Available online at www.sciencedirect.com
SCIENCE DIRECT®
Carbohydrate Research 338 (2003) 451–453
CARBOHYDRATE RESEARCH
www.elsevier.com/locate/carres

Note

Regioselective sulfonylation at O-2 of cyclomaltoheptaose with 1-(*p*-tolylsulfonyl)-(1*H*)-1,2,4-triazole

Ho Law,[a,1] Isabelle Baussanne,[a] José M. García Fernández,[b] Jacques Defaye[a,*]

[a]*Département de Pharmacochimie Moléculaire, CNRS and Université Joseph Fourier-Grenoble 1 (UMR 5063), BP 138, F-38243 Meylan, France*
[b]*Instituto de Investigaciones Químicas, CSIC, Américo Vespucio s/n, Isla de la Cartuja, E-41092 Sevilla, Spain*

Received 6 August 2002; accepted 11 November 2002

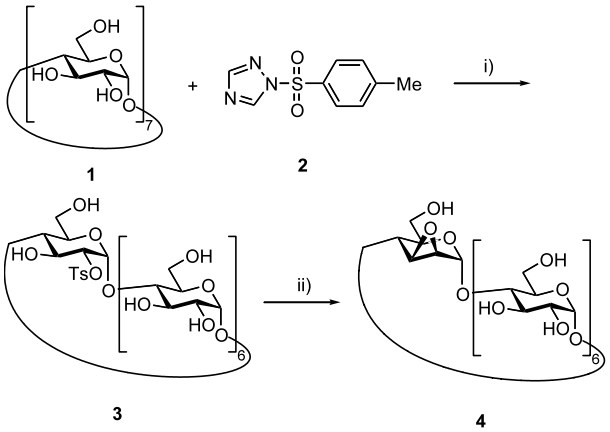
Abstract

2^I-*O*-*p*-Tolylsulfonylcyclomaltoheptaose was obtained in 42% yield by reaction of 1-(*p*-tolylsulfonyl)-(1*H*)-1,2,4-triazole on NaH-deprotonated cyclomaltoheptaose in DMF and further converted into the corresponding mono-2^I,3^I-*manno*-epoxide. © 2003 Elsevier Science Ltd. All rights reserved.

Keywords: 2^I-*O*-*p*-Tolylsulfonylcyclomaltoheptaose; β-Cyclodextrin; 1-(*p*-Tolylsulfonyl)-(1*H*)-1,2,4-triazole; 2^I,3^I-Anhydro-*manno*-β-cyclodextrin

Supramolecular interactions between cyclomaltooligosaccharides (cyclodextrins, CDs) and guest molecules depend on various contributions which are still being discussed and may include *inter alia* release of cavity-bound high-energy water, CDs-ring strain release on complexation, and van der Waals and hydrogen-bonding interactions.[1] Modifications at the secondary hydroxyl groups rim offers an opportunity to introduce recognition features different from the well studied rigid cyclodextrins core. 2^I-*O*-*p*-Tolylsulfonylcyclomaltoheptaose (**3**, Scheme 1), a convenient precursor of the corresponding β-CD 2^I,3^I-*manno*-epoxide,[2] is a key compound for such minimal modification of the most commonly available CD, namely cyclomaltoheptaose (β-cyclodextrin, β-CD, **1**). Monosulfonylation at C-2 of β-cyclodextrin has already been elegantly achieved by Ueno and Breslow[3] by reaction with 3-nitrophenyl *p*-toluenesulfonate in DMF, although in only ~10% yield. Regioselective opening of a β-CD 2,3-stannylidene acetal is however a more convenient approach[4] in terms of yield (32%). More recent syntheses include reaction of *p*-toluenesulfonyl chloride on NaH-deprotonated β-CD in DMF[5] or reaction of 1-*p*-tolylsulfonylimidazole in the presence of molecular sieves in the same solvent.[6] Since 1,2,4-triazolides are known to be more reactive towards nucleophiles as compared to imidazolides,[7] we anticipated that 1-(*p*-tolylsulfonyl)-(1*H*)-1,2,4-triazole (**2**) could result in improved tosyl group transfer by reaction with deprotonated β-cyclodextrin.

1-(*p*-Tolylsulfonyl)-(1*H*)-1,2,4-triazole (**2**) was obtained in 90% yield by a modification of the method of Katigiri et al.[8] Reaction of molar proportions of **2** and NaH-deprotonated β-cyclodextrin in DMF at room



Scheme 1. (i) DMF/NaH + **2**/rt; (ii) aq K_2CO_3/rt.

* Corresponding author. Tel.: +33-476041018; fax: +33-476041013
E-mail address: j.defaye@ujf-grenoble.fr (J. Defaye).
[1] Present address: Eras Labo, F-38330 Saint Nazaire Les Eymes.

PII: S0008-6215(02)00482-2

temperature, followed by concentration, acetone precipitation from an aqueous solution of the residual unreacted β-cyclodextrin, and filtration over an RP_{18} Sep-Pack reverse-phase column, resulted in a pure compound in 42% yield, which proved to be the β-CD 2^I-*p*-toluenesulfonate **3** by ^1H and ^{13}C NMR spectroscopy, and comparison with literature data. Conversion into the known[2] β-CD $2^I,3^I$-*manno*-epoxide **4** was a further proof of the expected structure.

The significant increase in O-2 monotosylation yield by use of 1-(*p*-tolylsulfonyl)-(1*H*)-1,2,4-triazole, in comparison with previously reported methodologies,[3–6] must be ascribed, essentially, to the favorable reactivity and stability features of the reagent. The formation of a β-CD inclusion-complex intermediate, which was postulated by Ueno and Breslow[3] in the case of tosyl transfer from 3-nitrophenyl *p*-toluenesulfonate to the C-2 hydroxyl group of β-CD, was rejected on the basis of NMR titration experiments in DMF-d_6. Thus, no change in the resonance of H-3 and H-5 of β-CD was observed in the presence of an up to 10-fold molar excess of **2**. The other protons were as well unaffected.

1. Experimental

1.1. General methods

β-Cyclodextrin was 'Pharmaceutical grade' from Wacker Chemie, dried at 110 °C for 24 h before use. *p*-Toluenesulfonyl chloride (99 + %) and 1,2,4-triazole (98%) were purchased from Aldrich and used without further purification. DMF was freshly distilled over calcium hydride and stored over molecular sieves. TLC was performed on E. Merck plastic sheets coated with Silica Gel 60 F_{254}, using 7:7:5:4 EtOAc–2-propanol–28% aq NH_4OH–water as eluent. The spots were visualized in UV light and also by dipping into 15% aq H_2SO_4 containing 2% of ammonium dimolybdate and 1% cerium(IV) sulfate followed by heating at 150 °C. Solvents were concd under diminished pressure with a rotary evaporator. Melting points were measured in a capillary Gallenkamp melting point apparatus. Optical rotations were measured at 20 °C, using a Perkin–Elmer 341 polarimeter. NMR spectra were recorded in D_2O with a Bruker 500 AMX spectrometer. Assigment of the proton resonances was assisted by 2D COSY and 1D TOCSY experiments.

1.2. 1-(*p*-Tolylsulfonyl)-(1*H*)-1,2,4-triazole (2)

To a soln of 1,2,4-triazole (2.07 g, 30 mmol) and Et_3N (3.03 g, 30 mmol) in dry CH_2Cl_2 (60 mL), *p*-toluenesulfonyl chloride (5.73 g) was added at 0 °C. The mixture was stirred at room temperature (rt) for 2 h and then washed with water (3 × 20 mL) to remove triethylammonium chloride. The organic phase was dried over anhyd Na_2SO_4, and concd to a syrup which crystallised in cyclohexane to give **2** as a white solid (5.95 g, 90%): mp 106–108 °C, lit.[8] 107 °C; ^1H NMR ($CDCl_3$): δ 8.81 (d, 2 H, Ar), 8.10 (d, 2 H, Ar), 2.01 (s, 3 H, Me).

1.3. 2^I-*O*-*p*-Tolylsulfonylcyclomaltoheptaose (3)

To a soln of β-CD (**1**, 2 g, 1.70 mmol) in DMF (50 mL) at 0 °C was added NaH (60% in mineral oil, 70 mg, 1.76 mmol) and the soln was stirred for 2 h at this temperature. 1-(*p*-Tolylsulfonyl)-(1-*H*)-1,2,4-triazole (0.392 g, 1.76 mmol) in DMF (15 mL) was then added dropwise and the mixture was further stirred for 2 h while allowing it to reach the rt. It was then concd and to the resulting solid in water (10 mL), acetone (70 mL) was added in order to precipitate the residual β-CD. The filtrate was concd and filtrated on a RP_{18} Sep-Pack column (reverse phase) using 9:1 MeCN–water as eluent to give the pure title compound (95 mg, 42%) as a white solid; mp 225–228 °C, $[\alpha]_D$ + 105° (*c* 1, DMF), no physicochemical data in lit.; NMR ^1H (D_2O): δ 7.84 (d, 2 H, *J* 8.5 Hz, Ar), 7.37 (d, 2 H, *J* 8.5 Hz, Ar), 4.96–4.91 (m, 6 H, H-$1^{II–VII}$), 4.79 (br s, 1 H, H-1^I), 4.28 (br s, 1 H, H-2^I), 4.01 (t, 1 H, $J_{2,3} = J_{3,4} = 9.0$ Hz, H-3^I), 3.80–3.60 (m, 27 H, H-$3^{II–VII}$, H-$5^{I–VII}$, H-$6a^{I–VII}$, H-$6b^{I–VII}$), 3.55–3.41 (m, 12 H, H-$2^{II–VII}$, H-$4^{I–VI}$), 3.27 (t, 1 H, $J_{3,4} = J_{4,5} = 9.0$ Hz, H-4^{VII}), 2.32 (s, 3 H, Me); ^{13}C (D_2O): spectrum identical to that reported in Refs. 3–5. Anal. Calcd for $C_{49}H_{76}O_{37}S{\cdot}7H_2O$: C, 41.58; H, 6.41; S, 2.27. Found: C, 41.31; H, 6.34; S, 2.07.

1.4. Cyclo{4)-(2,3-anhydro-α-D-mannopyranosyl)-(1 → 4)-α-D-glucopyranosyl-[(1 → 4)-α-D-glucopyranosyl]$_4$-(1 → 4)-α-D-glucopyranosyl-(1 →} (4)

A soln of **3** (0.1 g, 0.078 mmol) in aq K_2CO_3 (0.25%, 10 mL) was stirred for 16 h at rt, then neutralized by addition of dilute HCl, and passed onto a Sephadex G-15 column with elution with water to give, after freeze-drying, pure **4** (79 mg, 91.5%) as a white solid; mp 260–263 °C; $[\alpha]_D$ + 86.5° (*c* 1, DMF), no physicochemical data in lit. FAB$^+$MS: *m*/*z* 1139 $[M + Na]^+$. ^1H NMR: spectrum identical to that reported in Ref. 2. Anal. Calcd for $C_{42}H_{68}O_{34}{\cdot}6H_2O$: C, 41.18; H. 6.58. Found: C, 41.09; H, 6.32.

1.5. Titration experiment

This was carried out at 303 K using a 500 MHz NMR instrument. A 5.6 mM soln of β-CD in DMF-d_6 was

prepared. A 450 μL aliquot was transferred to a 5 mm NMR tube and the initial ^{1}H NMR spectrum was recorded and fully assigned with the assistance of a 2D COSY spectrum. The H-1 (δ 4.95, d, $J_{1,2}$ 3.5 Hz), H-2 (δ 3.44, dd, $J_{2,3}$ 9.7 Hz), H-3 (δ 3.84, t, $J_{3,4}$ 9.7 Hz), H-4 (δ 3.48, t, $J_{4,5}$ 9.7 Hz), H-5 (δ 3.77, ddd, $J_{5,6a} = J_{5,6b} =$ 9.7 Hz), and H-6a, H-6b (δ 3.84, m) signals were monitored in the subsequent titration experiment. A 0.5 M soln of **2** in the previous β-CD soln was prepared and then added via a microsyringe to the NMR tube, initially in 10 μL portions. These amounts were increased until a 10-fold molar excess of **2** was reached. The ^{1}H NMR spectrum of each soln was recorded and the chemical shifts of the diagnostic CD protons obtained at the various **2**: β-CD concentration ratios. No significant variation ($\Delta\delta < \pm 0.001$ ppm) was observed.

References

1. Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325–1357.
2. (a) Breslow, R.; Czarnik, A. W. *J. Am. Chem. Soc.* **1983**, *105*, 1390–1391;
   (b) Breslow, R.; Czarnik, A. W.; Lauer, M.; Leppkes, R.; Winkler, J.; Zimmerman, S. *J. Am. Chem. Soc.* **1986**, *108*, 1969–1979.
3. Ueno, A.; Breslow, R. *Tetrahedron Lett.* **1982**, *23*, 3451–3454.
4. (a) Murakami, T.; Harata, K.; Morimoto, S. *Tetrahedron Lett.* **1987**, *28*, 321–324;
   (b) Namazi H.; Grindley T.B. *Int. Carbohydr. Symp. 18th, Milano 1996*, abstract BP 007, p. 265.
5. Rong, D.; D'Souza, V. T. *Tetrahedron Lett.* **1990**, *31*, 4275–4278.
6. Teranishi, K.; Watanabe, K.; Hisamatsu, M.; Yamada, T. *J. Carbohydr. Chem.* **1998**, *17*, 489–494.
7. Staab, H. A. *Angew. Chem.* **1962**, *74*, 407–423.
8. Katagiri, N.; Itakura, K.; Narang, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 7332–7337.