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Synthesis, and characterization of a new series of sulfite and sulfate derivatives of D-Mannitol

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KEYWORDS

D-Mannitol;
Sulfite;
Sulfate;
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Abstract In this work, synthesis and characterization of a series of D-Mannitol derivatives with sulfite **2a–d** and sulfate **3a–d** moieties have been investigated. The method entails a two-step synthesis. The first step involves the Sharpless-type reaction of DIOL **1a–d** with $SOCl_2$ in CH_2Cl_2 in the presence of Et_3N to afford the intermediate sulfite derivatives **2a–d** in good yield. The second step includes the oxidation reaction of the resulting intermediate in the presence of $NaIO_4$ in a mixture of $CCl_4/CH_3CN/H_2O$ (3/3/2 ratio) in the presence of catalytic amount of $RuCl_3{\cdot}H_2O$ to afford the desired sulfate moiety **3a–d** in a moderate to high yield (66–96%). The structures of all newly synthesized compounds have been elucidated by ^1H, ^{13}C NMR, GCMS, and IR spectrometry.

1. Introduction

The incidences of drug resistance of microorganisms to antibacterial agents were constantly reported for the past few years [6]. Subsequently, there is an urgent need for the development of new drug molecules with newer targets, more potent, selective non-traditional antimicrobial agents and with an alternative mechanism of action. Organic molecules possessing sulfate moieties are increasingly gaining importance as modulators of physiological or pathological function [12]. These functions include inhibition of viral infection [10,15,20,26], and clotting [2,3,6,7,13,14,18,21,23,24]. Yet, the number of multiple sulfated synthetic, organic molecules available for investigation remains small, primarily because of difficulties in synthesis and isolation. As the structural diversity in organic sulfate molecules increases, better modulators are expected.

For decades natural and synthetic polymers carrying sulfate groups (dextran sulfate, carrageenan, heparin, polyvinyl sulfate, chondroitin sulfate, and others) have been known to have strong complement-inhibiting properties [19,16,22,25,27].

Xing et al. had found that all kinds of sulfated chitosans possessed antioxidant activities and free radical scavenging activities [28,29]. Different bulkyarenesulfonylquinolones based on norfloxacin and ciprofloxacin scaffolds were reported with significant antibacterial activity [1].

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In continuation of our research [4,5,8], the present work describes the synthesis, and characterization of some new sulfite and sulfate moieties.

2. Experimental

2.1. General

All the moisture and air sensitive reactions were carried out under an inert atmosphere of argon filled glove box and standard Schlenk-line techniques. All the chemicals were purchased from Aldrich, Sigma–Aldrich, Fluka etc., and were used without further purification, unless otherwise stated. Toluene was distilled using Na/benzophenone. CH_2Cl_2 was dried from CaH_2. Silica gel (SiO_2; 100–200 mesh) was used for Flash column chromatography. All melting points were measured on a Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR Spectra were measured as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer. The NMR spectra were recorded on a Varian Mercury Jeol-400 NMR spectrometer. ^{1}H-NMR (400 MHz), ^{13}C-NMR (100 MHz) and ^{31}P-NMR were run in deuterated chloroform ($CDCl_3$). Chemical shifts (δ) are referred in terms of ppm and *J*-coupling constants are given in Hz. Mass spectra were recorded on a Jeol of JMS-600 H. Elemental analysis was carried out on Elmer 2400 Elemental Analyzer; CHN mode. Specific optical rotations were measured on a highly sensitive automatic 'A. KRÜSS OPTRONOCS' polarimeter using sodium light (D line 589 nm).

2.1.1. General procedure for the synthesis of sulfite derivatives **2a–d** (GP1)

In a two neck round bottom flask, DIOL **1a–d** (2.8 mmol) and Et_3N (1.57 mL) were dissolved in CH_2Cl_2 (10 mL). The reaction mixture was cooled at 0 °C, and $SOCl_2$ (0.3 mL, 4.2 mmol) in CH_2Cl_2 (1.0 mL) was added drop wise over 15 min, then the reaction was continued for further 15 min, (TLC: EtOAc/Pet.ether 1:2). The reaction mixture was extracted with CH_2Cl_2, washed with brine, and dried over $MgSO_4$, passed through short pad of silica gel, washed with CH_2Cl_2, and solvent was evaporated to afford the desired sulfites **2a–d**.

2.1.2. (4aR,7aR,11aS,11bS)-2,10-Diphenylhexahydrobis([1,3]dioxino)[5,4-d:4′,5′-f][1,3,2]dioxathiepine 6-oxide **2a**

2a was prepared according to general procedure (GP1), Yield (930 mg, 2.3 mmol, 82%). m.p: 230 °C; IR (KBr, cm^{-1}): 1610, 1545, 1071;^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.49–7.35 (*m*, 10H, 2Ph), 5.53 (s, 2H, PhC*H*), 5.03 (*m*, 1H, C*H*OSO), 4.36 (*m*, 2H, C*H*O), 4.26 (*m*, 1H, C*H*OSO), 4.06 (t, 1H, *J* = 8.8 Hz, OCH_2), 3.94 (t, 1H, *J* = 8.8 Hz, OCH_2), 3.85 (t, 2H, *J* = 10.2 Hz, OCH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 136.6, 129.3, 128.4, 126.3, 101.2, 101.0, 81.4, 79.5, 68.4, 64.8, 59.8; MS (*m*/*z*): 405.40 $(M+1)^+$, 47%; Anal. for $C_{20}H_{20}O_7S$; calcd: C, 59.40; H, 4.98; Found: C, 59.42; H, 5.00.

2.1.3. (4aR,7aR,11aS,11bS)-2,10-di-p-tolylhexahydrobis([1,3]dioxino)[5,4-d:4′,5′-f][1,3,2]dioxathiepine 6-oxide **2b**

2b was prepared according to general procedure (GP1), Yield (1.058 g, 2.44 mmol, 95% yield). M.p: 240 °C; IR (KBr, cm^{-1}): 3200, 1600, 1540, 1072; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36–7.35 (dd, 2H, *J* = 5.1 Hz, *J* = 7.3 Hz, Ph), 5.48 (s, 2H, PhC*H*), 5.00 (*m*, 1H, C*H*OSO), 4.38 (*m*, 2H, C*H*O), 4.25 (*m*, 1H, C*H*OSO), 4.02 (t, 1H, *J* = 8.0 Hz OCH_2), 3.91 (t, 1H, *J* = 8.8 Hz, OCH_2), 3.82 (t, 2H, *J* = 10.2 Hz, OCH_2), 2.33 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 139.2, 133.9, 129.0, 126.2, 101.2, 81.4, 79.5, 68.5, 59.9, 21.4; MS (*m*/*z*): 433.50 $(M+1)^+$, 78%; Anal. for $C_{22}H_{24}O_7S$; calcd: C, 61.10; H, 5.59; Found: C, 61.12; H, 5.60.

2.1.4. (4aR,7aR,11aS,11bS)-2,10-bis(4-methoxyphenyl)hexahydrobis([1,3]dioxino)[5,4-d:4′,5′-f][1,3,2]dioxathiepine 6-oxide **2c**

2c was prepared according to general procedure (GP1), Yield (580 mg, 1.03 mmol, 71% yield) m.p.: 122 °C; IR (KBr, cm^{-1}): 3100, 1578, 1543,1072; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.88 (d, 2H, *J* = 6.6 Hz, Ph), 7.44 (d, 2H, *J* = 8.8 Hz, Ph), 7.05 (d, 2H, *J* = 8.8 Hz, Ph), 6.92 (d, 2H, *J* = 6.6 Hz, Ph), 5.51 (s, 2H, PhC*H*), 5.02 (*m*, 1H, C*H*OSO), 4.37 (*m*, 2H, C*H*O), 4.34 (*m*, 1H, C*H*OSO), 4.05 (t, 1H, *J* = 8.0 Hz, OCH_2), 3.91 (t, 1H, *J* = 8.0 Hz, OCH_2), 3. 85 (m, 2H, OCH_2), 3.82 (s, 3H, OCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 132.1, 130.0, 127.7, 114.4, 113.7, 101.2, 81.4, 68.5, 64.9, 55.4; MS (*m*/*z*): 465.49 $(M+1)^+$, 94%; Anal. for $C_{22}H_{24}O_9S$; calcd: C, 56.89; H, 5.21; Found: C, 56.88; H, 5.20.

2.1.5. (4aR,7aR,11aS,11bS)-2,10-bis(2,4-dichlorophenyl)hexahydrobis([1,3]dioxino)[5,4-d:4′,5′-f][1,3,2]dioxathiepine 6-oxide **2d**

2d was prepared according to general procedure (GP1), Yield (880 mg, 1.62 mmol, 81% yield) m.p.: 95 °C; IR (KBr, cm^{-1}): 1578, 1543, 1072; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 2H, Ph), 7.38 (m, 4H, Ph), 6.02 (s, 2H, PhC*H*), 5.00 (*m*, 1H, C*H*OSO), 4.66 (*m*, 2H, C*H*O), 4.34 (*m*, 1H, C*H*OSO), 4.19 (t, 1H, *J* = 8.0 Hz, OCH_2), 4.08 (t, 1H, *J* = 8.0 Hz OCH_2), 3. 95 (m, 2H, OCH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 136.0, 133.0, 129.9, 128.7, 127.2, 101.3, 84.2, 83.0, 67.9, 65.6; MS (*m*/*z*): 543.21 $(M+1)^+$, 85%; Anal. for $C_{20}H_{16}C_{l4}O_7S$; calcd: C, 44.30; H, 2.97; Found: C, 44.33; H, 3.00

2.1.6. General procedure for the synthesis of sulfate derivatives **3a–d** (GP2)

A two necked round bottom flask was charged with sulfite (1.81 mmol) in CCl_4 (15 mL), and CH_3CN (15 mL). After cooling at 0 °C, H_2O (10 mL) was added and then a mixture of $RuCl_3{\cdot}H_2O$ (0.011 mmol) and $NaIO_4$ (4.57 mmol) was added in one portion. The mixture was stirred vigorously at 0 °C for 90 min (TLC: EtOAc/Pet.Ether 3:1), extracted with Et_2O, washed with brine, $MgSO_4$, and the solvent was removed to afford **3a–d**.

2.1.7. (4aR,7aR,11aS,11bS)-2,10-diphenylhexahydrobis([1,3]dioxino)[5,4-d:4′,5′f][1,3,2]dioxathiepine 6,6-dioxide **3a**

3a was prepared according to general procedure (GP2), Yield (white solid, 550 mg, 1.30 mmol, 66% yield); m.p: 124 °C; IR (KBr, cm^{-1}): 1560, 1532, 1070; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.49–7.34 (m, 10H, Ph), 5.54 (s, 21H, PhC*H*), 4.73 (*m*, 2H, C*H*OSO), 4.53 (*q*, 2H, *J* = 5.5 Hz, C*H*O), 4.14 (dd, 2H, *J* = 7.3 Hz, *J* = 1.8 Hz, OCH_2) 3.87 (t, 2H, *J* = 10.6 Hz, OCH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 136.0, 129.6, 128.5, 126.2, 101.4, 79.4, 70.8, 67.2; MS (*m*/*z*): 421.44 $(M+1)^+$, 86%; Anal. for $C_{20}H_{20}O_8S$; calcd: C, 57.13; H, 4.79; Found: C, 57.12; H, 4.80.

2.1.8. (4aR,7aR,11aS,11bS)-2,10-di-p-tolylhexahydrobis([1,3]dioxino)[5,4-d:4′,5′-f][1,3,2]dioxathiepine 6,6-dioxide ***3b***

3b was prepared according to general procedure (GP2), Yield (white solid, 700 mg, 1.56 mmol, 86% yield); m.p: 160 °C; IR (KBr, cm^{-1}): 1563, 1520, 1060; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35 (d, 4H, J = 8.0 Hz, Ph), 7.18 (d, 4H, J = 8.0 Hz, Ph), 5.49 (s, 2H, PhC*H*), 4.68 (*m*, 2H, C*H*OSO), 4.50 (*q*, 2H, J = 5.5 Hz, C*H*O), 4.10 (dd, 2H, J = 7.3 Hz, J = 1.8 Hz, OCH_2) 3.84 (t, 2H, J = 10.6 Hz, OCH_2), 2.34 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 139.5, 133.3, 129.1, 129.0, 126.2, 101.5, 79.5, 70.9, 67.2, 64.9; MS (*m*/*z*): 449.47 $(M+1)^+$, 86%; Anal. for $C_{22}H_{24}O_8S$; calcd: C, 58.92; H, 5.39; Found: C, 58.93; H, 5.38

2.1.9. (4aR,7aR,11aS,11bS)-2,10-bis(4-methoxyphenyl) hexahydrobis([1,3]dioxino)[5,4-d:4′,5′-f][1,3,2]dioxathiepine 6,6-dioxide ***3c***

3c was prepared according to general procedure (GP2), Yield (white solid, 600 mg, 1.25 mmol, 96% yield); m.p.: 105 °C; IR (KBr, cm^{-1}): 1560, 1523,1055; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.84 (d, 2H, J = 8.8 Hz, Ph), 7.39 (dd2H, J = 8.0 Hz, J = 4.4 Hz, Ph), 7.00 (d, 2H, J = 8.8 Hz, Ph), 6.88 (dd, 2H, J = 8.8 Hz, J = 2.2 Hz, Ph), 5.46 (s, 2H, PhC*H*), 5.00 (*m*, 2H, C*H*OSO), 4.40 (*q*, 2H, J = 5.5 Hz, C*H*O), 4.00 (dd, 2H, J = 7.3 Hz, J = 1.8 Hz, OCH_2) 3.84 (t, 2H, J = 10.6 Hz, OCH_2), 3.88 (s, 3H, OCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 132.1, 130.0, 127.7, 114.4, 113.6, 101.2, 81.4, 64.9, 59.9; MS (*m*/*z*): 481.48 $(M+1)^+$, 82%; Anal. for $C_{22}H_{24}O_{10}S$; calcd: C, 54.99; H, 5.03; Found: C, 55.00; H, 5.02.

2.1.10. (4aR,7aR,11aS,11bS)-2,10-bis(2,4-dichlorophenyl) hexahydrobis([1,3]dioxino)[5,4-d:4′,5′-f][1,3,2]dioxathiepine 6,6-dioxide ***3d***

3d was prepared according to general procedure (GP2), Yield (white solid, 580 mg, 1.03 mmol, 71% yield); m.p.: 122 °C; IR (KBr, cm^{-1}): 1566, 1501,1045; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 2H, Ph), 7.20 (*m*, 4H, Ph), 6.10 (s, 2H, PhC*H*), 4.85 (*m*, 2H, C*H*OSO), 4.63 (*m*, 2H, C*H*O), 4.41 (dd, 2H, J = 9.5 Hz, J = 2.2 Hz, OCH_2), 4.13 (d, 2H, J = 8.8 Hz, OCH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 136.3, 134.1, 132.6, 129.9, 128.7, 127.3, 101.5, 81.8, 80.8, 74.4, 66.9; MS (*m*/*z*): 559.20 $(M+1)^+$, 79%; Anal. for $C_{20}H_{16}C_{l4}O_8S$; calcd: C, 43.03; H, 2.89; Found: C, 43.09; H, 2.92.

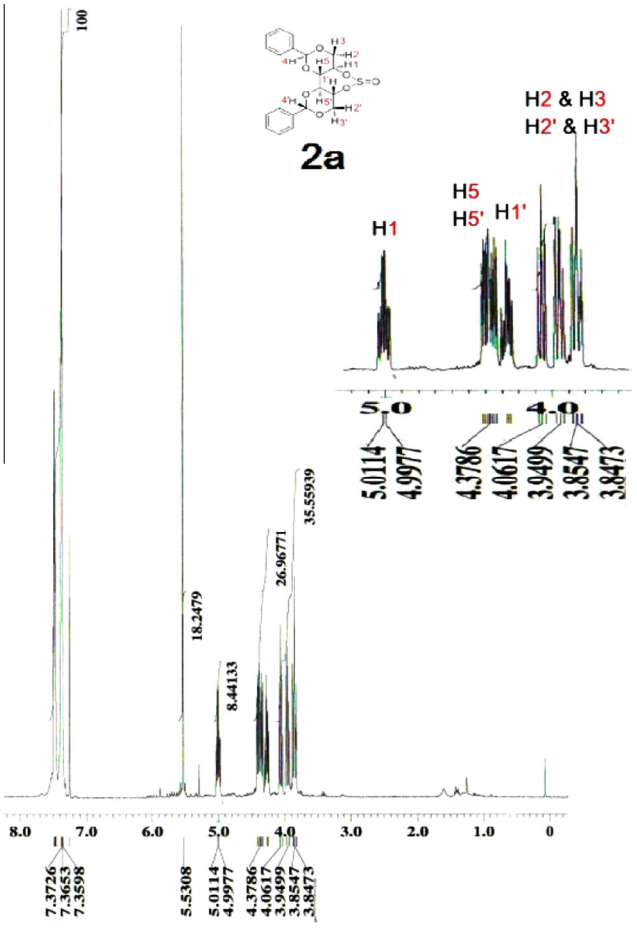


Figure 1 ^{1}HNMR spectrum of **2a**.

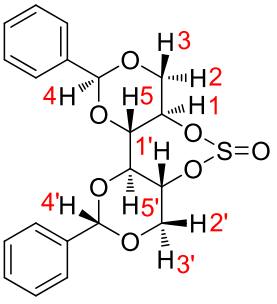
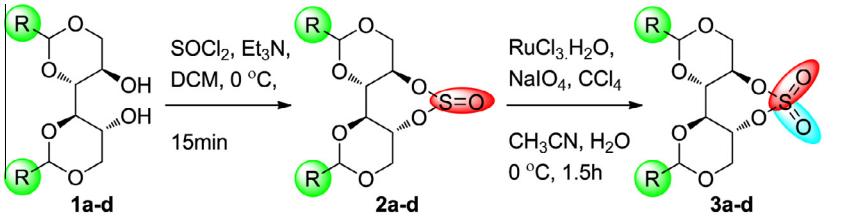


Figure 2 The chemical structure of **2a**.



1a, R = Ph
1b, R = *p*-CH_3-C_6H_4
1c, R = *p*-CH_3O-C_6H_4
1d, R =2,4-diChloro-C_6H_3

2a, R = Ph
2b, R = *p*-CH_3-C_6H_4
2c, R = *p*-CH_3O-C_6H_4
2d, R =2,4-diChloro-C_6H_3

3a, R = Ph
3b, R = *p*-CH_3-C_6H_4
3c, R = *p*-CH_3O-C_6H_4
3d, R =2,4-diChloro-C_6H_3

Scheme 1 Synthesis of sulfite derivatives **2a**–**d** and sulfate derivatives **3a**–**d**.

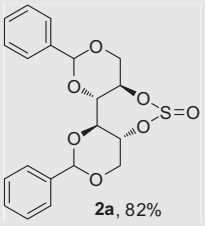
3. Results and discussion

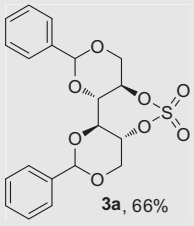
In continuation of our research program [9,11,17], according to the procedure described by K. Sharpless some modification treatment of DIOL **1a–d** with $SOCl_2$ in CH_2Cl_2 in the presence of Et_3N as base at 0 °C afforded sulfite intermediates **2a–d** in good yield as depicted in Scheme 1.

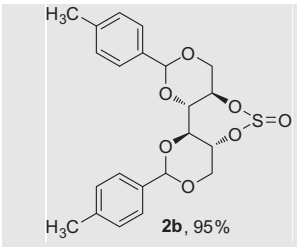
It is assumed that the product **2a–d** was formed *via* double nucleophilic attack of the hydroxyl group of DIOL **1a–d** on the S═O group followed by elimination of Cl as the leaving group. The disappearance of the stretching band of OH group at 3400 cm^{-1} was confirmed by IR. The structures of all new compounds **2a–d** are in good agreement with their analytical and spectroscopic data.

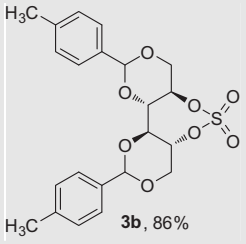
Subsequently, **2a–d** was subjected to oxidation using $NaIO_4$ in a mixture of $CCl_4/CH_3CN/H_2O$:3/3/2 ratio in the presence of catalytic amount of $RuCl_3{\cdot}H_2O$ to afford **3a–d** in a moderate to high yield (66–96%). Their formations were confirmed and elucidated by ^1H, ^{13}C NMR, MS and IR spectra in addition to elemental analysis.

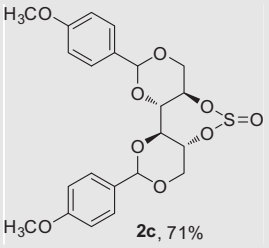
Sulfite derivatives **2a–d** Sulfate derivatives **3a–d**

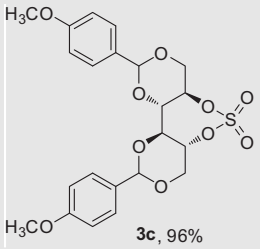


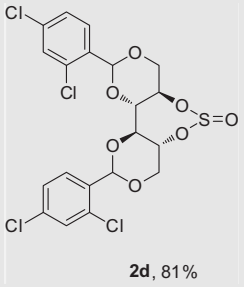


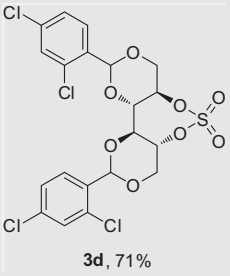












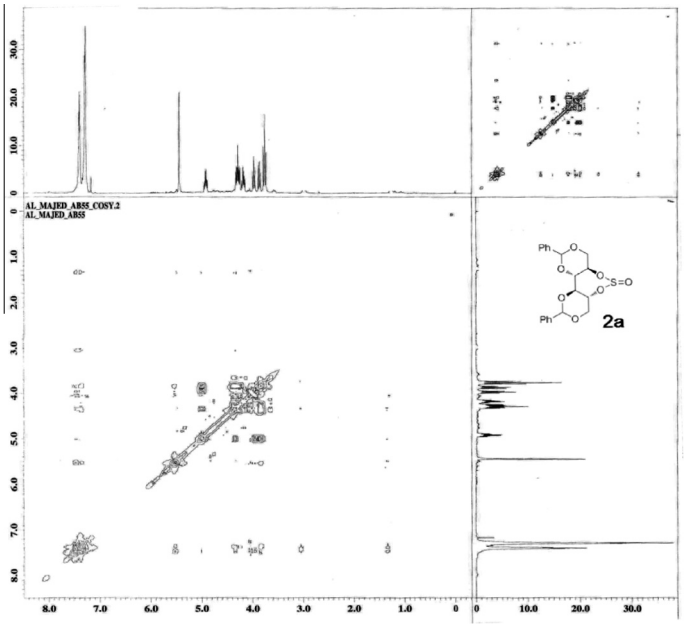


Figure 3 COSY-NMR ($CDCl_3$) of **2a**.

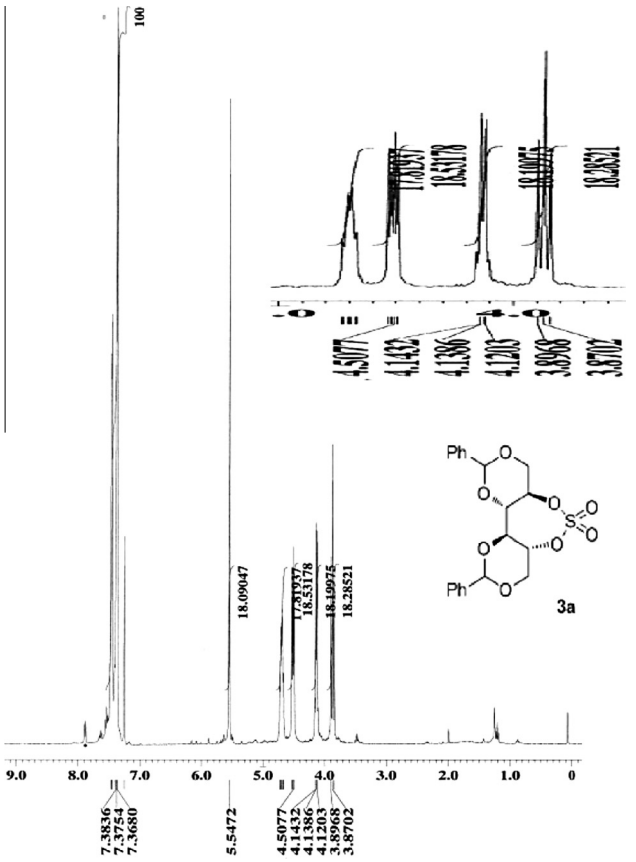


Figure 4 ^{1}HNMR spectrum of **3a**.

The ^{1}H-NMR ($CDCl_3$) spectrum of **2a** displayed a multiplet signal in the aromatic region assignable to phenyl protons. A singlet signal at δ 5.53 ppm is due to benzylic protons. The region of δ 5.01–3.84 is assigned to the 8 protons from $2CH_2$, 4CH as depicted in Fig. 1.

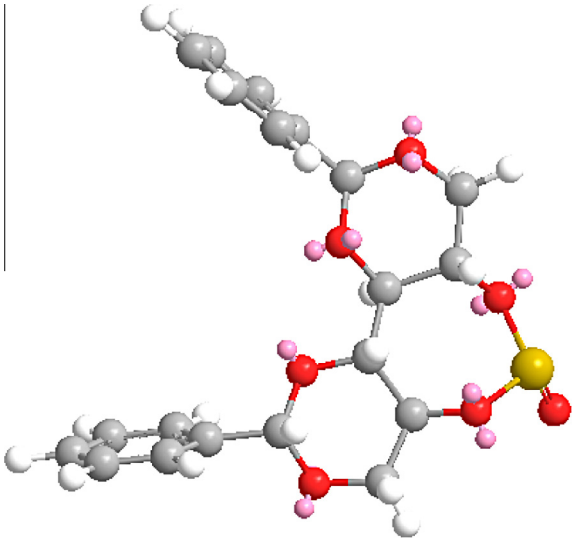


Figure 5 3D-using ChemDraw after minimization energy and run stereochemistry detection for **2a**.

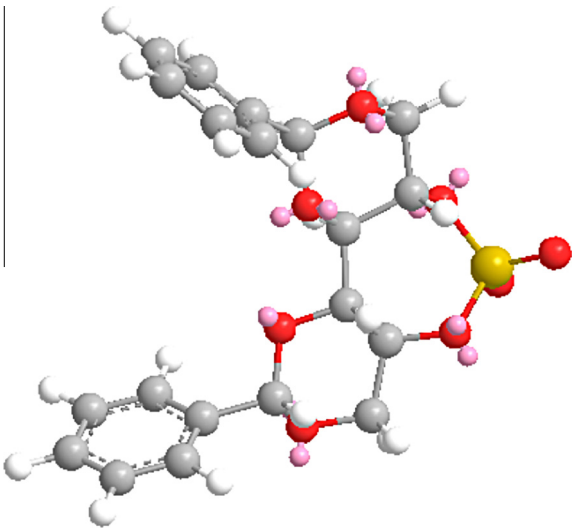


Figure 6 3D-using ChemDraw after minimization energy and run stereochemistry detection **3a**.

In order to assign the ^{1}H-NMR, a sample was submitted to COSY-NMR Fig. 3.

The COSY-NMR ($CDCl_3$) spectrum of **2a** displayed that proton of H1 at δ 5.01 ppm as multiplet that because coupled with H2, H3 and H5. A multiplet signal at δ 4.37 ppm assigned for H5 and H5′ where coupled with H1, H2 and H3. At δ 4.26 ppm multiplet signal assigned for the H1′ at δ 5.01 ppm as multiplet that because coupled with H2′, H3′ and H5′. A triplet signal at δ 4.06 ppm assigned for H2 and coupled with H1, H3. A triplet signal at δ 3.94 ppm assigned for H2′ and coupled with H1′, H3′. Finally, triplet signal at δ 3.85 ppm assigned for two proton H3 and H3′ where coupled with H1, H2 and H1′, H2′, respectively (Fig. 2).

The ^{1}H-NMR ($CDCl_3$) spectrum of **3a** displayed a multiplet signal in the aromatic region assignable to phenyl protons. A singlet signal at δ 5.54 ppm is due to benzylic protons. The region of δ 4.50–3.87 is assigned to the 8 protons from $2CH_2$, 4CH as depicted in Fig. 4. The spectra show that the compound became more rigid and seems to be symmetrical (Figs. 5 and 6).

4. Conclusion

From the obtained results, we can summarize that we have successfully prepared a series of sulfite derivatives **2a**–**d** and sulfate derivatives **3a**–**d** in excellent yield up 96% in two steps starting from DIOL **1a**–**d**. The full scope, asymmetric transformations and its application in the synthesis of biologically active molecules are currently underway in our laboratory.

Conflict of interest

The authors declare no conflict of interest.

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