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ORIGINAL ARTICLE

Synthesis of some novel sulfonyl ester derivatives derived from D-mannitol

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Abstract The preparation of sulfonate-derivatives of D-mannitol i.e. 1,2:3,4-di-*O*-isopropylidene-3,4-di-*O*-*p*-toluenesulfonate-D-mannitol (**3a**), 1,2:3,4-di-*O*-isopropylidene-3,4-di-*O*-methanesulfonate-D-mannitol (**3b**), and 1, 2:3,4-di-*O*-isopropylidene-3,4-di-*O*-trifluoromethanesulfonate-D-mannitol (**3c**) is described. Full characterization and methodologies of these sulfonate-D-mannitol derivatives have been described as well.

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1. Introduction

The chiral compounds which possess C_2 -symmetry (Orsini* and Pelizzoni, 1996; Whitesell, 1989) such as D-mannitol (**2**) with terminal protected moieties is quite useful starting material to prepare different types of chiral ligands (Padmakumari Amma and Stille, 1982; Schmid et al., 1991; Hertel et al., 1991). Many features are found in such sugar compounds, for instance: availability, cheap, chirality and being non-toxic (Al-Majid et al., 2003). It is expected that such ligands will chelate to metal complexes which will prevent the dissociation of these metals during the reaction course (Kagan, 1985). The main objective of this work is to prepare new intermediate sulfonate-deriva-

tives **3(a–c)** as shown in Scheme 1. It is expected that such sulfonate intermediates at non-protected chiral centres will be good leaving groups to obtain a valuable chiral ligands by various nucleophiles e.g. R_2P (Littke and Fu, 1999; Wolfe et al., 2000; Wolfe, 1999), NH_2 (Nakadai et al., 2002; Rasappan and Reiser*, 2009) and SH (Moore et al., 1990; Wei et al., 2005) groups. These sulfonate intermediates were obtained via S_N2 pathway where the nucleophilic substitution was achieved at an oxygen atom rather than a chiral carbon atom.

2. Experimental

Melting points were determined on Tottoli capillary melting point apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer FT Spectrophotometer, 1000. 1H and ^{13}C NMR spectra were taken on JEOL ECP 400 NMR spectrometer operating at 400 MHz in $CDCl_3$ and $DMSO-d_6$ with TMS as internal standard. Mass spectra were carried out on Shimadzu GCMSQP5050A spectrometer, ionization energy 70 eV at college of Science, King Saud University. Polarimeter POLAX-2L (ATAGO), LED + inter reference filter (589 nm). Silica gel column chromatography and Sephadex LH-25-100 (micro miter) were used for purification of the some prepared

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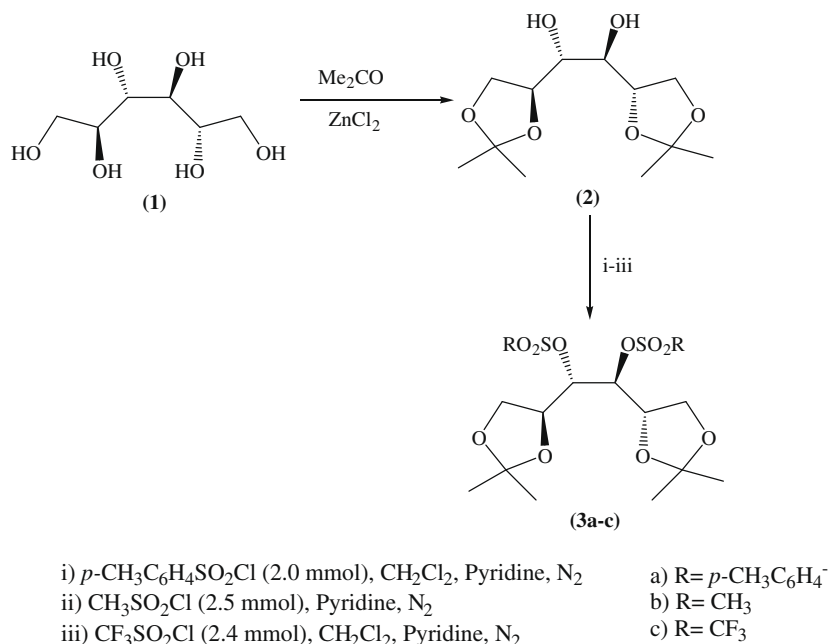
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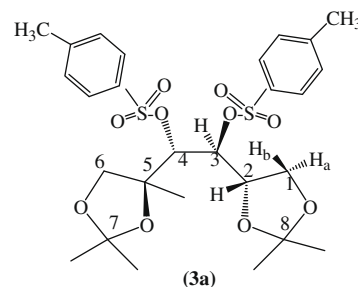
Scheme 1

compounds. TLC with UV 254-indicator was used. Reactions involving moisture sensitive compounds (**3a–b**) were carried out under argon atmosphere. D-Mannitol, anhydrous pyridine, methane sulfonyl chloride, *p*-toluenesulfonyl chloride and trifluoromethanesulfonyl anhydride were supplied from Aldrich Chemical Company and used without further purification.

2.1. Preparation of 3,4-bis-*o*-tosyl-1,2:5,6-di-*o*-isopropylidene-*D*-mannitol (**3a**)

In a 3-necked round-bottomed flask were added 1,2:5,6-di-*o*-isopropylidene-*D*-mannitol (Schmid et al., 1991) (10.0 g, 38.16 mmol) and dry dichloromethane (15.0 ml), the mixture was stirred at 25 °C under an inert atmosphere of nitrogen. A mixture of the *p*-toluenesulfonyl chloride (14.55 g, 76.32 mmol) and freshly-distilled pyridine (50.0 ml) was then added drop wise over a period of 15 min and the reaction mixture was allowed to react at 70 °C for 8 h and then cooled down to the room temperature. The reaction mixture was then extracted with dichloromethane (3 × 70.0 ml) and the organic extracts were washed with 10% CuSO₄ (2 × 50.0 ml), saturated NaHCO₃ (100.0 ml), H₂O (100.0 ml) followed by brine (100.0 ml), dried over anhydrous MgSO₄ and filtered off and finally evaporated to yield an oily crude product which when dissolved in a cold diethyl ether and evaporated repeatedly gave the desired bistosylate (**3a**) as colorless crystals (16.30 g, 28.60 mmol, 75%), m.p 118 °C, [α]₅₈₉ –128° (c 0.023, CHCl₃), IR(KBr): ν_{max}(cm⁻¹): 3090 w, 3040 w, 3015 (C–H, aromatic, str.), 2990 s, 2974 s (C–H alkane, str.), 1371 (SO₂, asym.str.), 1211 (SO₂, symm. str.) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ_H: 1.27 (6H, s, 2 × CH₃), 1.37 (6H, s, 2 × CH₃), (6H, s, 2 × CH₃ aromatic), 3.80–3.83 (2H, m, 2 × H₂), 3.86–3.90 (2H, dd, ³J 5.58 Hz, ³J 5.8 4 Hz, 2 × H_a), 3.97–4.00 (2H, dd, ³J 4.4 Hz, ³J 5.12 Hz, 2 × H_b), 4.93–4.95 (2H, d, ³J 8.08 Hz, 2 × H-3), 7.78–7.8 (4H, d, ³J 8.08 Hz, aromatic) ppm; ¹³C NMR (CDCl₃): δ_C: 21.8 (2 × CH₃ aromatic), 25.3 (2 × CH₃), 26.7 (2 × CH₃), 66.7 (C-1 and C-6), 72.9 (C-2 and C-5), 78.9 (C-3

and C-4), 110.2 (C-7 and C-8), 128 (C-11 and C-13), 129.8 (C-10 and C-14), 133.8 (C-12), 145.2 (C-9) ppm; MS: *m/z*: 571 (M + H)⁺ 2.4%, 555 (M – CH₃)⁺ 62.9%.

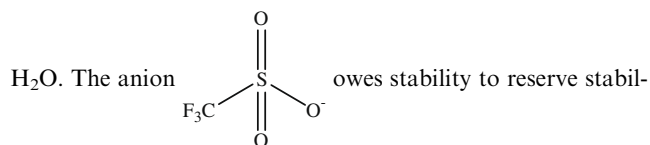


2.2. Preparation of 3,4-bis-*o*-mesyl-1,2:5,6-di-*o*-isopropylidene-*D*-mannitol (**3b**)

In a 3-necked round-bottomed flask equipped with equalizing funnel were added 1,2:5,6-di-*o*-isopropylidene-*D*-mannitol (5.0 g, 19.08 mmol) in dry pyridine (25.0 ml), the mixture was stirred at 0.0 °C under an inert atmosphere of nitrogen. Methanesulfonyl chloride (3.5 ml, 5.20 g, 45.5 mmol) was then added drop wise over a period of 15 min and the reaction mixture was allowed to stir at 0.0 °C for 90 min and kept in the fridge overnight. Water (3.0 ml) was then added, extracted with chloroform (3 × 50.0 ml) and the organic extracts were washed with 10% HCl followed by H₂O (1 × 100.0 ml), 5% Na₂CO₃ (1 × 100.0 ml), H₂O (1 × 100.0 ml) followed by brine (100.0 ml), dried over anhydrous MgSO₄ and filtered off and evaporated to yield yellow oily crude product which upon dissolved in a cold diethyl ether and evaporated repeatedly gave colorless crystals of the desired bimesylate (**3b**) (7.11 g, 17.01 mmol, 88%), m.p 130 °C, [α]₅₈₉ –97.0° (c 0.023, CHCl₃), IR(KBr): ν_{max}(cm⁻¹): 2990 s, 2953 s, 2940 m (C–H alkane, str.), 1418, 1455, 1424 (C–

ing band of the asymmetric SO_2 at 1374 cm^{-1} in addition to the symmetric one at 1219 cm^{-1} . The formation of bismesylate (**3b**) has been confirmed by ^1H NMR spectrum, thus, the four methyl groups of the ketal moieties were seen as two singlets at δ 1.34 and 1.42 ppm. The methyl group of the mesylate was also obtained as singlet with more down field at δ 3.16 ppm. The methylene protons have followed a *ABX* pattern *i.e.* the H_a was seen as doublet at δ 4.16 with J 8.3 Hz and the H_b was also seen as doublet at δ 4.174 at the same J value. A multiplet peak was given for assignment of the H-2 and H-5, while the H-3 and H-4 absorption were obtained as a doublet at 4.95 with J 7.36 Hz. The ^{13}C NMR in denaturated chloroform showed all the required seven carbon lines for C_2 -symmetry of the molecule as follows: δ_C : 25.2 and d 26.6 (all four methyl groups of the terminal ketals), 38.9 (SCH_3) 66.5 (C-1 and C-6), 73.5 (C-2 and C-5), 79.0 (C3 and C4) and 110.3 for C-7 and C-8 ppm. Finally the desired product of the mesylate (**3b**) was confirmed by mass spectrum by giving the molecular ion $[\text{M}-\text{CH}_3]^+$ at m/z : 403 with 44% intensity.

The third sulfonate group is the preparation of the trifluoromethanesulfonate (triflate) (**3c**). A triflate group CF_3SO_3 is an excellent leaving group used in certain organic reactions such as *Suzuki coupling* (Miyaura and Suzuki, 1995; Saito and Fu, 2007) and *Heck reaction* (Heck, 1982). Since alkyl triflate is extremely reactive in $\text{S}_{\text{N}}2$ reactions, they must be stored in cold-dry conditions to preventing from nucleophiles such as



ization which causes the negative charges to be spread over the three oxygen atoms and the sulfur atom. An additional stabilization is achieved by the trifluoromethyl group as strong electron-withdrawing group (Kobayashi, 1999; Dubreail et al., 1999; Netscher and Bohrer, 1996).

When 3,4-diol-D-mannitol (**2**) was treated with an excess of triflic anhydride in the presence of dichloromethane and pyridine at $0.0\text{ }^\circ\text{C}$. Because of highly moisture sensitivity of the triflic anhydride and the expected product (**3c**), the reaction was carried out in an inert atmosphere of argon. After a period of 90 min a colorless crystalline product of the bistriflates (**3c**) was obtained in 61%. The resulting product was confirmed by standard analytical methods; Infra red spectrum showed a strong band at 1242 cm^{-1} represents the stretching vibration of the triflyl group, a stretching band of the asymmetric $\text{S}(=\text{O})_2$ at 1390 cm^{-1} was observed. The OH group peak was absent confirming that the nucleophilic substitution has taken place. ^1H NMR spectrum showed two singlet peaks of the terminal isopropylidene moieties at δ 1.35 and 1.43 ppm. A doublet of doublet (*dd*) at δ 4.03–4.06 was observed which represent H_a . Another doublet of doublet (*dd*) was also seen at δ 4.16–4.20 for H_b . A multiplet was obtained in the region of δ 4.25–4.30 representing the H-2, while H-3 was seen as duplet (*d*) in the range of δ 5.20–5.23. The triflate was also confirmed by ^{13}C NMR by obtaining the expected chemical shifts as follows: δ_C : 24.7 and 26.6 represent the four methyl groups of the two terminal ketals. The two methylene carbons (C-1 and C-6) were appeared at δ_C 66.7 and the asymmetric carbons (C-2 and C-5) were given at δ_C 72.0. The other asym-

metric methine carbons (C-3 and C-4) were observed at δ_C 82.2. The peak of C-7 and C-8 was seen at δ_C 111.0. The remaining two lines at δ_C 74.4 were attributed to the CF_3 group. Additionally the ^{19}F NMR spectrum showed a single line at δ_F 74.4 ppm confirming that the formation of bistriflates (**3c**) has been taken place.

Finally the resulting bistriflates product (**3c**) was confirmed by mass spectrum by giving the molecular ion $[\text{M}-\text{CH}_3]^+$ at m/z : 511 with 100% integration.

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