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### Synthesis of C-Glycosylacetylenes: Applications to the 2-Azidosugars

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COMMUNICATION

**SYNTHESIS OF C-GLYCOSYLACETYLENES:  
APPLICATIONS TO THE 2-AZIDOSUGARS**

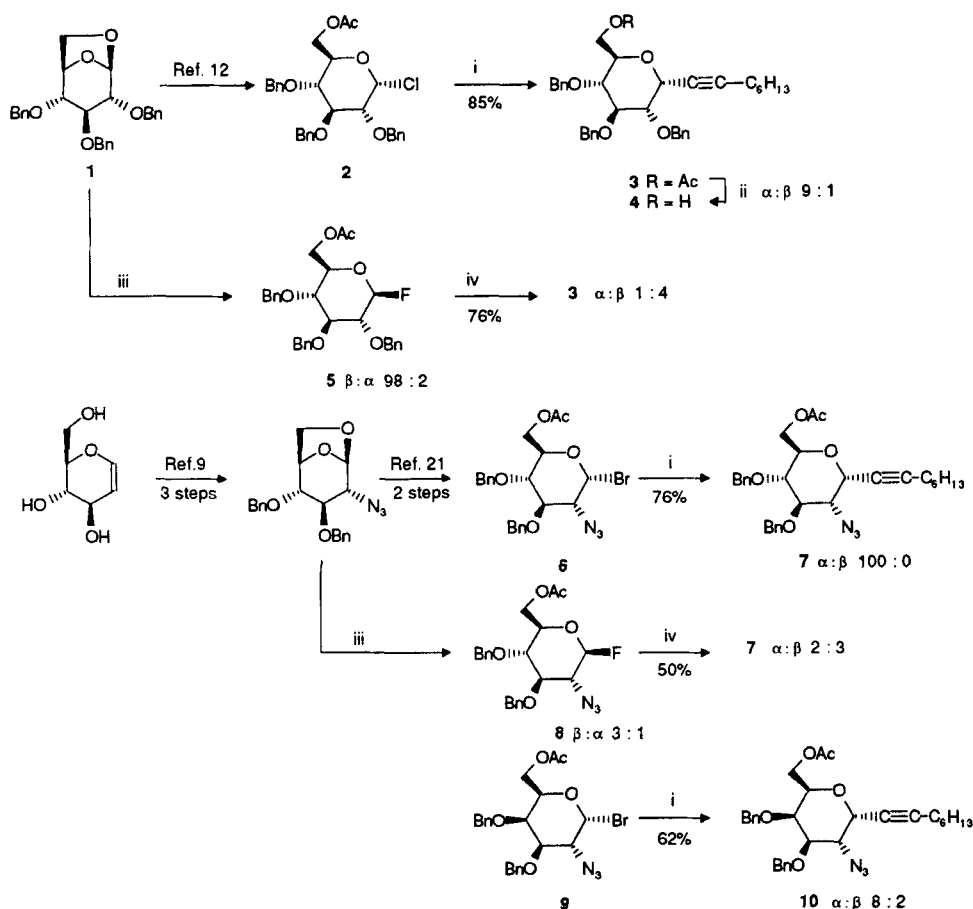
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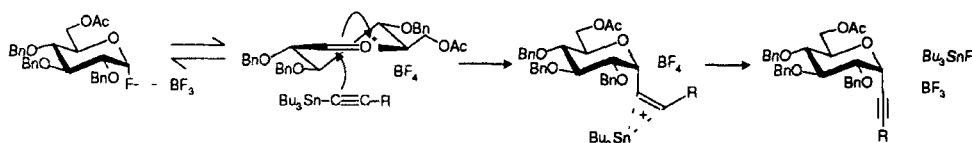
The formation of C-C bonds at the anomeric center of carbohydrates has become an important area in organic synthesis.<sup>1</sup> The Lewis acid catalyzed addition of carbon nucleophiles to electrophilic sugar derivatives is the most popular method generally affording  $\alpha$ -C-glycosides in the pyranose series. Because of the kinetic anomeric effect<sup>2</sup> of the ring oxygen, the pyran oxonium species usually accepts nucleophiles from the  $\alpha$ -face.<sup>3</sup> It is, however, surprising that C-glycosyl derivatives of 2-azidosugars have been scarcely reported in the literature<sup>4,5</sup> in spite of their interest as precursors of potential inhibitors for various hexosamine transferases.

Alkyne transfer<sup>6,7</sup> to the anomeric center of 2-azidosugars is an attractive approach since reactive alkynyl nucleophiles are readily accessible<sup>8</sup> and should lead to stable compounds.<sup>5</sup> We recently reported<sup>9</sup> a new access to 1,6-anhydro-2-azido-2-deoxy- $\beta$ -D-glucopyranose from D-glucal which prompted us to examine the reactivity of alkynyl nucleophiles towards 1,6-anhydrosugars,<sup>10</sup> the *D-gluco* compound **1** being taken first as a model substrate. It soon appeared that the use of strong Lewis acids such as TiCl<sub>4</sub> gave rise to complexation of the substrate and partial deprotection.<sup>11</sup>



**Scheme.** Reagents and conditions : i)  $C_6H_{13}C\equiv CSnBu_3$ ,  $AgBF_4$ ,  $(CH_2Cl)_2$ ,  $0\text{ }^\circ C$ ; ii)  $MeOH-NEt_3-H_2O$ ,  $20\text{ }^\circ C$ ; iii)  $Ac_2O-CF_3CO_2H$ ,  $20\text{ }^\circ C$ , then  $BnNH_2$ ,  $Et_2O$ ,  $20\text{ }^\circ C$ , then  $DAST$ ,  $THF$ ,  $20\text{ }^\circ C$ , iv)  $C_6H_{13}C\equiv CAIEt_2$ , toluene-hexane,  $0\text{ }^\circ C$ .

Coupling of the more electrophilic  $\alpha$ -chloride **2**<sup>12</sup> with 1-tributylstannyloct-1-yne<sup>13</sup> could be promoted<sup>7</sup> by catalytic  $ZnCl_2$  at  $100\text{ }^\circ C$  but only in a modest yield (40%). We now report that *silver tetrafluoroborate*<sup>14</sup> is a much more efficient promoter giving at  $0\text{ }^\circ C$  the *C*-oct-1-ynyl glycoside **3** ( $\alpha:\beta$ , 9:1) in 85% yield.<sup>15</sup>



The alkyne  $\pi$  system adds preferentially to the  $\alpha$ -face of the oxonium species generated from the chloride giving rise to a vinyl cation stabilized by the  $\beta$ -tin atom.

The counteranion  $\text{BF}_4^-$  provides fluoride ions captured by the tributyltin moiety thus establishing the acetylenic bond. When the reaction was quenched with diethyl ether, a transient  $\alpha$ -fluoride **5** could be detected.<sup>16</sup>

Diethyl oct-1-ynylalane<sup>17</sup> did not react with chloride **2** but underwent a fast coupling with the glucosyl fluoride **5**<sup>18</sup> ( $\beta$ : $\alpha$ , 98:2) in toluene-hexane at 0 °C to give the *C*-glycosides **3** ( $\beta$ : $\alpha$ , 4:1) in 76% yield.<sup>19</sup> The strong affinity of aluminum for fluoride ions suggests a complexation between the alane and the substrate leading to an ion pair where the nucleophilicity of acetylide has increased.<sup>20</sup> However, the preferential  $\beta$ -selectivity of the reaction cannot be simply explained by a direct collapse of a  $\beta$ -ion pair since tetra-*O*-benzyl- $\alpha$  and  $\beta$ -D-glucopyranosyl fluorides were found to give similar ratios of coupling products ( $\beta$ : $\alpha$ , 1:1 and 3:2, respectively) when treated under the same conditions.

The *gluco*-azido bromide **6** easily obtained from D-glucal<sup>9,21</sup> when treated with 1-tributylstannyl-oct-1-yne in the presence of  $\text{AgBF}_4$  gave the *C*-glycoside **7** ( $\alpha$ : $\beta$ , 100:0) in 76% yield.<sup>22</sup> The *galacto* azido bromide **9**<sup>23</sup> under the same conditions gave the *C*-glycoside **10** ( $\alpha$ : $\beta$ , 4:1) in 62% yield. The azido fluoride **8** ( $\beta$ : $\alpha$ , 3:1) reacted with diethyl oct-1-ynylalane at 0 °C to give **7** ( $\alpha$ : $\beta$ , 2:3) in 50% yield.

In conclusion, coupling of alkynylstannanes with pyranosyl chlorides or bromides in the presence of  $\text{AgBF}_4$  affords a convenient access to  $\alpha$ -*C*-glycosides including the 2-azidosugars. Its compatibility with an ester function at the primary alcohol group makes it attractive for further functionalization of the pyranose ring. As to alkynylalane couplings, further studies should bring better understanding of the mechanism and influence of protective groups upon the stereoselectivity.

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**4 $\beta$** , oil,  $[\alpha]_D^{20} -2$  (c 1,  $\text{CHCl}_3$ ),  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.40-7.30 (m, 15 H, 3 Ph), 5.01, 4.91, 4.86, 4.83, 4.81, and 4.64 (6 d, 6 H,  $J$  11 Hz, 3  $\text{CH}_2\text{Ph}$ ), 4.08 (dt, 1 H,  $J_{1,2}$  9.5,  $J_{1,\text{CH}_2}$  2 Hz, H-1), 3.72-3.49 (m, 5 H, H-2,3,4,6a,6b), 3.33 (ddd, 1

H, H-5), 2.26 (dt, 2 H,  $J$  7 Hz,  $\text{CH}_2\text{C}\equiv\text{C}$ -), 1.58-1.20 (m, 8 H, 4  $\text{CH}_2$ ), and 0.85 (t, 3 H,  $J$  7 Hz,  $\text{CH}_3$ ). Anal. Calcd for  $\text{C}_{35}\text{H}_{42}\text{O}_5$ : C, 77.46; H, 7.80. Found: C, 77.37; H 7.93.

**7 $\alpha$** , oil,  $[\alpha]_{\text{D}}^{20} +57$  (c 1.06,  $\text{CHCl}_3$ ),  $\nu_{\text{max}}^{\text{film}}$  2220, 2090, 1730  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.40-7.25 (m, 10 H, 2 Ph), 4.93 and 4.88 (2 d, 2 H,  $J$  11 Hz,  $\text{CH}_2\text{Ph}$ ), 4.85 and 4.57 (2 d, 2 H,  $J$  11 Hz,  $\text{CH}_2\text{Ph}$ ), 4.78 (dt, 1 H,  $J_{1,2}$  5.5,  $J_{1,\text{CH}_2}$  2.2 Hz, H-1), 4.32 (dd, 1 H,  $J_{5,6a}$  2.5,  $J_{6a,6b}$  12 Hz, H-6a), 4.26 (dd, 1 H,  $J_{5,6b}$  4 Hz, H-6b), 4.06 (ddd, 1 H, H-5), 3.93 (dd, 1 H,  $J_{2,3}$  10,  $J_{3,4}$  9 Hz, H-3), 3.55 (dd, 1 H, H-2), 3.51 (dd, 1 H,  $J_{4,5}$  10 Hz, H-4), 2.27 (dt, 2 H,  $J$  7 Hz,  $\text{CH}_2\text{C}\equiv\text{C}$ -), 2.05 (s, 3 H, OAc), 1.60-1.25 (m, 8 H, 4  $\text{CH}_2$ ), and 0.89 (t, 3 H,  $J$  7 Hz,  $\text{CH}_3$ ). Anal. Calcd for  $\text{C}_{30}\text{H}_{37}\text{N}_3\text{O}_5$ : C, 69.34; H, 7.18; N, 8.08. Found: C, 69.29; H, 7.30; N, 8.04.

**7 $\beta$** ,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data from a mixture of **7 $\alpha$** ,**7 $\beta$** :  $\delta$  4.31 (dd, 1 H,  $J_{5,6a}$  2,  $J_{6a,6b}$  12 Hz, H-6a), 4.17 (dd, 1 H,  $J_{5,6b}$  4.5 Hz, H-6b), 3.92 (dt, 1 H,  $J_{1,2}$  9.5,  $J_{1,\text{CH}_2}$  2 Hz, H-1), 2.26 (dt, 2 H,  $J$  7 Hz,  $\text{CH}_2\text{C}\equiv\text{C}$ -), and 2.04 (s, 3 H, OAc).

**10 $\alpha$** , oil,  $[\alpha]_{\text{D}}^{20} +74$  (c 1.05,  $\text{CHCl}_3$ ),  $\nu_{\text{max}}^{\text{film}}$  2215, 2090, 1730  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.45-7.25 (m, 10H, 2 Ph), 4.90 and 4.55 (2 d, 2 H,  $J$  11 Hz,  $\text{CH}_2\text{Ph}$ ), 4.81 (dt, 1 H,  $J_{1,\text{CH}_2}$  2 Hz, H-1), 4.77 (m, 2 H,  $\text{CH}_2\text{Ph}$ ), 4.15-4.04 (m, 3 H, H-5,6a,6b), 4.03 (dd, 1 H,  $J_{1,2}$  5.5,  $J_{2,3}$  10 Hz, H-2), 3.89 (dd, 1 H,  $J_{3,4}$  2.5,  $J_{4,5}$  1 Hz, H-4), 3.86 (dd, 1 H, H-3), 2.24 (dt, 2 H,  $J$  7 Hz,  $\text{CH}_2\text{C}\equiv\text{C}$ -), 2.00 (s, 3 H, OAc), 1.55-1.20 (m, 8 H, 4  $\text{CH}_2$ ), and 0.90 (t, 3 H,  $J$  7 Hz,  $\text{CH}_3$ ). Anal. Calcd for  $\text{C}_{30}\text{H}_{37}\text{N}_3\text{O}_5$ : C, 69.34; H, 7.18; N, 8.08. Found: C, 69.14; H, 7.28; N, 7.81.

**10 $\beta$** , oil,  $[\alpha]_{\text{D}}^{20} +26$  (c 1.02,  $\text{CHCl}_3$ ),  $\nu_{\text{max}}^{\text{film}}$  2230, 2090, 1730  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.45-7.25 (m, 10 H, 2 Ph), 4.93 and 4.60 (2 d, 2 H,  $J$  11 Hz,  $\text{CH}_2\text{Ph}$ ), 4.76 (m, 2 H,  $\text{CH}_2\text{Ph}$ ), 4.16 (dd, 1 H,  $J_{5,6a}$  6.5,  $J_{6a,6b}$  11.5 Hz, H-6a), 4.06 (dd, 1 H,  $J_{5,6b}$  5.5 Hz, H-6b), 3.91 (dd, 1 H,  $J_{1,2}$  10,  $J_{2,3}$  9.5 Hz, H-2), 3.84 (dt, 1 H,  $J_{1,\text{CH}_2}$  2 Hz, H-1), 3.77 (dd, 1 H,  $J_{3,4}$  2.5,  $J_{4,5}$  1 Hz, H-4), 3.48 (m, 1 H, H-5), 3.30 (dd, 1 H, H-3), 2.24 (dt, 2 H,  $J$  7 Hz,  $\text{CH}_2\text{C}\equiv\text{C}$ -), 1.98 (s, 3 H, OAc), 1.60-1.20 (m, 8 H, 4  $\text{CH}_2$ ), and 0.88 (t, 3 H,  $J$  7 Hz,  $\text{CH}_3$ ). Anal. Calcd for  $\text{C}_{30}\text{H}_{37}\text{N}_3\text{O}_5$ : C, 69.34; H, 7.18; N, 8.08. Found: C, 69.45; H, 7.16; N, 7.99.