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Stereospecific Cyclization To Form C-Furanosides¹

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Abstract: A cyclization of benzyl ethers with $S_N 2$ active site at γ -position to form C-furanoside was studied.

The major method for carbon-carbon bond formation at the anomeric carbon atom involves the nucleophilic attack on this position. Many electrophilic sugar derivatives have been employed, including glycosyl halides, thioglycosides, glycals, lactones, glycosyl imidates and O-protected glycosides. Some nucleophilic reagents (silyl enol ethers, alkenes, allylsilanes, allylstannanes, homoenolates, and organometallics such as Grignard reagents, organolithiums, cuprates and aluminates) have also been used to synthesize the C-glycosides^{2a-o}.

In our research on the synthesis of C-glycosides, we have discovered a novel stereospecific cyclization in which C-glycosides can be formed under mild condition and benzyloxy group participates in the reaction. It has long been recognized ³ that the benzyloxy group can act a nucleophile in intramolecular displacement reactions with concomitant debenzylation and Dehmlow *et al* ⁴ introduced a stereocontrolled formation of polysubstituted tetrahydrofurans, which gave a mixture of acyclic product and tetrahydrofuran derivatives in lower yields. However this type of reaction has rarely been exploited to prepare C-glycosides. Herein we report an efficient method to synthesize C-furanosides in high yield and stereospecificity, through treatment of compound <u>1</u> or <u>3</u>, <u>5</u>, <u>7</u>, <u>9</u>, <u>11</u> with trifluoromethanesulfonic anhydride to affording cyclic products <u>2</u> or <u>4</u>, <u>6</u>, <u>8</u>, <u>10</u>, <u>12</u> in the yield of 85-90%. The Structures of all synthesized C-furanosides were determined by elementary analysis, ¹H NMR and mass spectrum ⁵. The protons of furanose ring were assigned by selective decoupling experiments or ¹H-¹H COSY and their stereochemistry was deduced by ¹H-¹H NOESY data (see Table). The cyclization reaction was performed by the treatment of the starting alcohols with trifluoromethanesulfonic anhydride in pyridine and dichloromethane at -20°C. In compound <u>1</u> 6'-hydroxy group was triflated and a back side attack by the oxygen atom of the 3'-OBn occurred, forming a furanose ring with concomitant debenzylation and inversion of configuration at $C_{6'}$ (in <u>1</u>, <u>3</u>, <u>5</u>) or $C_{5'}$ (in <u>7</u>, <u>9</u>, <u>11</u>).



In an example of a general procedure, trifluoromethanesulfonic anhydride (0.3 mmol) was added dropwise with stirring to a solution of 3'S, 4'R, 5'R, 7'-tetra-O-benzyl-6'R-hydroxy-heptene-1' (0.25 mmol) (1)⁶ in dichloromethane (5 ml) and pyridine (0.2 ml) at -20 °C under nitrogen. After stirring for 3 h at -20°C, the reaction mixture was warmed to room temperature and dichloromethane was added. The mixture was washed with saturated sodium bicarbonate solution and concentrated to yield a residue which was purified by column chromatography on silica gel with petroleum ether (b.p. 60-90°C) and ethyl acetate (10:1; v/v). 1-deoxy-1- α -ethenyl-2,3,5-tri-O-benzyl-L-xylose (2) was obtained in high yield of 90%. Compound 2 is a syrupy substance, [α]²⁵_D +10.4° (c 0.3, HCCl₃), which gave a satisfactory elementary analysis (Calc. C, 78.11%, H, 7.02%; Found. C, 78.08%, H, 7.11%). The ¹H NMR spectrum of 2 has three ethenyl protons, 15 phenyl protons, 6 methylene protons of benzyloxy groups and 6 furanose-ring protons. The ¹³C NMR data of 2 was in accord with the assigned structure. The stereochemistry of 2 was determined by ¹H-¹H 2D NOESY showing clearly the substantial NOE between C₁-H and C₂-H and between C₃-H and C₄-H, an indication of *cis* relation between those protons.

In order to confirm the stereospecificity of the cyclization reaction, we synthesized a compound, 3'R, 4'R, 5'R, 7'-tetra-O-benzyl-6'R-hydroxy-heptene-1' ($\underline{3}$) from methyl D-mannopyranoside *via* benzylation, hydrolysis and Wittig reaction, and treated it under the same conditions as described for $\underline{1}$. The product, 1-deoxy-1- β -ethenyl-2,3,5-tri-O-benzyl-L-xylose ($\underline{4}$) was obtained in 86 % yield, it's structure being proved by elementary analysis, ¹H NMR, mass spectrum. The stereochemistry ($\underline{4}$) was also determined by ¹H-¹H 2D NOESY, which showed clearly the substantial NOE between C₁-H and C₄-H, C₃-H and C₄-H, C₁-Ha and C₂-H as well as C₂-H and C₂-H. The results indicated the *cis* relation of C₁-H, C₃-H and C₄-H. Similar treatment of $\underline{5}$ that was produced from methyl α -D-galactopyranoside gave 85 % of expected product $\underline{6}$, whose structure determination and the stereochemistry were shown in Table and reference 5.

Tetrahydrofuran type cyclization was observed also in compound $\underline{7}$, which was synthesized from methyl- α -D-glucopyranoside by sequential benzylation, hydrolysis, reduction with LiAlH₄ and tritylation. The



product <u>8</u>, which absolute configuration was the same as compound <u>2</u>, was produced in the yield of 90 %. The same results were generated by compounds <u>9</u> and <u>11</u>, which were prepared from methyl α -D-

mannopyranoside and methyl α -D-galactopyranoside as described in <u>7</u>, respectively, and their structure determination and the stereochemistry were listed in Table and reference 5.

This reaction provided an efficient method to synthesize the C-furanoside derivatives that could be afforded by suitable selection of starting materials. The vinyl group and trityloxy group can be further transformed to a series of modified C-furanosides, which were the useful synthetic intermediates.

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REFERENCES AND NOTES

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- 5. ¹H NMR (AMX-600, 600MHz, CDCl₃, TMS): (2) δ_{nom} 7.2-7.35 (m,15H,3 Ph), 6.0 (m, 1H, H-2'), 5.25 (d, 1H, H-1'a), 5.3(dd, 1H, H-1'b, $J_{1'b-2'}=10.4$, $J_{1'a-2'}=17.3$, $J_{1'a-1'b}=0.9$), 4.45-4.65 (m, 7 H, 3CH₂+H-1, $J_{2'-1}=7.5$, $J_{1-2}=4.0$), 4.4 (m,1H, H-4), 4.05 (dd, 1H, H-3, $J_{3.4}$ = 4.1, $J_{2.3}$ = 1.4), 3.95 (dd, 1H, H-2, $J_{1.2}$ = 4.0, $J_{2.3}$ = 1.4), 3.65-3.75 (dd, 2H, 3.65-3.75) H-5, J_{5a-5b} = 9.7, J_{4-5a} = 6.2, J_{4-5b} = 6.0). Ms: m/z 431 (M+1), 339 (M-Bn). (4) 7.1-7.3 (m, 15 H, 3 Ph), 5.8-5.9 (m, 1H, H-2'), 5.05 (d, 1 H, H-1'a, $J_{1'e-2'}=10.3$), 5.25 (dd, 1H, H-1'b, $J_{1'e-1'b}=1.1$, $J_{1'b-2'}=17.2$,), 4.35-4.6 (m, 6H, 3CH₂), 4.20 (m, 1H, H-4), 4.25 (dd, 1 H, H-1, $J_{1,2}$ =3.7, $J_{2'-1}$ =7.5), 3.95 (dd, 1 H, H-3, $J_{2,3}$ =1.4, $J_{3,4}$ =4.2), 3.80 (dd, 1 H, H-3, J_{2,3}=1.4, $J_{3,4}$ =4.2), 3.80 (dd, 1 H, H-3, J_{3,4}=1.4, $J_{3,4}$ =1.4, $J_{3,4}$ =1.4, H-2, $J_{1-2}=3.7$, $J_{2-3}=1.4$), 3.65-3.76 (ddd, 2 H, H-5, $J_{5a-5b}=10.0$, $J_{5a-4}=5.6$, $J_{5b-4}=6.3$). Ms: m/z 431 (M+1), 339 (M-Bn). ($\underline{6}$) 7.15-7.25 (m, 15 H, 3Ph), 6.15 (m, 1H, H-2', $J_{2'-1'b}=10.3$, $J_{2'-1'a}=17.2$), 5.25 (dd, 1 H, H-1'b, $J_{1'b-2'}=10.3$), 5.35 $(dd, 1 H, H-1'a, J_{J'a-1'b}=0.7, J_{1'a-2'}=17.2), 4.4-4.7 (m, 7 H, 3 CH_2+H-1), 4.25 (dd, 1 H, H-4, J_{4-5a}=3.2, J_{4-5b}=3.7),$ $4.1 (dd, 1 H, H-3, J_{3.4} = 6.8, J_{3.2} = 4.6), 4.0 (t, 1 H, H-2, J_{2.3} = 4.4, J_{2.1} = 4.4), 3.5 - 3.65 (ddd, 2 H, H-5, J_{5a-5b} = 10.7, J_{5a$ J_{5n-4} = 3.2, J_{5h-4} = 3.8). Ms: m/z 431 (M+1), 339 (M-Bn). (8) 7.2-7.5 (m, 30 H, 6 Ph), 4.4-4.7 (m, 6 H, 3 CH₂), 4.4 (m, 1H, H-1, $J_{1-1} = 6.6$, $J_{1-2} = 3.3$), 4.3 (m, 1 H, H-4), 4.2 (d, 1 H, H-2, $J_{1-2} = 3.3$), 4.15 (d, 1 H, H-3, $J_{3-4} = 3.7$), $3.65-3.8 \text{ (ddd, 2 H, H-5, J_{5e-5b} = 9.9, J_{5e-4} = 5.8, J_{5b-4} = 6.3), 3.2-3.4 \text{ (ddd, 2 H, H-1', J_{1'e-1'b} = 9.4, J_{1'e-1} = 6.6, J_{1'b-1} = 5.8), J_{1'e-1'b} = 9.4, J_{1'e-1} =$ Ms: m/z 433 (M-Ph₃C), 243 (Ph₃C). (<u>10</u>) 7.2-7.5 (m,30 H, 6 Ph), 4.4-4.6 (m, 6 H, 3 CH₂), 4.25 (m, 1H, H-4), 4.15 (m, 1 H, H-1), 4.0 (d, 1 H, H-2), 3.95 (d, 1 H, H-3), 3.7 (ddd, 2 H, H-5, J_{5a-5b} = 10, J_{5a-4} = 4.5, J_{5b-4} = 6.5), 3.1-3.4 (ddd, 2 H, H-1', $J_{1'a-1'b} = 9.3$, $J_{1'a-1} = 5.2$, $J_{1'b-1} = 7.3$). Ms: m/z 433 (M-Ph₃C), 243 (Ph₃C). (<u>12</u>) 7.1-7.5 (m, 30 H, 6 Ph), 4.4-4.65 (m, 6 H, 3 CH₂), 4.32 (m, 1 H, H-1), 4.18 (t, 1 H, H-2), 4.10 (m, 1 H, H-4), 4.05 (q, 1H, H-3, $J_{3-2} = 4$, $J_{3-4} = 7.7$), 3.6 (ddd, 2 H, H-5, $J_{5a-5b} = 10.8$, $J_{5a-4} = 2.8$, $J_{5b-4} = 4.4$), 3.4 (ddd, 2 H, H-1', $J_{1'a-1'b} = 9.3$, $J_{5b-4} = 1.4$), 3.4 (ddd, 2 H, H-1', $J_{1'a-1'b} = 9.3$, $J_{5b-4} = 1.4$), $J_{5b-4} = 1.4$, J_{5b-4 $J_{1'e-1} = 7.1$, $J_{1'b-1} = 5.8$). Ms: m/z 433 (M-Ph₃C), 243 (Ph₃C).
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