Pergamon

Tetrahedron Letters 39 (1998) 2919–2920

TETRAHEDRON LETTERS

An Improved Synthesis of 6-*O*-Monotosyl-6-deoxy-β-cyclodextrin

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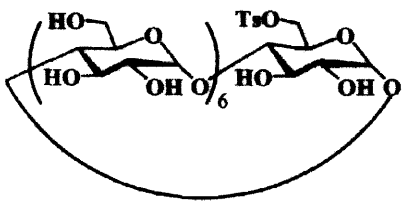
Received 28 January 1998; revised 13 February 1998; accepted 15 February 1998

Abstract: Addition of *p*-toluenesulfonic anhydride (Ts_2O) to β-cyclodextrin (CD) in water, followed by treatment with 10% aqueous NaOH solution for 10 min and removal of excess Ts_2O by filtration, gave mono-6-deoxy-6-(*O*-*p*-toluenesulfonyl)-CD (**1**) in 61% yield.

The lipophilic cavity of cyclodextrins makes these cyclic oligosaccharides useful for solubilizing and transporting many biologically active molecules.[1] Recent applications of β-cyclodextrin (CD) derivatives bearing substituents such as *O*-2-hydroxypropyl- and *O*-methyl as catalysts for rapid depletion of cholesterol,[2] bile acids,[3] and other lipids[4] from biological membranes has prompted the development of methods for the preparation of other water-soluble CDs with improved lipid-solubilizing ability and reduced renal toxicity.[1, 5] For modification of one of the 6-hydroxy groups of CD into other functional groups on the primary side such as amino,[6] alkylamino,[7] thioalkyl,[8] halo,[9] and formyl,[10] a convenient and widely used synthon is mono-6-deoxy-6-(*p*-tolylsulfonyl)-CD (**1**). The latter is generally prepared by the reaction of CD with *p*-toluenesulfonyl chloride in dry pyridine[6a, 11] or in aqueous acetonitrile at alkaline pH.[6a, 8, 11b, 12] This route has the disadvantages that **1** is obtained in very poor yield, often as low as only 6%,[12] 11%,[6b] or 17%,[8] and that **1** must be separated from multitosylated byproducts by chromatography.[11a, 11b] Here we report a large-scale synthesis of **1** that is easy to carry out and proceeds in satisfactory yield.

p-Toluenesulfonic anhydride (Ts_2O) is added to an aqueous solution of CD; subsequent addition of 10% aqueous NaOH solution induces the tosylation reaction, affording pure **1** in 61% yield without the need for purification by chromatography. A typical procedure for the preparation of **1** is as follows. A suspension of CD hydrate (11.5 g, 10 mmol) and Ts_2O (4.9 g, 15 mmol)[13] in 250 mL of water was stirred at room temperature for 2 h. A solution of NaOH (5.0 g in 50 mL of H_2O) was added, and after 10 min unreacted Ts_2O was removed by filtration through a sintered glass funnel. The filtrate was brought to pH ~8 by the

0040-4039/98/$19.00
PII: S0040-4039(98)00417-1



6-*O*-Monotosyl-6-deoxy-β-CD (1)

addition of NH_4Cl (13.4 g), affording **1** as a precipitate that was collected after cooling at 4 °C overnight; yield, 9.0 g (61%).[14] Molecular modeling studies (results not shown) suggest that an inclusion complex between CD and Ts_2O is formed prior to NaOH addition.

In summary, this study describes the use of Ts_2O for the preparation of **1**, a frequently used precursor of many CD derivatives.

Acknowledgment: Support for this work by NIH Grant HL-16660 is gratefully acknowledged. NSF Grant CHE-9408535 provided funds for the purchase of the 400-MHz NMR spectrometer.

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13. Multitosylation of CD was observed when more than 1.5 equiv of Ts_2O was used. Ts_2O was made by the following procedure: A mixture of TsCl (80 g, 0.43 mol) and $TsOH{\cdot}H_2O$ (20 g, 0.11 mol) in 500 mL of CH_2Cl_2 was stirred overnight. The reaction mixture was filtered through silica gel. Pure Ts_2O (70 g, 88% yield) was obtained when the filtrate was precipitated from hexane.
14. The product was washed with cold H_2O (to remove salts), then with acetone. Compound **1** was obtained as a fine white powder after drying under high vacuum overnight. TLC: (one spot) (a) R_f 0.78 (1-PrOH: H_2O:EtOAc:conc. NH_4OH = 5:3:1:1), (b) R_f 0.49 (*n*-BuOH: EtOH:H_2O = 5:4:3), compared with secondary-side CD-tosylate, R_f 0.52.[15] The structure was confirmed by ^1H and ^{13}C NMR spectroscopy, by comparison with the spectra of **1** obtained by using TsCl,[6b] and by conversion of **1** to various 6-amino- and 6-(aminoalkyl)-6-deoxy-CD derivatives.
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