1D AND 2D NMR STUDIES OF BENZYL *O*–VANILLIN

Mohammed Hadi Al–Douh, Shafida Abd Hamid* and Hasnah Osman

School of Chemical Sciences,
Universiti Sains Malaysia (USM), Minden 11800, Pinang, Malaysia.

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ABSTRACT

*The reaction of o–vanillin **A** with benzyl bromide **B2** in acetone as the solvent and K_2CO_3 as a base in the presence of tetra–n–butylammonium iodide (**TBAI**) as catalyst formed benzyl o–vanillin, **C**. The complete assignments of **C** using PROTON, APT, DEPT–135, COSY, NOESY, HMQC and HMBC NMR in both $CDCl_3$ and acetone–d_6 are discussed, and the coupling constants J are reported in Hertz (Hz).*

Keywords: *^{1}H NMR; ^{13}C NMR; 2D NMR; Benzyl o–Vanillin.*

INTRODUCTION

The benzylation of phenols and hydroxy benzaldehydes are early described, which it is called as Williamson reaction or Williamson ether synthesis [1–2]. It is used for a variety of heteroatomic functional groups as well as carbon nucleophiles, so, this benzylation is used to protect hydroxyl group. The benzylation of *o*–vanillin **A** as phenol was chosen because of his high industrial, biological and pharmaceutical importance. Zaugg et al studied inhibition of sickle haemoglobin cells in whole blood by react the vanillins with amino groups of intracellular haemoglobin, which they found *o*–vanillin **A** significantly inhibit sickling at reduced partial pressures of oxygen [3]. Additionally, *o*–vanillin **A** and hydroxy benzaldehydes are extensively used as raw material to synthesized pancratistatin [4], coumarin [5] neolignan [6] EUK–8, EUK–134, JD–29 [7–8], narciclasine [9–10], aromatic C–ring in taxane [11], and alibendol derivatives [12], which have highly biological active. It is reported that the *o*–vanillin **A** induced mutations and it has also enhanced the chromosomal aberrations *in vitro* systems [13].

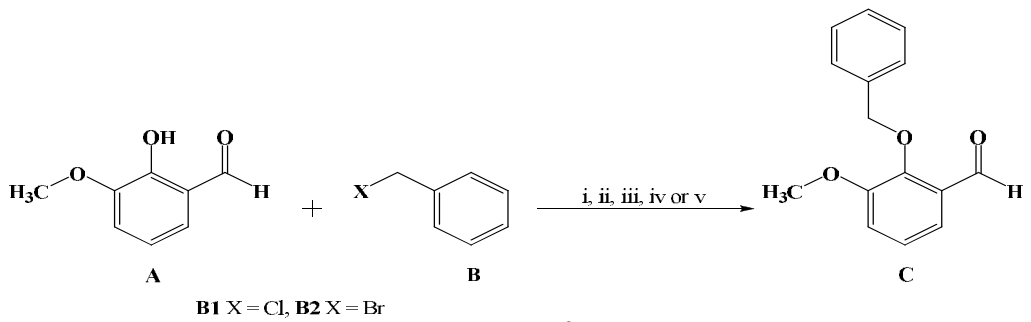
2–Benzyloxy–3–methoxybenzaldehyde or Benzyl *o*–vanillin **C** was early prepared [14–19] (Scheme 1), which it is used as a key for synthesizing a new anticancer drugs [16], and it is evaluated as anticancer drug against HL–60 cells [19]. In view of its importance, we have recently reported the crystal structure of **C**, determined by X–ray crystallography [20–22]. In this work, we have reported the complete assignments of **C** using PROTON, APT, DEPT–135, COSY, HMQC and HMBC NMR in both $CDCl_3$ and acetone–d_6.

EXPERIMENTAL SECTION

All NMR experiments were performed on Bruker Avance 400 Ultrashield^{TM} NMR for ^{1}H operating at 400.123 MHz, and Avance 300 NMR spectrometers for ^{13}C operating at 71.478 MHz in $CDCl_3$ and acetone–d_6 at 298 K using Bruker XWINNMR software equipped with a 5 mm BBI inverse gradient and QNP probe, respectively [23–24]. Chemical shifts were reported downfield in parts per million (ppm) from a tetramethylsilane (TMS) reference, and coupling constants (*J*) were measured in Hertz (Hz). The concentration of solute molecule was 100 mg in 1.0 ml $CDCl_3$ or acetone–d_6.

RESULT AND DISCUSSION

Benzyl *o*–vanillin **C** was prepared following several published methods (Scheme 1). Merz et al and Krohn *et al* reacts benzyl chloride **B1** with



Scheme 1 *Reagents and conditions*: i. **B1**, NaOH, DMSO, 20 ^{o}C, 8 hr; ii. **B1**, KOH, EtOH, refl., 12 hr; iii. **B2**, K_2CO_3, DMF, rt, 24 hr; iv. **B1**, K_2CO_3, KI, THF, refl., 6 hr; v. **B2**, K_2CO_3, TBAI, acetone, rt, 3.5 hr.

* Corresponding author. Tel/Fax : 604-653-3888/
604-657-4854; Email address : shafida@usm.my

Table 1 ^{1}H and ^{13}C NMR chemical shifts and coupling constants of **C** in $CDCl_3$ and acetone–d_6:

Atom No.	^{1}H NMR (ppm)				^{13}C NMR (ppm)	
	$CDCl_3$	*J* (Hz)	acetone–d_6	*J* (Hz)	$CDCl_3$	acetone–d_6
CHO	10.22, *d*	0.72	10.24, *d*	0.77	190.80	190.17
CH_3	3.82, *s*	–	3.98, *s*	–	56.52	56.52
CH_2	5.12, *s*	–	5.23, *s*	–	76.76	76.49
1	–	–	–	–	130.74	131.10
2	–	–	–	–	151.48	151.76
3	–	–	–	–	153.47	154.23
4	7.10–7.08, *dd*	8.09, 1.88	7.30–7.28, *dd*	7.87, 1.66	118.43	119.12
5	7.06–7.02, *td*	7.78, 0.64	7.20–7.15, *td*	7.91, 0.76	124.67	125.09
6	7.29–7.26, *dd*	7.83, 1.96	7.38–7.35, *dd*	7.87, 1.86	119.47	119.19
1`	–	–	–	–	136.77	137.82
2`	7.35–7.33, *dd*	7.49, 1.93	7.47–7.45, *dd*	7.78, 1.76	129.01	129.23
3`	7.31–7.28, *t*	6.33	7.39–7.34, *t*	7.41	129.08	129.59
4`	7.32–7.28, *t*	8.01	7.42–7.39, *t*	4.67	128.94	129.10

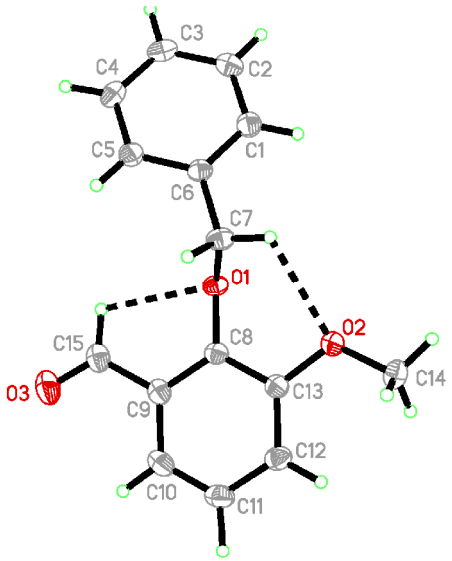


Figure 1 The molecular structure of Benzyl *o*–vanillin **C**, showing 50% probability displacement ellipsoids and atomic number. The dashed lines indicate intrarmolcular hydrogen bonds.

o–vanillin **A** in DMSO at 20 °C using NaOH as a base for 4–8 hours [14,17], while Profft and Cotterill et al used KOH as a base and refluxing the mixture in EtOH for 12 hours, the melting point of **C** 45°C [15–16]. Both reactions produce 95% yield in powder form with melting points of 45–47 °C. Recently, Berger performed similar reaction using benzyl bromide **B2** in DMF and K_2CO_3 as the base [18]. Although the reaction can be done at room temperature, it took 24 hours to complete with 96% yield. However, the product was obtained as an oily liquid. Lin et al yielded **C** as 89% by using **B1** and **A** in THF under reflux for 6 hours, they used K_2CO_3 as a base and KI as catalyst, the melting points of 58–59°C [19].

On the other hand, we prepared **C** by reacting benzyl bromide **B2** with **A** in acetone as the solvent and K_2CO_3 as a base [20, 25]. As previous methods needed considerable time to achieve a good yield, therefore, **TBAI** was added in an attempt to accelerate the reaction. **TBAI** seemed to do the trick and proved to be an excellent catalyst for the reaction, whereby the reaction conducted at room temperature took only 3.5 hours with 99.6% yield [22, 25]. Furthermore, **C** was obtained as single crystals with melting point of 35–35.5 °C [20–22], Figure 1.

The title compound **C** was used and conformed in the solution state, the conventional 1D ^{1}H NMR, ^{13}C NMR, APT, DEPT–135 along with 2D COSY, HMQC and HMBC to assign all proton and carbon chemical shifts. The splitting patterns for the aromatic protons of **C** were obtained from spectra acquired using 400 MHz ^{1}H NMR. The ^{1}H and ^{13}C NMR chemical shift and coupling constants data in $CDCl_3$ and acetone–d_6 are

Table 2 ^{1}H–^{1}H COSY and ^{1}H–^{13}C HMQC NMR of **C** in $CDCl_3$ and acetone–d_6:

Atom	COSY		^{1}J HMQC (ppm)	
	$CDCl_3$	acetone–d_6	$CDCl_3$	acetone–d_6
CHO	CH_2, H_5	H_5, H_6, $H_{2`}$	190.80	190.17
CH_3	H_4	H_4	56.52	56.52
CH_2	$H_{2`}$, CHO	$H_{2`}$	76.76	76.49
H_4	CH_3	CH_3, H_5	118.43	119.12
H_5	CHO	CHO, H_4, H_6	124.67	125.09
H_6	x	H_5, CHO	119.47	119.19
$H_{2`}$	CH_2	CH_2, CHO	128.94	129.10
$H_{3`}$	–	–	129.08	129.59
$H_{4`}$	–	–	129.01	129.23

x: not clear observation.

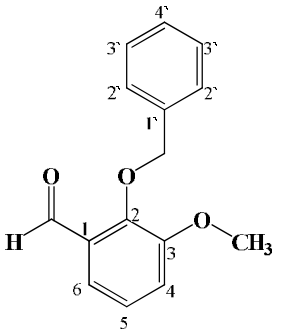


Figure 2 The chemical structure and the NMR numbering scheme of Benzyl *o*–vanillin **C**.

listed in Table 1, while Table 2 shows the COSY signals and Table 3 shows the HMQC and HMBC signals of **C**. The structure was further substantiated by complete ^{1}H and ^{13}C NMR assignments in both solvents, which have not been previously reported for **C**, using 2D NMR COSY, HMQC and HMBC experiments. Figure 2 shows the chemical structure and the NMR numbering scheme of **C.**

1D NMR spectra

^{1}H NMR spectra

The ^{1}H NMR spectra in $CDCl_3$ and acetone–d_6 of **C** were obtained and shown in Figure 3. The ^{1}H NMR spectrum in acetone–d_6 shows similar splitting patterns

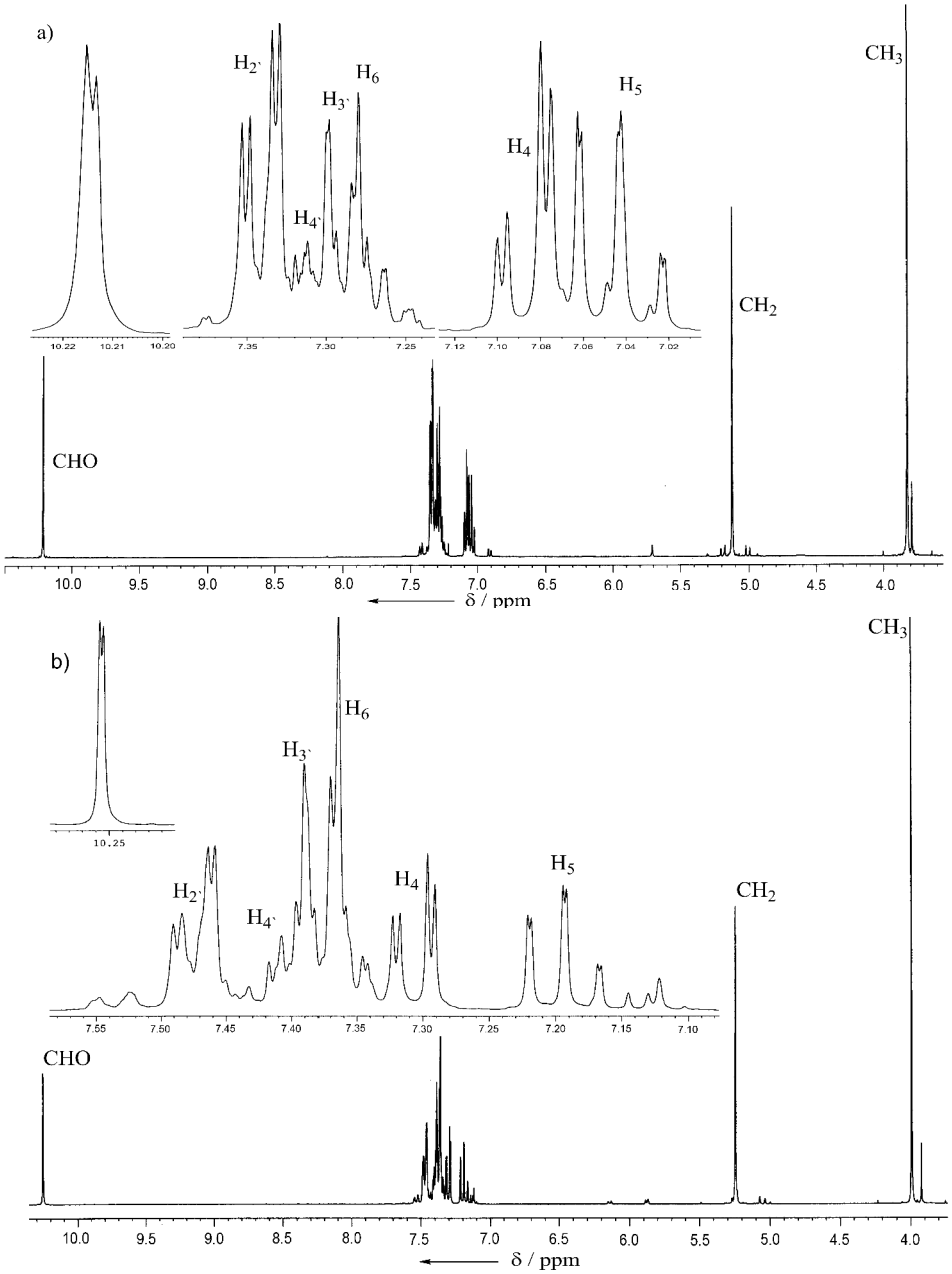


Figure 3 ^{1}H NMR spectrum of **C** in a) $CDCl_3$ and b) in acetone–d_6.

as those in $CDCl_3$ except that all the peaks shifted to more downfield. However, in acetone–d_6 clearer splitting patterns are observed. In $CDCl_3$ the ^1H NMR spectrum shows the chemical shift of the aldehydic proton at δ = 10.22 ppm as a doublet, (J = 0.72 Hz). The doublet may be due to coupling of aldehydic proton with H_5, which it is in a long-range couplings or zigzag configuration [26]. On the benzyl ring, two $H_{2'}$ protons exhibited a signal at δ = 7.35–7.33 ppm as doublet of a doublet, (J = 7.49 and 1.93 Hz). The signal for $H_{4'}$ (δ = 7.42–7.39 ppm) was overlapped with that of $H_{3'}$ and is not clearly shown, although in acetone–d_6, it appears as a triplet (J = 4.67 Hz). $H_{3'}$ exhibited a signal at δ = 7.39–7.34 ppm (J = 7.41 Hz) as a triplet which was shown clearly in acetone–d_6.

Meanwhile, H_6 appears as doublet of a doublet due to coupling with H_5 and H_4 (δ = 7.38–7.35 ppm, J = 7.87 and 1.86 Hz). On the trisubstituted ring, H_4 exhibited doublet of a doublet at □ = 7.10–7.08 ppm, (J = 8.09 and 1.88 Hz) due to coupling of the proton to H_5 and H_6. Finally, H_5 exhibited a signal at δ = 7.06–7.02 ppm as triplet of a doublet, (J = 7.78 and 0.64 Hz) in $CDCl_3$, and at δ = 7.20–7.15 ppm as triplet of a doublet, (J = 7.91 and 0.76 Hz) in acetone–d_6 which is more clearly observed in Figure 3(b). The protons on methylene group of benzyl ring and the methyl protons exhibited signals at δ = 5.12 and 3.82 ppm, respectively.

^{13}C NMR spectra

The ^{13}C NMR spectrum of **C** was obtained and shown in Figure 4. In $CDCl_3$, the peak appears at δ = 190.80 ppm in the ^{13}C NMR spectrum of **C** was assigned to the C=O group, while the quaternary

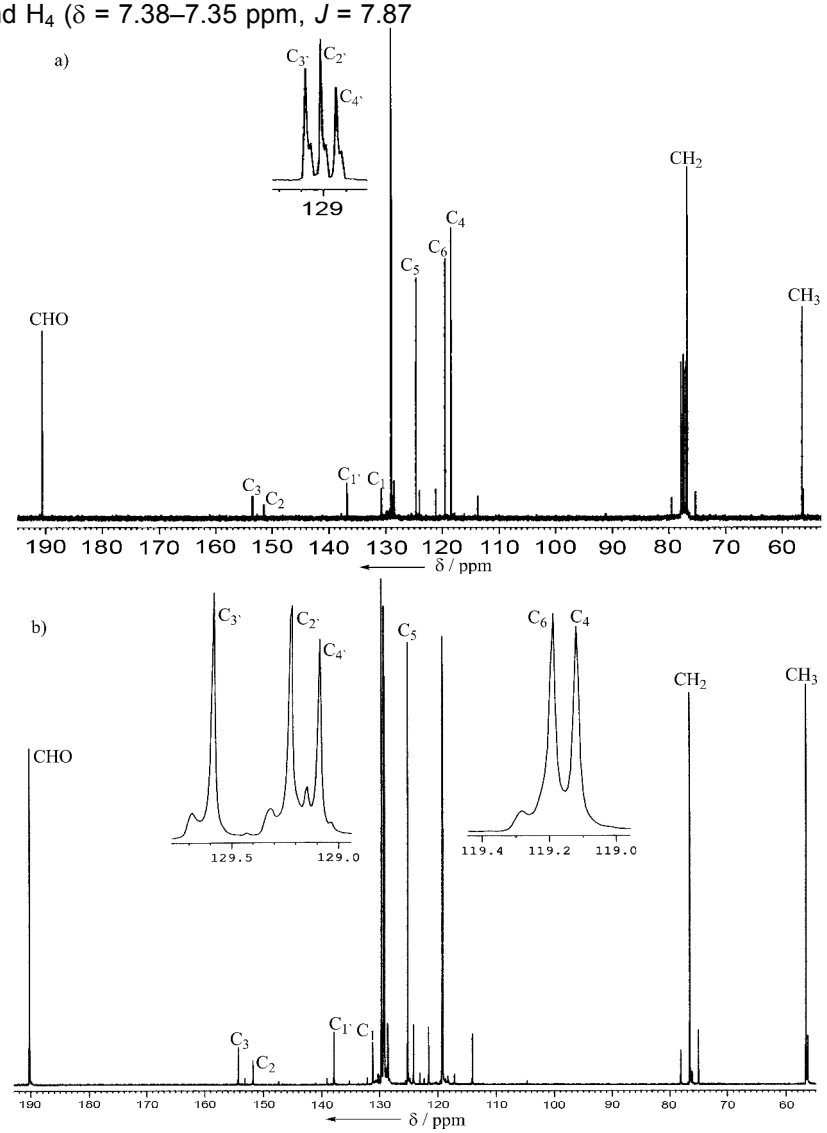


Figure 4 ^{13}C NMR spectrum of **C** in a) $CDCl_3$ and b) in acetone–d_6.

carbon signals were observed at δ = 153.47, 151.48, 136.77 and 130.74 ppm for C_3, C_2, $C_{1'}$ and C_1, respectively. Other aromatic carbon signals of benzyl ring were observed at δ = 129.08, 129.01 and 128.94 ppm for $C_{3'}$, $C_{2'}$ and $C_{4'}$, respectively, while C_5, C_6 and C_4 at the trisubstituted aromatic carbon showed signals at δ = 124.67, 119.47 and 118.43 ppm, respectively.

The ^{13}C NMR spectrum also shows CH_2 signal at δ = 76.76 ppm and 56.52 ppm for OMe. Similar to ^1H NMR spectra, ^{13}C NMR spectrum in acetone–d_6 shows the values of carbons being shifted to about 0.16–1.05 ppm downfield with the exception of C_6. Attached proton test (APT) and DEPT–135 NMR experiments in both solvents were also performed to confirm our postulation. Further confirmation was done by HMQC experiments. Table 1 summarises the ^1H and ^{13}C NMR in both solvents.

2D NMR spectra

^1H–^1H COSY NMR

The signals of **C** are assigned with an aid by the Correlation spectroscopy or COSY experiment which is a homonuclear 2D technique that explains which pairs of ^1H nuclei in a molecule are coupled to one another. Figure 5 shows the ^1H–^1H COSY NMR spectrum of **C**. The COSY spectrum confirmed the correlation assignments in both solvents $CDCl_3$ and acetone–d_6 of H_4 with methoxy group OMe at δ = 3.82 and 3.98 ppm, respectively. While the homonuclear connectivities observed between CH_2 with $H_{2'}$ in the benzyl ring and the aldehydic proton. From both spectra it can be seen that the one of the methylene protons is correlated with $H_{2'}$, probably because the proton is H–bonded to the O atom in OMe. However, the ^1H NMR for methylene protons only show a singlet at δ = 5.12 ppm, indicating the both protons are equivalent. We propose that the rapid movement at the methylene carbon cause this phenomena providing the interchange between the two protons.

^1H–^{13}C HMQC NMR

Heteronuclear multiple quantum coherence or the 2D HMQC NMR spectrum was conducted to determine which hydrogens are connected to which carbons. The HMQC NMR spectrum for **C** was shown in Figure 6, and it confirms the attachments between the aromatic hydrogens and their corresponding carbons. The signals owing to C_4, C_6, C_5, $C_{2'}$, $C_{4'}$ and $C_{3'}$ atoms are observed at δ = 118.43, 119.47, 124.67 and 128–130 ppm in $CDCl_3$, and at δ = 119.12, 119.19, 125.09, 129.10, 129.23 and 129.59 ppm in acetone–d_6, respectively. The one bond ^{13}C–^1H connectivities are also well observed for OMe and CH_2 atoms whereby the cross peaks appear at the respective δ = 56.52 and 76.76 ppm in $CDCl_3$, and at δ = 56.52 and 76.49 ppm in acetone–d_6.

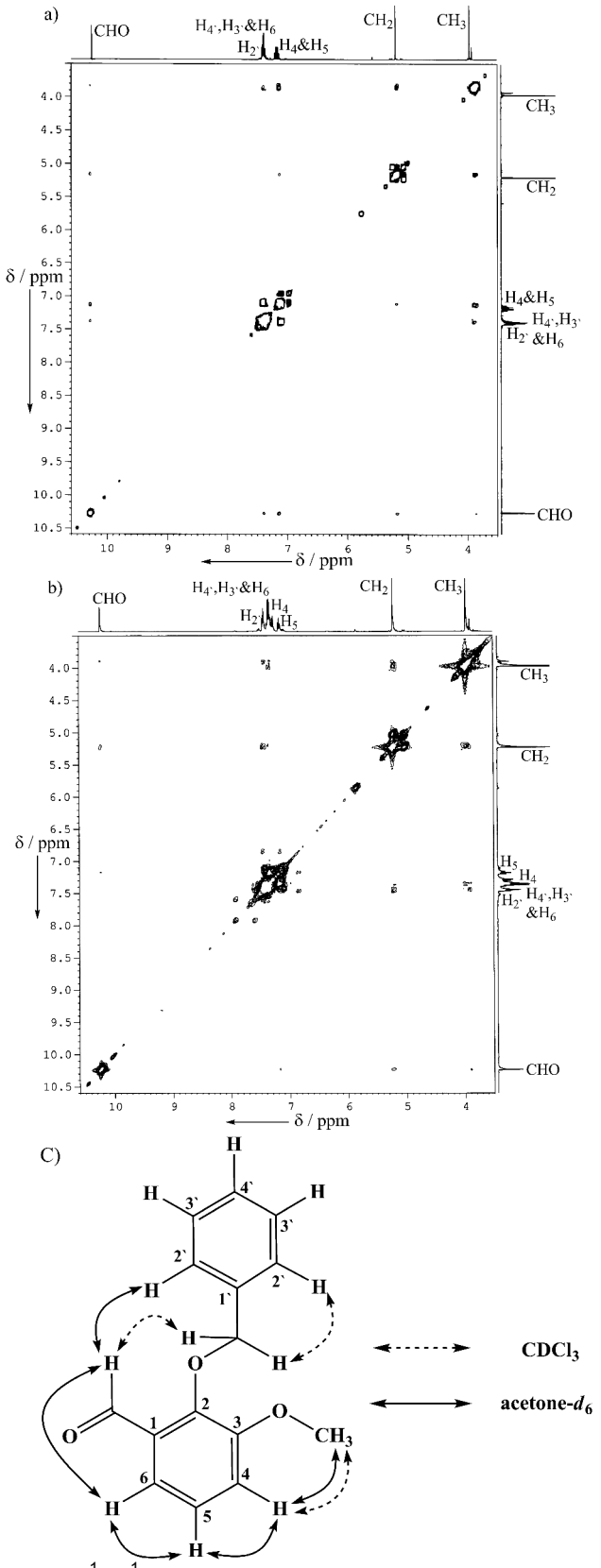


Figure 5 ^1H–^1H connectivities in the COSY a) in $CDCl_3$, b) in acetone–d_6 and c) the most important correlations observed in COSY spectrum of **C**.

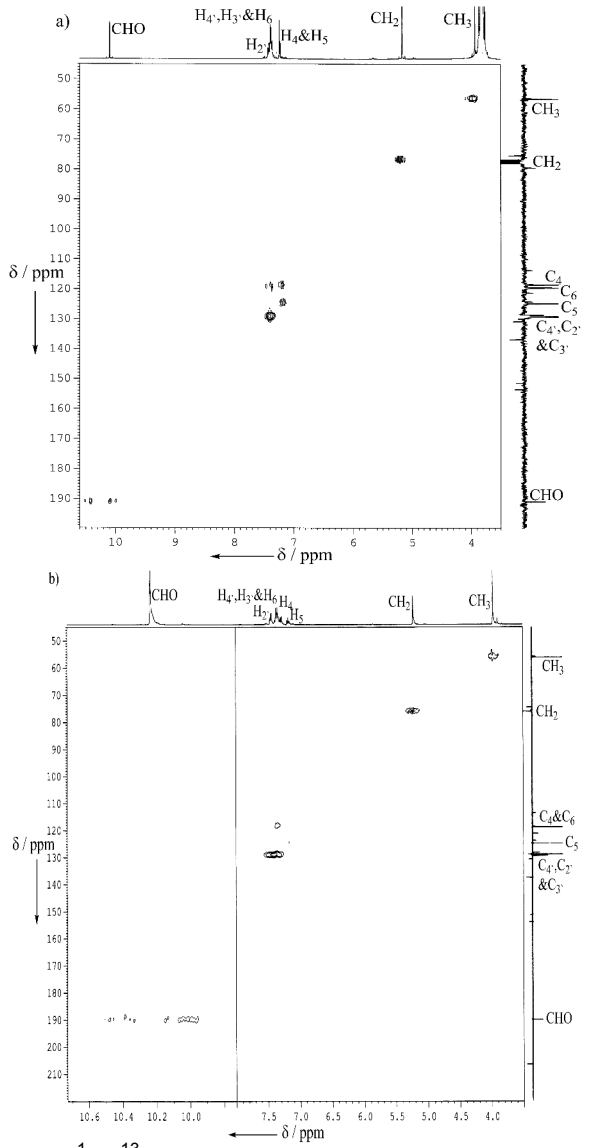


Figure 6 $^{1}H–^{13}C$ connectivities of **C** in the HMQC a) in $CDCl_3$ and b) in acetone–d_6.

Table 2 summarises the values of COSY and HMQC experiments in both $CDCl_3$ and acetone–d_6.

CONCLUSION

We have reported the complete assignments of Benzyl *o*–van **C** using ^{1}H, ^{13}C, COSY and HMQC NMR in both $CDCl_3$ and acetone–d_6. Attached proton test (APT) and DEPT–135 NMR experiments in both solvents were also performed to confirm our postulation although the results were not discussed here. Further reactions using the compound to synthesise biologically important compounds are in progress.

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21. ***Crystal data*** for **C**: $C_{15}H_{14}O_3$, M = 242.26, monoclinic, space group $P2_1/c$, a = 13.7203(3), b = 4.6599(10), c = 19.1552(5) Á, β = 97.736(1)°, V = 1213.55(5) Á^3, Z = 4, D_c = 1.326 g cm^{-3}, μ(Mo–$K\alpha$) = 0.092 mm^{-1}, F(000) = 512, T = 297 K, 3905 independent reflections. Data were collected on Bruker SMART APEX2 CCD areadetector using ω–scans [27], and the non–hydrogen atoms were refined anisotropically using full matrix least squares based on F^2 to give R_1 = 0.0514, wR_2 = 0.1878 for 2949 independent observed reflections [$F^2 > 2\sigma(F^2)$, 2θ = 31.2°] and 164 parameters. The structure was solved and refined by SHELXTL against F^2 [28]. The software was used SHELXTL [28] and PLATON [29]. These data can be obtained free of charge from International Union of Crystallography IUCr ci2177 or The Cambridge Crystallographic Data Centre CCDC 627450. (Reference: doi:10.1107/S1600536806039250).
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