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An Improved Synthesis of Tn Antigen

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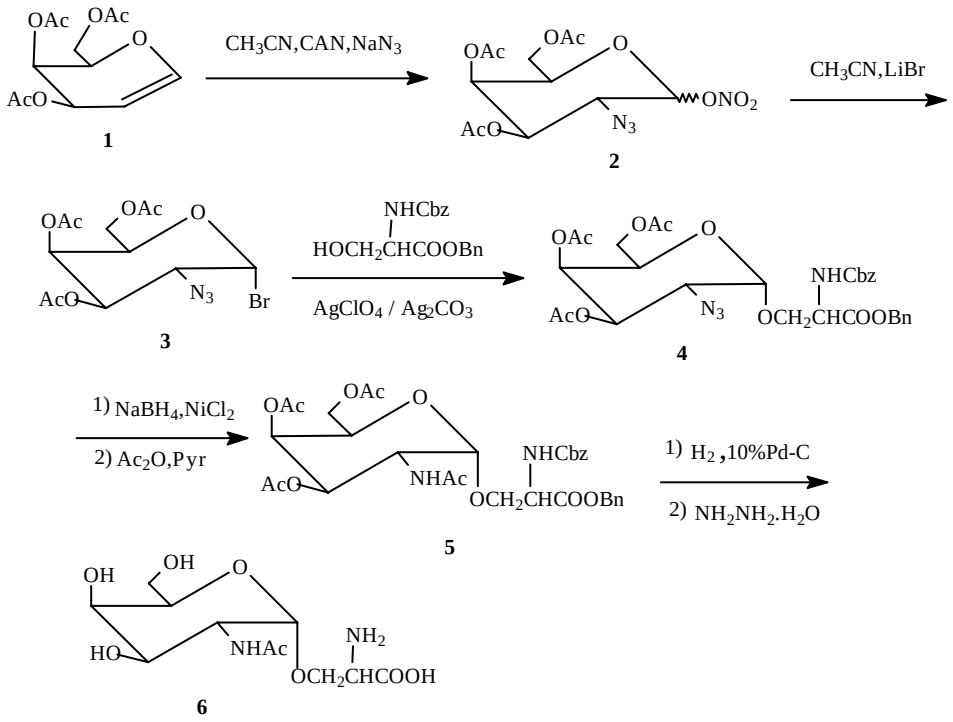
Abstract: We have developed an alternative route to synthesize Tn antigen. The synthetic product was characterized by IR, ^{1}H-NMR and elemental analysis.

Keywords: Total synthesis, Tn antigen.

Tn (GalNAcα1→O-Ser/Thr) **6** is a human tumor-associated carbohydrate antigen[1]. Protein conjugates of Tn antigen have a role for the active specific immunotherapy of cancer. The total synthesis of Tn antigen has been reported[2] by glycosidating between 3,4,6-tri-O-acetyl-2-azido-2-deoxy-β-D-galactopyranosyl chloride and L-serine derivative, then removing the protecting groups. In this route, the key intermediate 3,4,6-tri-O-acetyl-2-azido-2-deoxy-β-D-galactopyranosyl chloride was afforded by reaction of 3,4,6-tri-O-acetyl-D-galatal **1** with excess ceric ammonium nitrate and sodium azide to produce 2-azide-1-nitrate addition products **2**, then reacting with lithium iodide to get 3,4,6-tri-O-acetyl-2-azide-2-deoxy-α-D-galactopyranosyl iodide, subsequent treating with a solution of tetraethylammonium chloride in acetonitrile. Herein we designed another route as shown in **scheme 1**. 3,4,6-tri-O-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl bromide **3** was used to glycosidate with L-serine derivative. The compound **3** was produced by **2** with lithium bromide. Compared with reference, our scheme have two advantages: (1) less reaction stages, (2) LiBr is more stable and inexpensive than LiI.

The compound **4** was prepared in good yield by glycosidating **3** with L-serine derivative. Selective reduction of the azido group in **4** by $NaBH_4$-$NiCl_2$, followed by acetylation, afforded **5**. Subsequent hydrogenolysis and selective O-deacetylation, we obtained **6**. The product was purified by column chromatography and characterized by IR, ^{1}H-NMR and elemental analysis[3].

Scheme 1 The synthetic route of Tn antigen



CAN = $(NH_4)_2Ce(NO_2)_6$ Cbz = $OCOCH_2C_6H_5$ Bn = $CH_2C_6H_5$

References and Notes

1. H.Takahashi, R. Metoki ,S.Hakomori..*Cancer Res*.,**1988**,*48*,4361.
2. H. Paulsen ,J.P. Holck..*Carbohydrate Res*.,**1982**,*109*,89.
3. For compound 4. $[\alpha]^{20}_D$+71.5 (c, 1.0 $CHCl_3$). ($[\alpha]^{20}_D$+73.5 (c, 1.55 $CHCl_3$))[2]; IR (film): 2100, 1750, 1660;. ^{1}HNMR, 500 MHz, $CDCl_3$ δ ppm: 7.39～7.27 (m, 10H, Ar-H), 5.88 (d, J=8.11, 1H, NH), 5.35 (d, J=3.17, H- 4),5.38～5.11 (m, 5H, -CH_2Ph and H-3), 4.90 (d, J=3.54, 1H, H-1), 4.62 (m, 1H ,Serα-H), 4.13 (dd, J=2.98, J=10.63, 1H, Serβ-H), 4.07～3.99 (m, 4H, H-5 and 2H-6 and Serβ-H), 3.59 (dd, J=11.18, J=3.47, 1H, H-2), 2.13, 2.06, 2.00 (3s, 9H, 3OAc); For compound 6. $[\alpha]^{20}_D$+141 (c, 0.5 H_2O); mp:190-192℃; yield:62.4% (from compound 3). ($[\alpha]^{20}_D$+144 (c, 1.25 H_2O); mp:186-187 ℃ ; yield: 66.7% (from 3,4,6-tri-O-acetyl-2-azido-2-deoxy-β-D-galactopyranosyl chloride))[2]; IR (KBr): 3400, 3100, 1730, 1640, 1120; ^{1}HNMR, 500 MHz, D_2O δppm: 4.82 (d, J=3.74, 1H, H-1), 4.19 (dd, J=3.72, J=11.08, 1H, H-2), 4.02 (dd, J=2.9, J=11.08, 1H, H-3), 3.90～3.79 (m, 5H), 3.72～3.65 (m, 2H), 1.95 (s, 3H, NAc); Anal. calcd. for $C_{11}H_{20}N_2O_8$: C 42.85, H 6.54, N 9.09; found: C 42.65, H 6.58, N 8.97.

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