Novel Chiral Compound: (*R*) and (*S*) 1-(2-Benzyloxy-3-Methoxyphenyl)-2,2,2-Trichloroethyl Benzensulfonate, Synthesys and characterization

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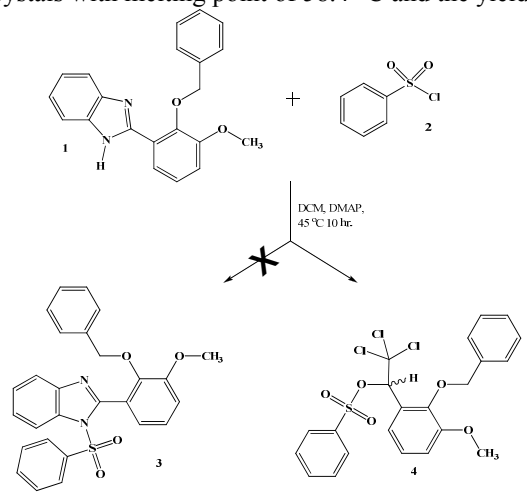
Abstract: The reaction between benzimidazole **1** and benzenesulfonyl chloride **2** in dichloromethane (DCM) at 45 °C for 10 hr in the presence of dimethyl aminopyridine (DMAP) as a catalyst was expected to obtain 2-(2-benzyloxy-3-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-benzimidazole, **3**. Unfortunately, a novel chiral compound (*R*) and (*S*) 1-(2-benzyloxy-3-methoxyphenyl)-2,2,2-trichloroethyl benzenesulfonate **4** was obtained as a single crystal (59% yield) with melting point of 58.4 °C. However, the mechanism of this reaction still is under investigation. The molecular structure of this compound was confirmed by FTIR, HRMS, X–Ray crystallography, 1D and 2D NMR spectroscopy. The crystal of **4** is in the monoclinic space group $P2_1/c$ with a = 8.1638 (1) Å, b = 8.8536 (1) Å, c = 30.7221 (5) Å, β = 90.670 (1)°, D_{calc} = 1.501 μg m^{-3}, V = 2220.41 (5) Å^3 and R_{int} = 0.059. The complete assignments of **4** were made using 1D and 2D NMR including APT, DEPT–135, COSY, HMQC and HMBC in $CDCl_3$.

Key words: ^{1}H NMR; ^{13}C NMR; 2D NMR; X–Ray Crystallography; 2,2,2-Trichloroethyl Benzenesulfonate.

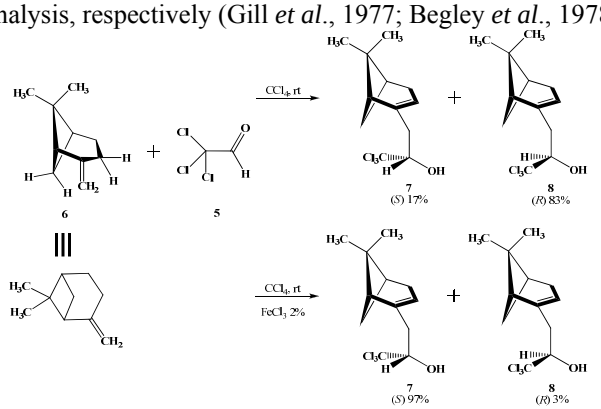
Introduction

The reaction between benzimidazole **1** and benzene sulfonyl chloride **2** in DCM at 45 °C for 10 hr in the presence of DMAP as a catalyst was hoped to obtain 2-(2-benzyloxy-3-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-benzimidazole **3** (Li *et al*., 2006), but it was given (*R*) and (*S*) 1-(2-benzyloxy-3-methoxyphenyl)-2,2,2-trichloroethyl benzenesulfonate **4** (Al–Douh *et al*., 2007, Scheme 1). It was obtained as single crystals with melting point of 58.4 °C and the yield was 59%.

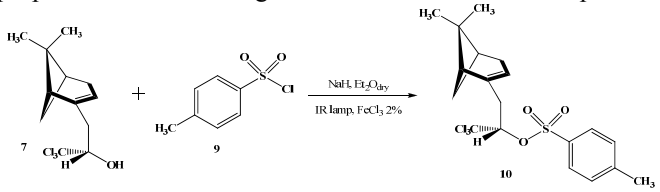


Scheme 1: Synthetic route towards the compound **4**.

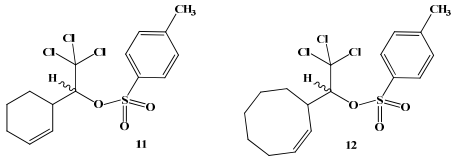
The addition of chloral **5** to (–)-(1*S*,5*S*)-pin-2(10)-ene **6** was formed diastereoisomers (*S*) **7** and (*R*) **8** with ratio 17:83, while the ratio was enhanced in the presence of $FeCl_3$ 2% as a bulky Lewis acid catalyst to 97:3, which were confirmed by ^{1}H and ^{13}C NMR experiments and X–ray analysis, respectively (Gill *et al*., 1977; Begley *et al*., 1978, Scheme 2).



Scheme 2: Gill *et al*. method to prepare derivative of **4**.Begley *et al*. (1978) were synthesized derivatives of **4** from the reaction of **7** with toluene-*p*-sulphonyl chloride or tosyl chloride **9** to produce **10** as (*S*) diastereoisomer (Scheme 3), while Gill *et al*. (1979) were synthesized other derivatives from the reaction of cyclohex-1-ene and cycloocta-1-ene with **9** to produce **11** and **12** as diastereoisomers (*R*) and (*S*), respectively (Scheme 4). Figure 1 shows the chemical structure and the numbering scheme of **4** for discussion purposes in the following sections. The mechanism of produce **4** still is unknown.



Scheme 3: Derivative **10** was prepared by Begley *et al*.



Scheme 4: Other derivatives of **4** were prepared by Gill *et al*.

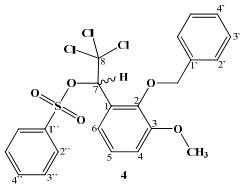


Figure 1: The chemical structure and the numbering scheme of **4**.

Experimental Part

General

All NMR experiments were performed on *Bruker Avance 400 Ultrashield*™ NMR for ^{1}H, operating at 400.132 MHz, and *Bruker Avance 300* NMR spectrometers for ^{13}C, operating at 71.478 MHz at 298 K using *Bruker XWINNMR* software equipped with a 5 mm BBI inverse gradient and QNP probes, respectively (Bruker, 1999; Berger and Braun, 2004). Chemical shifts were reported downfield in parts per million (ppm) from a tetramethylsilane (TMS) reference, and coupling constants (*J*) were measured in Hz. The concentration of solute molecule was 25 mg in 1.0 mL $CDCl_3$.

High–resolution mass spectrum (HRMS) was recorded by a *Bruker Daltonics' micrOTOF–Q*™ mass spectrometer, operated in electrospray ionization source ESI mode. In DCM, the sample was prepared in 1.0 µL–1.0 mL/min. The crystal structure was determined by an *APEX2 Bruker* (APEX2, 2005) and *SHELXTL* (Sheldrick, 1998, 2008) crystallographic software packages for determining molecular structure, and Infrared spectrum was recorded on a *Perkin-Elmer 2000 FT* spectrometer and was expressed in cm^{-1}. The compound was prepared using KBr cells. Melting point (uncorrected) was determined on Stuart melting point apparatus.

Synthesis

The synthetic method of **4** was described previously (Li *et al*., 2006; Al–Douh *et al*., 2007).

Results and Discussion

FTIR Spectroscopy

The FTIR spectrum of **4** is depicted in Figure 2 and selected FTIR data are listed in Table 1. The bands with weak intensity observed of benzene rings at 3096, 3067 and 3028 cm^{-1} are ascribed to the stretching of aromatic ν C=C–H. The bands observed at 2948 and 2873 cm^{-1} are assigned to ν_{as} and ν_{s} CH_3 of methoxy group, respectively, while the bands observed at 2927 and 2855 cm^{-1} assigned to ν_{as} and ν_{s} CH_2 of methylene group, respectively.

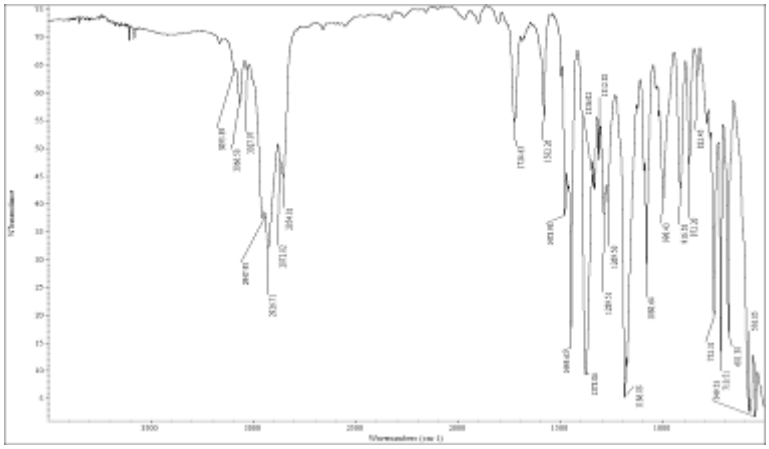


Figure 2: FTIR spectrum of **4**.

The asymmetrical bending vibration of δ_{as} CH_3 occurred at 1479 cm^{-1}, while the symmetrical bending vibration of δ_s CH_3 appeared at 1336 cm^{-1}, and the CH_2 scissoring vibration δ_s CH_2 appeared at 1450 cm^{-1}. The strong intensity bands appeared at 1378 and 1187 cm^{-1} are assigned to ν_{as} and ν_s SO_2 sulfonic esters (Silverstein *et al*., 2005). The free ν N–H stretching band of benzimidazole **1** at 3354 cm^{-1} was disappeared (Al–Douh, 2010).

Table 1: FTIR spectral data of compound **4** (cm^{-1}):

νC–H arom.	νCH_3 aliph.	νCH_2 aliph.	δCH_3	δCH_2	νS=O ester	νC–O–C aliph.	νC–Cl aliph.	ν aromatic
3096	as 2948	as 2927	as 1479	as	as 1378	as 1270	998	833, 752,
3067	sy 2873	sy 2855	sy 1336	1450	sy 1187	sy 1081	917	719,
3028							872	681, 577 & 550

HRMS Spectra

Figure 3 shows the HRMS spectrum of **4**. The HRMS of **4** shows a molecular formula of $C_{22}H_{19}Cl_3NaO_5S^-$ at *m/z* 522.9933 ($M+Na^+$). The peaks at *m/z* 523.9940, 524.9903, 525.9912, 526.9862, 527.9885 and 528.9830 for the isotopes of the benzenesulfonate **4**, M+2, M+4, M+6, M+8, M+10 and M+12, respectively, which it has three chlorine atoms (Silverstein *et al*., 2005).

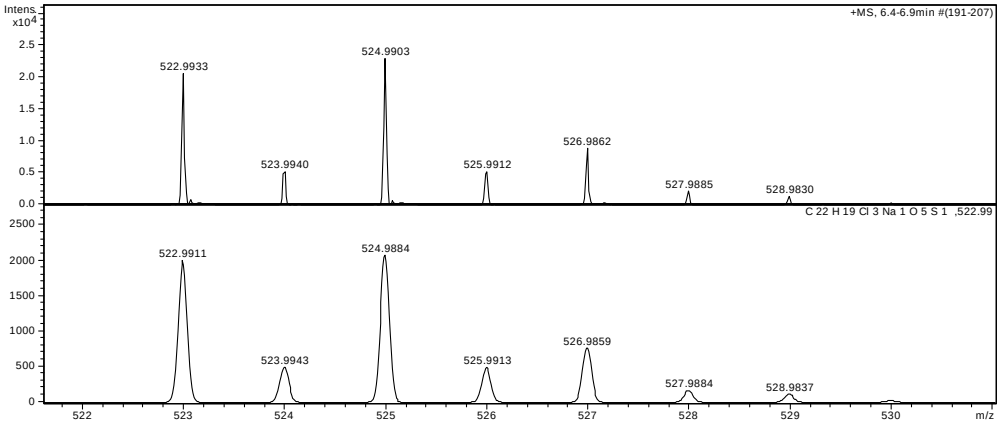


Figure 3: HRMS spectrum of **4**.

^{1}H NMR

The ^{1}H NMR spectrum in $CDCl_3$ of **4** was shown in Figure 4. The spectrum shows the chemical shift of the aromatic protons of the benzyloxy ring $H_{2'}$ were observed signal as double doublet at δ = 7.69–7.66 ppm (*J* = 8.46 and 1.19 Hz), and $H_{3'}$ were exhibited signal as a triplet at δ = 7.36–7.32 ppm (*J* = 7.92 Hz), while proton $H_{4'}$ was displayed triplet at δ = 7.52 ppm, (*J* = 1.05 Hz), due to its coupled with $H_{3'}$. The signals as multiplet at δ = 7.58–7.54, 7.48–7.43 and 7.41–7.38 ppm are proposed to be assigned to $H_{2''}$, $H_{3''}$ and $H_{4''}$ in the benzenesulfonyl ring, respectively. The double doublet were overlapped with $CDCl_3$ peak and were observed at δ = 7.28–7.25 ppm (*J* = 7.56 and 1.82 Hz) was assigned to H_6 in the trisubstituted ring, while both protons H_5 and H_4 were observed two signals as triplet and double doublet at δ = 7.06–7.01 and 7.00–6.96 ppm (*J* = 7.92, 8.21 and 1.83 Hz), respectively. The methoxy group OCH_3 of **4** was shown as singlet at δ = 3.89 ppm, and the methine H_7 was also observed signal at δ = 6.46 ppm as singlet.

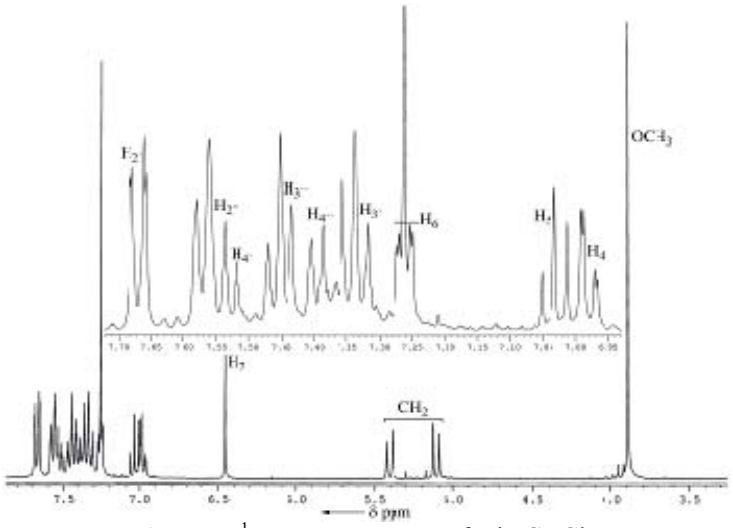


Figure 4: ^{1}H NMR spectrum of **4** in $CDCl_3$.

On the other hand, the methylene group CH_2 was exhibited signal as double doublet at δ = 5.41–5.12 ppm, (J = 88.34 and 11.48 Hz). These values of coupling constant are unexpected specially 88.34 Hz. We suggest the reasons of these values to be due to the configuration of those hydrogen atoms between benzyloxy ring and the 2,2,2-trichloroethyl benzenesulfonate group, which ^{1}H–^{1}H COSY experiment was performed to further confirmed the assigned peak between the methine proton H_7 with one proton of methylene group CH_2 and one proton of benzene ring $H_{2'}$ (see ^{1}H–^{1}H COSY analysis, Figure 7), while ^{1}H–^{13}C HMBC experiment was performed to further confirmed the assigned peak between the protons of benzene ring $H_{2'}$ and the protons of methylene group CH_2 (see ^{1}H–^{13}C HMBC, Figure 11). Additionally, the crystal structure of **4** confirmed the posture of that groups (see X–ray analysis, Figures 5, 13 and 14).

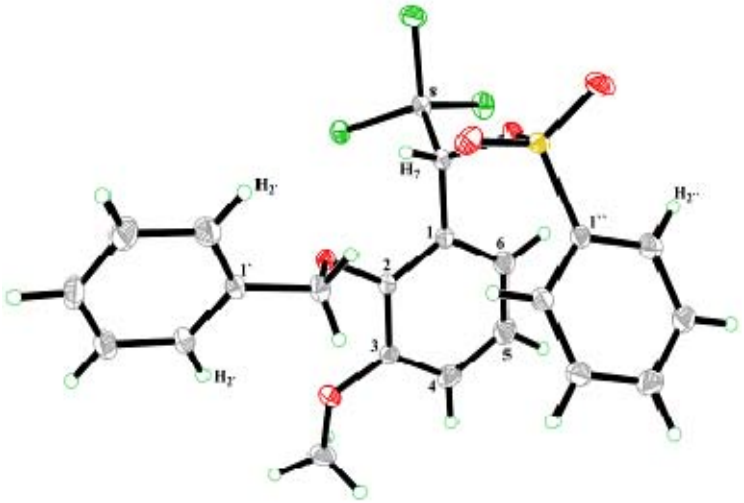


Figure 5: The crystal structure of **4**.

^{13}C APT NMR

The ^{13}C NMR spectrum of **4** was obtained with using APT NMR experiment and shown in Table 2 and Figure 6. The peak in $CDCl_3$ appears at δ = 56.26 ppm of **4** was assigned to the methoxy group OCH_3, while methylene group CH_2 and methine carbon C_7 were showed at δ = 74.79 and 82.70 ppm, respectively. The quaternary carbon signals were observed at δ = 152.42, 147.40, 138.35, 136.18, 126.84 and 98.35 ppm for C_3, C_2, $C_{1'}$, $C_{1''}$, C_1 and C_8, respectively. Other aromatic carbon signals of benzenesulfonyl ring were observed at δ = 128.97, 128.56 and 127.62 ppm for $C_{4''}$, $C_{3''}$ and $C_{2''}$, respectively, while C_4, C_6 and C_5 at the trisubstituted aromatic carbon showed signals at δ = 114.47, 121.13 and 124.08 ppm, respectively. Aromatic carbons of benzyloxy ring observed signals of $C_{2'}$, $C_{3'}$ and $C_{4'}$ at the respective δ = 128.16, 129.31 and 134.30 ppm. Table 2 summarizes the ^{1}H and APT NMR of **4** in $CDCl_3$.

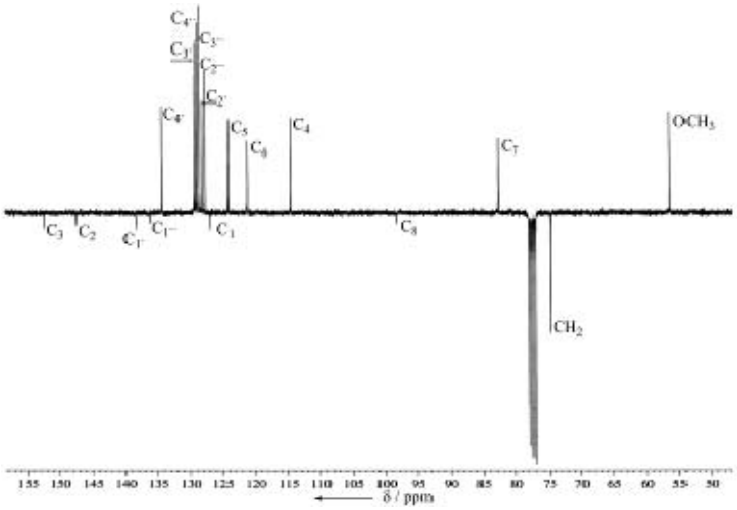


Figure 6: APT NMR spectrum of **4** in $CDCl_3$.

Table 3. ^{1}H and ^{13}C APT NMR chemical shifts (ppm) and coupling constants (Hz) of **4** in $CDCl_3$:

Atom No.	^{1}H NMR		^{13}C NMR
	δ	*J*	δ
OCH_3	3.89, *s*	–	56.26
CH_2	5.41–5.12, *dd*	88.34, 11.48	74.79
1	–	–	126.84
2	–	–	147.40
3	–	–	152.42
4	7.00–6.96, *dd*	8.21, 1.83	114.47
5	7.06–7.01, *t*	7.92	124.08
6	7.28–7.25, *dd*	7.56, 1.82	121.13
7	6.46, *s*	–	82.70
8	–	–	98.35
1`	–	–	138.35
2`	7.69–7.66, *dd*	8.46, 1.19	128.16
3`	7.36–7.32, *t*	7.92	129.31
4`	7.52, *t*	1.05	134.30
1``	–	–	136.18
2``	7.58–7.54, *m*	–	127.62
3``	7.48–7.43, *m*	–	128.56
4``	7.41–7.38, *m*	–	128.97

^{1}H–^{1}H COSY

Figures 7 and 8 were shown the ^{1}H–^{1}H COSY NMR spectra of **4** in $CDCl_3$ and the most important correlations observed were shown in Figure 9. In COSY spectrum confirmed the correlation assignments of H_4 with methoxy group OCH_3 and one proton of methylene group CH_2 in benzyloxy ring at δ = 3.89 and 5.41 ppm, respectively, but low correlation were observed with the second proton of CH_2 at δ = 5.12 ppm.

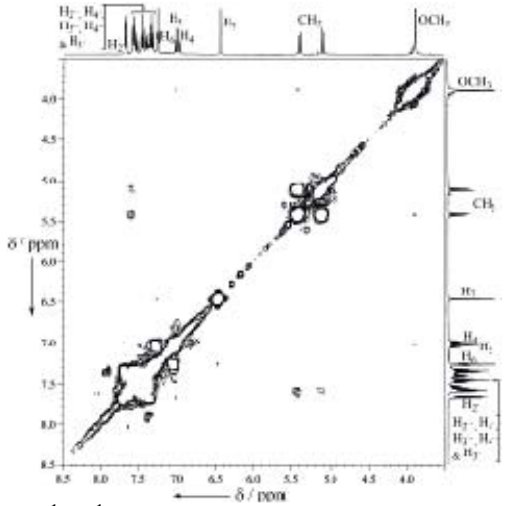


Figure 7: ^{1}H–^{1}H COSY NMR spectrum of 4 in $CDCl_3$.

On the other side, both CH_2 protons were correlated with $H_{3'}$ in the benzyloxy ring, but the second proton showed more correlated with $H_{3'}$ than the other one. The methine proton H_7 was observed assignment with H_6 in the trisubstituted ring at δ = 7.28–7.25 ppm. In the trisubstituted ring, proton H_4 in **4** showed ^3J with H_5 at δ = 7.06–7.01 ppm, while proton H_5 was showed ^3J–correlation with both H_4 and H_6 protons at δ = 7.00–6.96 and 7.28–7.25 ppm, respectively. However, the correlations between $H_{3'}$ with both protons $H_{2'}$ and $H_{4'}$ in benzyloxy ring were shown clearly at δ = 7.69–7.66 and 7.52 ppm, respectively, while in the benzenesulfonyl ring, $H_{3''}$ was observed ^3J–correlation with $H_{2''}$ at δ = 7.58–7.54 ppm (Figure 8).

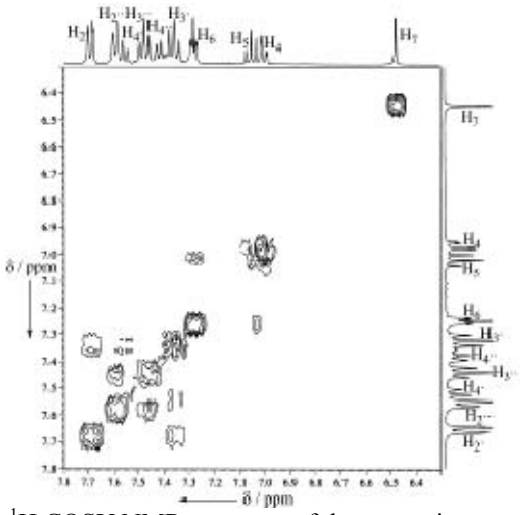


Figure 8: ^{1}H–^{1}H COSY NMR spectrum of the aromatic protons range of **4**.

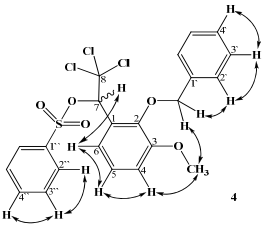


Figure 9: The most important correlations observed in COSY spectrum of **4**.

^{1}H–^{13}C HMQC

The HMQC NMR spectrum for **4** was shown in Figure 10 in $CDCl_3$. The signals owing to $C_{4'}$, $C_{3'}$, $C_{4''}$, $C_{3''}$, $C_{2'}$, $C_{2''}$, C_5, C_6 and C_4 atoms were observed at δ = 134.30, 129.31, 128.97, 128.56, 128.16, 127.62, 124.08, 121.13 and 114.47 ppm. The one bond ^{1}H–^{13}C connectivities were also well observed for OCH_3, CH_2 and C_7 atoms whereby the cross peaks appeared at the respective δ = 56.26, 74.79 and 82.70 ppm.

^{1}H–^{13}C HMBC

The HMBC NMR spectrum for **4** was shown in Figure 11 and the most important correlations observed shown in Figure 12. The long–range HMBC cross peaks of the methylene group CH_2 protons with $C_{2'}$ and $C_{1'}$ in the benzyloxy ring were appeared at δ = 128.16 and 138.35 ppm, respectively. The HMBC cross peaks of the methoxy protons OCH_3 with C_3 was observed at δ = 152.42 ppm. On the other hand, the methine proton H_7 was correlated with C_8, C_6, C_1 and C_2, at δ = 98.35, 121.13, 126.84 and 147.40 ppm, respectively.

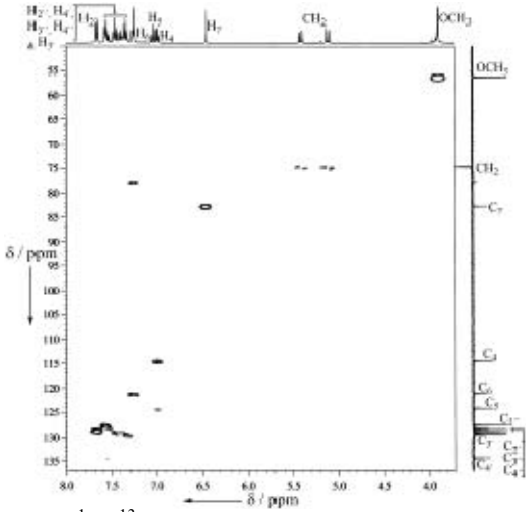


Figure 10: ^{1}H–^{13}C HMQC NMR spectrum of **4** in $CDCl_3$.

Additionally, the correlation between H_5 with both C_1 and C_3, both protons H_4 and H_6 with C_2, and CH_2 with $H_{2'}$ in the benzyloxy ring were observed clearly as ^3J–correlation. The homonuclear connectivities were observed between protons in C_4 with H_6 and C_6 with H_5 as ^3J–correlation, and C_5 with both H_4 and H_6 as ^2J–correlation. In addition, $C_{4'}$ was correlated with $H_{2'}$ in the same ring at δ = 7.58–7.54 ppm, while $C_{1'}$ was correlated as ^3J–correlation with $H_{3'}$ at δ = 7.36–7.32 ppm. However, in the benzenesulfonyl ring, the homonuclear connectivities were shown between $C_{1''}$ with $H_{3''}$ as ^3J–correlation. Other observed correlations between the aromatic protons and the carbons were showed in Table 3. All these correlation assignments were demonstrated and consistent with the crystal structure of **4**. Table 3 summarizes the values of COSY, HMQC and HMBC experiments in $CDCl_3$.

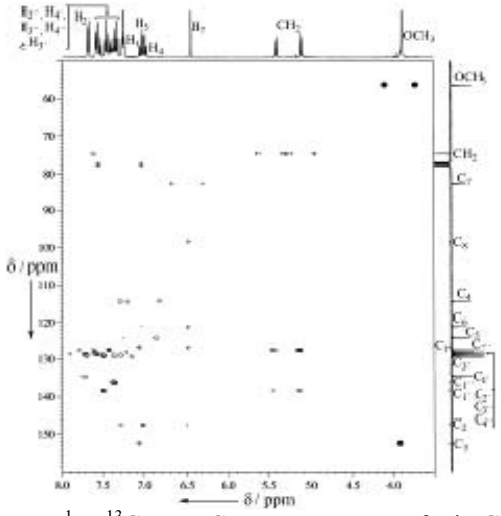


Figure 11: ^1H–^{13}C HMBC NMR spectrum of **4** in $CDCl_3$.

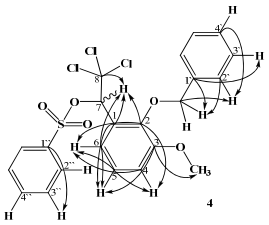


Figure 12: The most important correlations observed in HMBC spectrum of **4**.

Table 3: 2D ^1H–^1H COSY, ^1H–^{13}C HMQC and HMBC correlations for 4 in CDCl3:

Atom No.	COSY ^1H–^1H	HMQC ^1J	HMBC ^2J	HMBC ^3J	HMBC ^4J
OCH_3	CH_2, H_4	56.26	–	152.42, C_3	–
CH_2	OCH_3, $H_{2'}$	74.79	138.35, $C_{1'}$	128.16, $C_{2'}$	–
H_4	OCH_3, H_5	114.47	124.08, C_5	147.40, C_2	–
H_5	H_4, H_6	124.08	121.13, C_6	152.42, C_3	–
H_6	H_5, H_7	121.13	124.08, C_5	114.47, C_4	–
				147.40, C_2	
H_7	H_6	82.70	98.35, C_8	121.13, C_6	–
			126.84, C_1	147.40, C_2	
$H_{2'}$	$H_{3'}$	128.16	–[x]	74.79, CH_2	–
				134.30, $C_{4'}$	
$H_{3'}$	$H_{2'}$, $H_{4'}$	129.31	–[x]	138.35, $C_{1'}$	–
$H_{4'}$	$H_{3'}$	134.30	–[x]	–[x]	–
$H_{2''}$	$H_{3''}$	127.62	–[x]	–[x]	–
$H_{3''}$	$H_{2''}$, $H_{4''}$	128.56	–[x]	136.18, $C_{1''}$	–
$H_{4''}$	$H_{3''}$	128.97	–[x]	–[x]	–

[x]: is not observed

X–Ray Crystallography

The previous results of **4** by FTIR, HRMS, ^1H NMR and ^{13}C NMR were consistent with the result of X–ray crystallography, which the golden single crystal of **4** was obtained and determined by X–ray crystallography, Figures 13 and 14. Bond lengths and angles in **4** have normal values, and are comparable with those in the related structures (Begley *et al*., 1978; Gill *et al*., 1979). The methoxy group at C9 is slightly twisted from the plane of the attached benzene ring C22–O2–C9–C10 with a torsion angle of –18.96 (14)°. The dihedral angle between the benzene rings [(C1–C6) and (C8–C13)] is 22.64 (5)° whereas the torsion angle of C8–O1–C7–C6 is –157.96(7)°. In the crystal structure, the intramolecular C7–H7B···O2 interaction generated

an *S*(6) ring motifs, while other intramolecular C14–H14A···O1, C14–H14A···O3 and C21–H21A···O3 interactions generate *S*(5) ring motifs (Bernstein *et al*., 1995), Table 4, Figure 13. The molecules of benzenesulfonate **4** are linked by short inter Cl2···O4^{ii} contact of 3.0170 (8) Å (symmetry code: (ii) *–x*, *–y*, *–z*) into cyclic centrosymmetric R^2_2 (12) dimers. These dimers are interlinked by the C3–H3A···O2^{i} (symmetry code: (i) *–x*, *y + 1/2*, *–z + 1/2*) intermolecular interactions, Figure 14. H atoms were placed in calculated positions and constrained to ride on their carrier atoms, with C–H distances in the range 0.93–0.98 Å. Table 4 shows the summarized value for inter and intra hydrogen bonds of **4**. The crystal data of **4** was showed in Table 5 (Al–Douh *et al*., 2007).

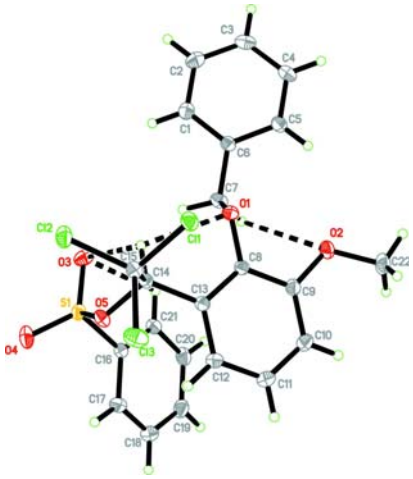


Figure 13: The crystal structure of **4** showing 50% probability displacement ellipsoids and the atomic numbering. The dashed lines indicate intramolecular hydrogen bonds.

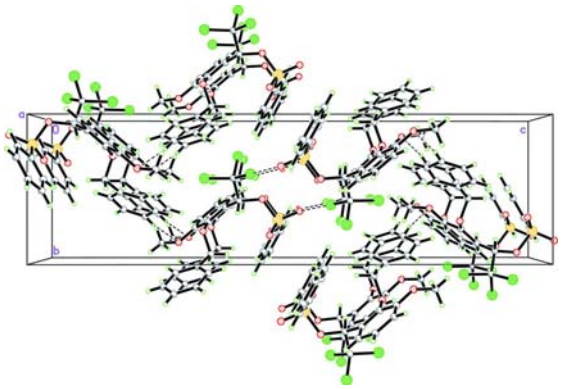


Figure 14: The crystal packing of **4**, viewed down the *a* axis. The intermolecular C–H···O hydrogen bonds and the short inter Cl···O contacts are shown as dashed lines.

Table 4: Hydrogen bond geometry of **4** (Å, °):

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
C7–H7*B*···O2	0.97	2.56	3.040 (1)	110
C14–H14*A*···O1	0.98	2.38	2.820 (1)	107
C14–H14*A*···O3	0.98	2.34	2.838 (1)	111
C21–H21*A*···O3	0.93	2.55	2.919 (1)	104
C3–H3*A*···O2^{i}	0.93	2.49	3.414 (1)	172

Symmetry code : (i) $-x, y+\frac{1}{2}, -z+\frac{1}{2}$.

Table 5: Crystal data of **4**

Empirical formula, Formula weight	$C_{22}H_{19}Cl_3O_5S$, 501.78
T, λ	293(2) K, 0.71073 Å
Crystal system, space group	$P2_1/c$, monoclinic
Unit cell dimensions	*a* = 8.1638(1) Å, *b* = 8.8536(1) Å, *c* = 30.7221(5) Å, α = 90°, γ = 90°, β = 90.670(1)°
V, Crystal size	2220.41(5) Å^3, 0.48 × 0.30 × 0.29 mm
Z, Calculated density	4, 1.501 μg/m^3
μ, *F*(000), θ	0.54 mm^{-1}, 1032, 1.33 to 40.00°
Limiting indices	$-14 \le h \le 14$, $-16 \le k \le 16$, $-54 \le l \le 54$
Reflections collected / unique	122837 / 13669 [$R_{(int)}$ = 0.059]
Data / restraints / parameters, *S*	11428 / 0 / 280, 1.08
Final *R* indices [$I>2\sigma(I)$]	R_1 = 0.040, wR_2 = 0.108
Largest diff. peak and hole	0.56 and -0.55 e.Å^{-3}

Conclusions

We have reported the complete assignments of the novel chiral compound (*R*) and (*S*) 1-(2-benzyloxy-3-methoxyphenyl)-2,2,2-trichloroethyl benzenesulfonate **4** using ^{1}H, ^{13}C APT, COSY, HMQC and HMBC NMR in $CDCl_3$. Compound **4** was obtained as single crystal and it was studied by X–ray crystallography. Further, it using the compound in biologically important is in progress. The formation mechanism of **4** is in progress to identify.

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