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

Abdullah M. Al Majid *

Chemistry Department, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia

Received 11 December 2009; accepted 11 January 2010
Available online 4 February 2010

Abstract  The preparation of sulfonate-derivatives of D-mannitol i.e. 1,2:3,4-di-O-isopropylidene-3,4-di-O-p-toluensulfonate-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.

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-

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. $^1$H 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
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 trifluoromethanesulfonic 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-isopropylidine-D-mannitol (3a)

In a 3-necked round-bottomed flask were added 1,2:5,6-di-o-isopropylidine-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]D589 97.0° (c 0.023, CHCl3), IR(KBr): νmax(cm−1): 3090 w, 3040 w, 3015 (C–H, aromatic, str.), 2990 s, 2974 s (C–H alkane, str.), 1371 (SO2, asymm.str.), 1211 (SO2, symm. str.) cm−1; 1H NMR (CDCl3, 400 MHz): δH: 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 Hz, 2·H), 3.97–4.00 (2H, dd, 3J 4.4 Hz, 3J 5.12 Hz, 2·H), 4.93–4.95 (2H, d, 3J 8.08 Hz, 2·H), 7.78–7.8 (4H, d, 3J 8.08 Hz, aromatic) ppm; 13C NMR (CDCl3): δC: 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-isopropylidine-D-mannitol (3b)

In a 3-necked round-bottomed flask equipped with equalizing funnel were added 1,2:5,6-di-o-isopropylidine-D-mannitol (5.0 g, 19.08 mmol) in dry pyridine (25.0 ml), the mixture was stirred at 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 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 evaporated to yield yellow oily crude product which upon dissolved in a cold diethyl ether and evaporated repeatedly gave colorless crystals of the desired bismesylate (3b) (7.11 g, 17.01 mmol, 88%), m.p 130°C, [α]D589 –97.0° (c 0.023, CHCl3), IR(KBr): νmax(cm−1): 2990 s, 2953 s, 2940 m (C–H alkane, str.), 1727, 1677, 1592, 1497 (C–O, str.), 1418, 1455, 1424 (C–
H alkane, def.), 1347 (SO2, asyr. str.), 1219 (SO2, symm. str.); 
1H NMR (CDCl3, 400 MHz): δH: 1.34 (6H, s, 2 × CH3): 1.42 (6H, s, 2 × CH3), 3.16 (6H, s, 2 × SCHR), 4.16 (2H, d, J = 5.12 Hz, 2 × CH=), 4.26 (2H, m, 2H-2), 4.95 (2H, J = 7.36 Hz, 2H-3) ppm; 13C NMR (CDCl3): δC: 25.2 (2 × CH3), 26.6 (2 × CH3), 39.0 (2 × SCHR), 66.5 (C-1 and C-6), 73.5 (C-2 and C-5), 79.0 (C-3 and C-4), 110.3 (C-7 and C-8) ppm MS: m/z: 419 (M + H)+ 0.2%, 403 (M–CH3)+ 44.2%.

2.3. Preparation of 3,4-bis-o-triflyl-1,2:5,6-di-o-isopropylidine-D-mannitol (3c)

In a 3-necked round-bottomed flask equipped with equalizing funnel were added 1:2.5:6-di-o-isopropylidine-D-mannitol (3.0 g, 11.45 mmol) and dichloromethane (25 ml), the mixture was stirred for 10 min at 0.0 °C under an inert atmosphere of nitrogen, dry pyridine (5.0 ml) was then added. A mixture of trifluoromethanesulfonic anhydride (4.8 ml, 8.0 g, 28.60 mmol) in dry pyridine (10.0 ml) was added drop wise over a period of 15 min and the reaction mixture was allowed to stir at 25.0 °C for 90 min and then poured into cold water (30 ml), extracted with dichloromethane (3 × 50 ml) and the organic extracts were washed by H2O (1 × 100.0 ml), dried over anhydrous MgSO4 and filtered off and evaporated to yield an oily crude product, kept in the fridge for 48 h. The crude product was then dissolved in cold diethyl ether and evacuated repeatedly gave the desired ditriflate (3c) as colorless crystals (3.70 g, 7.03 mmol, 62%), m.p 94 °C, IR(KBr): vmax (cm–1): 2992 s, 2937 s, 2903 m (C–H alkane, str.), 1406 (C–H alkane, def.), 1390 (SO2, asyr. str.), 1242 (CF3, str.), 1215 (SO2, symm. str.); 1H NMR (CDCl3, 400 MHz): δH: 1.35(6H, s, 2 × CH3), 1.43 (6H, s, 2 × CH3), 4.03-4.06 (2H, d, J = 4.4 Hz, 2 × CH2), 4.16–4.20 (2H, d, J = 5.84 Hz, 2 × CH2), 4.25–4.30 (2H, J = 7.36 Hz, 2H-2), 5.20–5.23 (2H, J = 8.04 Hz, 2H-3) ppm; 13C NMR (CDCl3): δC: 24.7 (2 × CH3), 26.6 (2 × CH3), 66.7 (C-1 and C-6), 72.0 (C-2 and C-5), 82.2 (C-3 and C-4), 111.0 (C-7 and C-8), 116.7–120.0 (2CF3) ppm; 19F NMR (CDCl3): δF = –74.36 ppm, m/z (MS): 527 (M + H)+ 0.6%, 511 (M–CH3)+ 100%.

3. Results and discussion

In order to prepare chiral sulfonate-intermediates derived from d-mannitol (3a–c) the two terminal hydroxyl groups of d-mannitol (1) need to be protected. The resulting terminal ketal-protected diol (2) is a well-known compound (Padmakumari Amma and Stille, 1982; Schmid et al., 1991; Hertel et al., 1991) and will be the key step to prepare different types of chiral bidentate ligands (Schmid et al., 1991; Hertel et al., 1991; Al-Majid et al., 2003; Kagan, 1985; Litke and Fu, 1999; Wolfe, 1999; Nakadai et al., 2002; Rasappan and Reiser*, 2009), so the starting material i.e. diol (2) was prepared according to the procedure described in the literature (Schmid et al., 1991).

One of the sulfonate-derivatives derived from d-mannitol is the preparation of tosylate ester (3a). It is known that the tosyl group p-CH2CH3H2SO2 is electron-withdrawing (Todd Whitaker et al., 2006). Hence, it is an excellent leaving group, and toluenesulfonyl chloride activates the alcohol (2) by nucleophilic attack at positively sulfur atom of the sulfonyl group. Thus, when the diol (2) was treated with two equivalents of p-toluenesulfonyl chloride in the presence of a moderate base such as pyridine (Kazemi et al., 2007) and heated at 70 °C for 8 h under an inert atmosphere conditions, the crystalline colorless product of the bistosylates (3a) was obtained in a reasonable yield (75%). The resulting product showed an optical activity [α]D20 = –128°, in chloroform maintaining the direction of the rotation which confirmed that the substitution has taken place at an oxygen atom rather than at the chloral carbon atom. The spectral data of (3a) supported the formation of the desired product. IR spectrum showed the familiar stretching bands of the phenyl ring at 3170 and 3090 cm–1 and the stretching band of the new formed sulfonyl group was observed at 1371 cm–1. Additionally IR showed the absence of absorption band for the OH group. In the 1H NMR spectrum, the four methyl groups of the ketal moieties appeared as two singlets at δ 1.27 and 1.37 ppm while the absorption of the methyl group of the aromatic ring was seen as singlet at δ 2.43 comparisons with those seen of the ketal moieties. A multiplet signal of δ 3.8–3.83 ppm represent the H-2 was obtained, while the H-3 was observed as doublet (d) at δ 4.93–4.95 ppm. The characteristic peaks of the aromatic ring were shown as two doublets at δ 7.29–7.31 and at δ 7.78–7.80 ppm following the pattern AA′XX′. Finally the mass spectrum of confirmed the proposed structure of bistosylate (3a) by obtaining the m/z 555 for the molecular ion [M–CH3]+ with 63% intensity and m/z 571 for the molecular ion [M + H]+ with 2.4% intensity. Addition molecular fragmental ions [CH3C6H4O2SO]+ and [C6H4CH3]+ were obtained at m/z 155 with 60% and m/z 91 with intensity 73% respectively. The ionization fragment of the ketal moiety was given at m/z: 101 with 100% intensity.

The second sulfonate-derivative i.e. bismesylate ester (3b) is considered too as an excellent leaving group in nucleophilic substitution reactions. Thus, bismesylate (3b) (Coates and Chen, 1969; Crossland and Servis, 1970) was prepared from the reaction of the diol (2) with an excess amount of methane sulfonyl chloride at 0.0 °C in the presence of freshly-distilled pyridine for 90 min under an anhydrous conditions to avoid any possible hydrolysis might be resulted. The precise mechanism for the reaction has not been fully determined. It appears that the mechanism is dependent on the substrate alcohol and the reaction conditions. A good yield (88%) was achieved, and the compound showed an optically activity maintaining the direction of optical rotation as reported earlier. All analytical data have supported the desired product: IR showed completely disappeared of the familiar peak of OH group, it is also showed the stretch-
The formation of bimesylate (3b) has been confirmed by $^1$H NMR spectrum, thus, the four methyl groups of the ketal moieties were seen as two singlets at $\delta$ 1.34 and 1.42 ppm. The methyl group of the mesylate was also obtained as singlet with more down field at $\delta$ 3.16 ppm. The methylene protons have followed a $ABX$ pattern i.e. the H$_3$ was seen as doublet at $\delta$ 4.16 with J 8.3 Hz and the H$_8$ was also seen as doublet at $d$ 4.174 at the same J value. A multiplet peak was given for assignment of the H-2 and H-5, while it was also seen as doublet at $\delta$ 4.174 at the same $J$ value. A multiplet peak was also seen at $\delta$ 4.16 with J 4.95 with J 7.36 Hz. The $^{13}$C NMR in denatured chloroform showed all the required seven carbon lines for C$_2$-symmetry of the molecule as follows: $\delta$C: 25.2 and 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 $[M-CH_3]^+$ at $m/z$: 403 with 44% intensity.

The third sulfonate group is the preparation of the trifluoromethanesulfonate (triflate) (3c). A triflate group CF$_3$SO$_3$ 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 $S_N2$ reactions, they must be stored in cold-dry conditions to prevent from nucleophiles such as H$_2$O. The anion

\[
\begin{align*}
\text{O} & \\
\text{S} & \\
\text{F}_3\text{C} & \\
\text{O} & \\
\end{align*}
\]

owes stability to reserve stabilization which causes the negative charges to 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; Dubreuil 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 °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 band of the asymmetric SO$_2$ at 1374 cm$^{-1}$ and a stretching band of the asymmetric SO$_2$ at 1390 cm$^{-1}$. When 3,4-diol-D-mannitol (2) was treated with triflic anhydride in the presence of dichloromethane and pyridine at 0.0 °C, an anion was formed $\left(S\left(\text{O}_2\right)\right)_2$ at 1390 cm$^{-1}$ 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 $[M-CH_3]^+$ at $m/z$: 511 with 100% integration.

**Acknowledgments**

The author gives his appreciation and much gratitude to the research centre at college of science in King Saud University for financial support. All analytical data were carried out at the chemistry department and the research centre-college of Science, King Saud University. Finally many thanks for Mr. Mohammad Al Shammy for his technical support in this research.

**References**