5), 5.33 (dd, 1H, $J_{3,4}$=4.8, $J_{4,5}$=3.6 Hz, H-4), 5.43 (d, 1H, H-3), 7.44 (dd, 1H, $J_{5',6'}$=4.4, $J_{4',6'}$=1.1 Hz, H-5'), 7.83 (dd, 1H, $J_{4',5'}$=8.4, $J_{4',6'}$=1.1 Hz, H-4'), 8.14 (dd, 1H, H-6'). See ref.[11] for other analytical data.
10. Chromatography on flash Silicagel 60 (Merck) with toluene/EtOAc (1:1, v:v) yielded first **4** (21%), mp. 190-191°C; $[\alpha]_D^{25}$ +24° ($CHCl_3$, c 1); CD: $\Delta\varepsilon_{231}$ +19.1, $\Delta\varepsilon_{252}$ -2.7, $\Delta\varepsilon_{268}$ +0.2, $\Delta\varepsilon_{294}$ +10.6 ($CHCl_3$, *c* 0.30); ^{1}H NMR (200 MHz, $CDCl_3$), δ 2.01 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 4.03 (m, 2H, H-6'a,b), 5.42 (m, 1H, H-5'), 5.72 (d, 1H, $J_{3',4'}$=10.6 Hz, H-3'), 6.11 (dd, 1H, $J_{3',4'}$=10.6, $J_{4',5'}$=3.7 Hz, H-4'), 7.05 (dd, 1H, $J_{6,7}$=4.9, $J_{7,8}$=7.5 Hz, H-7), 7.48 (d, 1H, $J_{7,8}$=7.5 Hz, H-8), 8.21 (d, 1H, $J_{6,7}$=4.9 Hz, H-6), 12.13 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$), δ 21.1 (CH_3), 21.3 (CH_3), 21.4 (CH_3), 66.2 (C-6'), 68.4 (C-5'), 69.8 (C-4'), 70.0 (C-3'), 98.3 (C-2), 120.0 (C-7), 126.0 (C-8), 137.0 (C-8a), 140.6 (C-4a), 141.9 (C-6), 161.0 (C-3), 170.1 (CO), 170.2 (CO), 170.8 (CO); EIMS, m/z (%): 394 (M^+, 33), 335 (6), 275 (3), 233 (5), 215 (11), 165 (8), 137 (24), 42 (100). See ref.[11] for other analytical data. On changing the eluent to $CHCl_3$/MeOH (7:3, v:v) **3** (57%) was obtained: mp. 125-127°C; $[\alpha]_D^{22}$ -55° ($CHCl_3$, c 1.00); CD: $\Delta\varepsilon_{224}$ +13.5, $\Delta\varepsilon_{252}$ -8.7, $\Delta\varepsilon_{291}$ +16.9 ($CHCl_3$, *c* 0.61).; ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.98 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.79 (m, 2H, H-6'a,b), 5.36 (m, 1H, H-5'), 5.64 (d, 1H, $J_{3',4'}$=10.4 Hz, H-3'), 6.03 (dd, 1H, $J_{3',4'}$=10.4, $J_{4',5'}$=3.7 Hz, H-4'), 7.06 (dd, 1H, $J_{6,7}$=5.1, $J_{7,8}$=7.6 Hz, H-7), 7.48 (d, 1H, $J_{7,8}$=7.6 Hz, H-8), 8.07 (d, 1H, $J_{6,7}$=5.1 Hz, H-6); ^{13}C NMR (50 MHz, $CDCl_3$), δ 21.0 (CH_3), 21.1 (2 x CH_3), 66.0 (C-6'), 68.0 (C-5'), 69.8 (C-4'), 69.8 (C-3'), 100.2 (C-2), 120.7 (C-7), 126.7 (C-8), 137.6 (C-8a), 140.9 (C-4a), 141.3 (C-6), 157.5 (C-3), 170.2 (CO), 170.3 (CO), 170.8 (CO); EIMS, m/z (%): 410 (M^+, 27), 394 (3), 368 (5), 340 (2), 233 (5), 181 (5), 137 (11), 126 (10), 108 (8), 85 (9), 42 (100).
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