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The First Selective per-Tosylation of the Secondary OH-2 of β-Cyclodextrin

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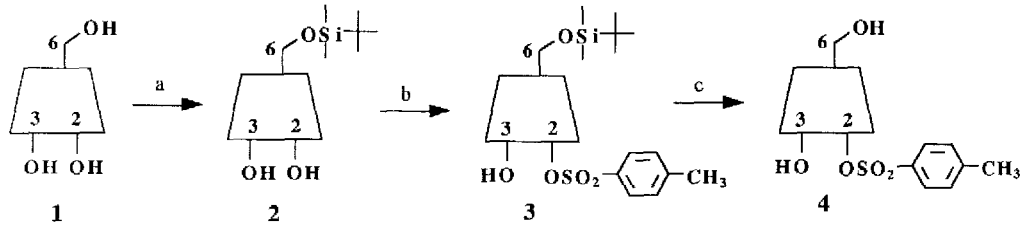
Key Words: *Synthesis, Cyclodextrin, Selective Substitution, Tosylation*

Abstract. *Use of the t-butyl dimethylsilyl group to selectively protect the primary OH-6 function allows the facile regioselective per-tosylation of the secondary OH-2 function The t-butyldimethylsilyl group can be removed without attack at the tosyl function*

Regioselective functionalisation of the hydroxyl groups of the cyclodextrins has received considerable attention[1], however even with regard to the more reactive primary OH-6 selective per-functionalisation has proved difficult[2]. In general methods to regio-selectively functionalise the secondary hydroxyl face are complex and yields low[3], however, promising new methods are being developped[4]. Recently efficient methods to protect the more reactive primary OH-6 via the t-butyldimethylsilyl[5] or thexyldimethylsilyl groups[6] have been developed These methods open possible routes to exploit the differences in reactivity between the OH-2 and OH-3 groups. In this communication we describe the utilisation of the t-butyldimethylsilyl protecting group to regioselectively per-tosylate the secondary OH-2 of ß-cyclodextrin.

The synthetic route is given below, ß-cyclodextrin **1** is first converted to key intermediate heptakis(6-t-butyldimethylsilyl-ß-cyclodextrin **2**, subsequent controlled reaction with p-toluenesulphonyl chloride (3 equivalents per silylated glucopyranose unit) in pyridine catalysed by 4-N,N-dimethylaminopyridine (DMAP) leads to complete substitution at the OH-2 giving **3**, and the complete desilylation is carried out with boron trifluoride etherate in chloroform (alcohol free, redistilled).



a: t-BuMe$_2$SiCl/pyridine b p-Toluenesulphonyl chloride/DMAP/pyridine c: $BF_3.Et_2O/CHCl_3$

The reaction is carried out at 50°C and carefully monitored by t.l.c. when the yield of **3** is maximised ; the reaction is halted by addition of water. Removal of pyridine in vacuo followed column chromatography (eluant $CHCl_3$/2-butanone: 97:3) allow isloation of **3** in 50% yield.

The ^1H nmr spectrum (200 MHz, $CDCl_3$) of **3** are fully consistent with a complete tosylation at the secodary OH-2 function. The phenyl resonances for **3** are present as a sharp AB pattern at 7.33 and 7.80 ppm. These resonances are highly sensitive to incomplete or over substitution yielding in both cases highly complex patterns. The cyclodextrin resonances of **3** have been fully assigned by use of COSY[7] Considerable displacement for certain resonances is observed relative to the parent compound **2**, notably for H-2 (4.26 ppm cf 3.62 ppm) and OH-3 (3.08 ppm cf 6.74 ppm). We ascribe the upfield displacement of OH-3 as arising from ring current effects due to the proximity of the phenyl rings as a result of an H-bonding interaction with an S=O of the tosyl group. For compound **4** the use of DMSO-d_6 as the nmr solvent removes this intramolecular hydrogen bonding and the OH-3 resonance is observed at 4.8 ppm.

We are currently studying the use of this versatile compound for the modification of ß-cyclodextrin at the secondary face

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7. NMR data (200 MHz for ^1H, 50 MHz for ^{13}C).
   3 ($CDCl_3$): ^1H: 5.19 (7H, d, H-1, J_{1-2}=3.49Hz),4.26 (7H, dd, H-2, J_{1-2}=3.49Hz, J_{2-3}=9.66Hz), 3.08 (7H, d, OH-3, J_{3-OH}=3.18Hz), 7.80 (14H, d, Tosyl), 7.33 (14H, d, Tosyl), 2.45 (21H, s, Tosyl), 0.86 (63H, s, $\underline{Me}_3CMe_2Si$-), 0.00(42H, s, $Me_3C\underline{Me}_2Si$-). 13C: 98.84 (C-1), 80.02, 79.85 (C-2, C-4), 72.62, 69.93 (C-3, C-5), 62.63 (C-6), 25.81, 18.23, -3.23, -3.41 (t-BuMe$_A$Me$_B$Si-), 145.03, 133.00, 129.55, 128.25, 21.70 (Tosyl).
   4 (DMSO-d_6): ^1H: 5.02 (7H, d, H-1), 4.86 (7H, d, OH-3), 4.45 (7H, brd. HO-6), 7.81 (14H, d, Tosyl), 7.41 (14H, d, Tosyl), 2.40 (21H, S, Tosyl). ^{13}C: 95.76 (C-1), 79.19, 76.72(C-4, C-2), 71.02, 68.37 (C-3, C-5), 59.15 (C-6), 144.46, 132.62, 129.36, 127.76, 20.85 (Tosyl)

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