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Graphycal Abstract

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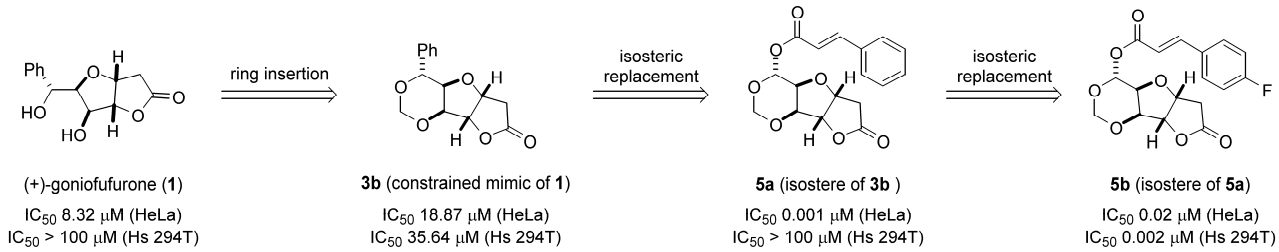

Conformationally constrained goniofufurone mimics as inhibitors of tumour cells growth: design, synthesis and SAR study

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Abstract

Synthesis of conformationally restricted (+)-goniofufurone (**1**) and 7-*epi*-(+)-goniofufurone (**2**) analogues, with embedded *O*-isopropylidene, *O*-methylidene or cyclic carbonate functions is disclosed starting from D-glucose. A number of potential bioisosteres of **1** and **2** bearing both 5,7-*O*-methylidene and 4-substituted cinnamoyloxy functions at the C-7 position have also been synthesized. In vitro cytotoxicity of target molecules against a number of human tumour cell lines were recorded and compared with those observed for the parent molecules **1** and **2**. Some of the analogues displayed powerful antiproliferative effects on selected human tumour cell lines, but all of them were devoid of any cytotoxicity towards the normal foetal lung fibroblasts (MRC-5). A SAR study reveals the structural features of these lactones that may increase their antiproliferative activity.

Keywords: styryl lactone, goniofufurone, conformational constrain, isosterism, antitumour activity, structure-activity relationships

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1. Introduction

(+)-Goniofufurone (**1**; Scheme 1) and 7-*epi*-(+)-goniofufurone (**2**) are naturally occurring styryl lactones that have attracted considerable attention since their isolation from the stem bark of *Goniothalamus giganteus* (Annonaceae) [1,2]. Their structures were elucidated by spectroscopic methods, and the relative configurations were determined by X-ray crystallography. The absolute configurations were established independently by Shing [3–5] and Jäger [6,7] from the syntheses of their opposite enantiomers, (−)-goniofufurone and 7-*epi*-(−)-goniofufurone, respectively. Due to their unique structural features and promising antitumour activities [8–11], both natural products **1** and **2**, along with a number of their analogues have been the targets of many total syntheses [12–14]. The development of practical and efficient routes for the synthesis of analogues of naturally occurring compounds is of considerable interest for drug design and discovery. More potent analogues can be designed by manipulation of functional groups, stereochemistry or by introduction of a conformational constrain.

Scheme 1

We have recently demonstrated that the embedment of an oxetane ring increases the antitumour potency originally displayed by lead **1** [15]. On the other hand, a study carried out previously in our laboratory shows that dephenylated analogues of **1**, and in particular the corresponding (3*S*,4*R*)-stereoisomer strongly inhibits the growth of certain human neoplastic cell lines [16]. Based on the above mentioned observations, we have planned the synthesis of tricyclic lactones of type **3** and **4** that represent conformationally constrained analogues of **1** and **2**, annelated with 1,3-dioxane or 2-substituted 1,3-dioxane heterocyclic rings. Furthermore, a series of new goniofufurone and 7-*epi*-goniofufurone bioisosteres of type **5** and **6** has been designed by combining both ring insertion and isosterism methods. Apparently, the structures **5** and **6** were formally obtained by isosteric replacement of the phenyl ring in **3** and **4** respectively with a cinnamoyloxy function, or with substituted cinnamate residues bearing an electron-withdrawing (F, NO_2) or electron-donating (OMe) substituents in the C-4 position. Special interest in the cinnamic acid ester group is associated with its presence in several naturally occurring styryl lactones that were isolated from the tropical plant *Polyalthia crassa* [17] and found to exhibit a potent and selective cytotoxicity against some human tumour cell lines [15, 17–19]. In addition to the synthesis of analogues **3**–**6**, simple and efficient routes to (+)-goniofufurone (**1**) and 7-*epi*-(+)-goniofufurone (**2**) have been developed in order to provide samples of the leads that would serve as control molecules in antitumour assays.

Furthermore, styryl lactones **1** and **2** represent possible starting materials for the preparation of conformationally restricted analogues **3** and **4**.

2. Results and discussion

2.1. Chemistry

Preparation of **1** and **2** started from alcohols **7** or **8**, which are readily available from D-glucose through a modified literature procedure [20,21] (Scheme 2). For the sake of synthesis of **2**, compound **7** was first converted to the corresponding di-*O*-benzyl ether **9a** by treatment with benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide. Hydrolytic removal of the isopropylidene protective group in **9a** with aqueous trifluoroacetic acid gave the expected lactol **9b**. Subsequent treatment of **9b** with Meldrum's acid in DMF in the presence of triethylamine, followed by final hydrogenolytic 5,7-di-*O*-deprotection furnished the natural product **2**. 7-*epi*-(+)-Goniofufurone (**2**) was thus prepared from **7** in an overall yield of 39%, over the four steps and a single chromatographic purification. Slightly better overall yield (48%) was obtained by using the compound **8** as a starting material.

Scheme 2

Next, we started a two-step synthetic sequence leading to the natural product **1**. Thus a selective oxidation of the benzylic alcohol function in **2** under the Hunsen conditions [22], first gave the corresponding ketone **10** in an almost quantitative yield. Subsequent reduction of the carbonyl group in **10** with $NaBH_4$ in the presence of L-tartaric acid [23] gave a 5:1 mixture of diastereomers, which after chromatographic separation furnished target **1** as the major product in 81% yield. All physical constants and spectroscopic data of thus prepared natural products **1** and **2** were in full agreement with those reported previously [15,21].

Preparation of conformationally constrained analogues of (+)-goniofufurone and 7-*epi*-(+)-goniofufurone (compounds **3** and **4**) is outlined in Scheme 3.

Scheme 3

The synthesis of 5,7-*O*-isopropylidene derivatives **3a** and **4a** was first attempted starting from **1** and **2**, respectively. It is interesting to note that the analogue **3a** actually represents a natural product that was isolated in 2001 from the roots of *Goniothalamus cheliensis* [24]. Its structure was determined on the basis of spectral and chemical evidence that included treatment of **1** with 2,2′-

dimethoxypropane in dry acetone and in the presence of a catalytic amount of toluene-4-sulphonic acid. We applied exactly the same reaction conditions to obtain analogues **3a** (from **1**) and **4a** (from **2**) both in 95% yield. The physical constants and the ^{13}C spectral data of thus obtained sample **3a** were consistent with those previously reported [24]. However, the published ^{1}H NMR spectral data for **3a** contain the erroneous assignments for H-5 and H-7 whose chemical shifts should be interchanged (for the comparison of NMR spectra, see Table S5 in the Supplementary data). The authors have probably been confused by a large vicinal coupling between H-6 and H-7 (8.1 Hz) which is inconsistent with a chair-like geometry of the six-membered ring but points to the *anti* arrangement of these protons. This is possible only if the six-membered ring occupies a twist-boat conformation with a pseudo-axially oriented H-7 atom, as confirmed by a NOE experiment. Namely, it was found that when the H-3 signal was irradiated, the H-7 peak was enhanced, suggesting that these protons have a *syn* orientation that means the phenyl group is pseudo-equatorially oriented. The single crystal X-ray analysis of **3a**, confirmed the twist-boat geometry of the six-membered ring (Figure 1), as well as the *anti* (*trans*-diaxial) arrangement of H-6 and H-7 (τ = 167.2 °), which is consistent with the observed vicinal couplings of 8.1 Hz. Finally, the distance between H-3 and H-7 (3.05 Å) is consistent with NOE results.

Figure 1

Twist-boat geometry of the six-membered ring in **3a** is not entirely unexpected, because the alternative chair-like conformation would be destabilized by strong 1,3-diaxial clashes of bulky Ph and Me groups. In contrast, a relatively small vicinal coupling between H-6 and H-7 (1.7 Hz) was observed in the ^{1}H NMR spectrum of 7-epimer **4a**, and no NOE contacts between non-contiguous H-atoms were detected. These findings are consistent with a *gauche* arrangement of H-6 and H-7, with the phenyl group in equatorial position, and with the six-membered ring occupying a chair-like conformation.

Methylene acetals were first prepared by treatment of alcohols **1** and **2** with para-formaldehyde and toluene-4-sulfonic acid in anhydrous CH_3CN at room temperature, following a slightly modified literature procedure [25]. Acetalisation of natural compound **1** gave two products: 1,3-dioxane **3b** (48%) and 1,3,5-trioxaepane **3c** (49%). In this case the exclusive formation of the dioxane derivative has been probably hampered by sterical crowding due to the 1,3-diaxial repulsion of Ph and H in the six-membered ring, while the formation of trioxaepane **3c** bearing the equatorial phenyl group is also favourable from the sterical reasons. However, methylidenation of **2** under the same reaction conditions exclusively gives the expected 5,7-*O*-methylidene derivative **4b** in 82%

yield. No derivative with 1,3,5-trioxaepane function has been obtained thus demonstrating the easier formation of the 1,3-dioxane cycle, evidently by sterical reasons. Stereochemistry of methylene acetals **3b**, **3c** and **4b** were confirmed by single crystal X-ray diffraction analysis (for the crystal structures of **3b**, **3c** and **4b**, see the Supplementary data). Methylidenation of both natural compounds **1** and **2** was also attempted by using an adopted procedure [26] that involved their treatment with $SOCl_2$ in dry DMSO at 65 °C. Under these reaction conditions compound **1** again gave a mixture of **3b** (38%) and **3c** (51%), while acetalisation of **2** solely gave the corresponding 5,7-*O*-methylidene derivative **4b** in 95% yield.

Finally, treatment of **1** and **2** with 1,1′-carbonyldiimidazole in anhydrous CH_3CN at 46–48 °C gave the expected cyclic carbonates **3d** and **4c** in 96 and 73% yield, respectively. The structure and purity of thus obtained products **3d** and **4c** was confirmed on the basis of spectroscopic data, and their stereochemical integrity was confirmed by X-ray analysis (for the crystal structure of **3d** and **4c**, see the Supplementary data).

The synthesis of cinnamic isosteres **5** and **6** commenced with the preparation of hemiacetal **12** (Scheme 4).

Scheme 4

As previously reported the reaction between lead tetraacetate [27] or sodium periodate [28] and 1,2-*O*-isopropylidene-α-D-glucofuranose (**11a**) gave 3,5-*O*-methylene derivative **12a** as the main reaction product. Accordingly, we assumed that lactone **11** [29] under similar conditions may give the desired intermediate **12**. It was subsequently shown that treatment of **11** with periodic acid in dry acetonitrile indeed gives **12** in 80% yield. Pure product **12** was isolated by flash column chromatography as a mixture of (7*S*)- and (7*R*)-stereoisomers. However, the slow crystallization from a mixture of acetone and hexane afforded pure (7*S*)-isomer in the form of colourless needles of X-ray quality (for the crystal structure of **12**, see the Supplementary data). The single crystal X-ray diffraction analysis of **12** confirmed a chair-like conformation of the newly formed 1,3-dioxane ring with the C-7 hemiacetal hydroxyl group in axial (*exo*) position.

Three independent procedures were used for the conversion of **12** to the cinnamic esters **5** and **6** and the results are presented in Table 1.

Table 1

In our first experiments, lactone **12** (a mixture of stereoisomers) was treated with cinnamoyl chloride (entry 1) or with 4-nitrocinnamoyl chloride (entry 4) in the presence of DMAP in dry acetonitrile, to afford ~2:1 mixtures of **5** and **6** in 86 and 96% combined yields, respectively. Interestingly, both ^{1}H and ^{13}C NMR spectra of **5a** contained the peaks at δ_H 5.29 (s, 2 H) and δ_C 53.5 ppm corresponding to a CH_2Cl_2 molecule in the crystalline sample **5a**. This indicated that product **5a** co-crystallized with the solvent molecule, as confirmed by single crystal X-ray diffraction analysis (for the crystal structure of **5a**, see the Supplementary data).

Next, the esterification step was attempted by using the Steglich esterification protocol [30]. We were pleased to find that treatment of **12** with 4-fluoro- or 4-methoxycinnamic acid, in the presence of DCC and DMAP in anhydrous dichloromethane gave the corresponding esters **5b** and **5d** as the only reaction products, both in 60% yield (entries 2 and 5). Exclusive formation of (7*R*)-configured products is probably a result of thermodynamic control of the process.

Finally, in order to provide an access to the (7*S*)-configured cinnamic esters **6b** and **6d** we treated lactol **12** under the standard Mitsunobu conditions [31]. Thus, when lactone **12** reacted with 4-fluorocinnamic acid, in the presence of Ph_3P and DEAD, a ~2:1 mixture of **6b** and **5b** was obtained in 65% combined yield (entry 3). However, when the same reaction was carried out with 4-methoxycinnamic acid, a 3.5:1 mixture of **6d** and **5d** was obtained in 45% combined yield (entry 6). The lower yield of previous reaction is probably a result of partial decomposition of the products observed during flash column chromatography. The assignment of (*S*) stereochemistry at the C-7 in products **6a**–**d** was confirmed by an NOE interaction between H-5 and H-7, indicating that these protons are in close proximity on the same side of the ring. This effect was not observed in epimers **5a**–**d**, thus implying the opposite (*R*) stereochemistry at C-7.

2.2. Biological evaluation and SAR

After completion of the synthesis, analogues **3**–**6** were evaluated for their in vitro cytotoxicity against a panel of human malignant cell lines, including myelogenous leukaemia (K562), promyelocytic leukaemia (HL-60), T cell leukaemia (Jurkat), Burkitt's lymphoma (Raji), ER^+ breast adenocarcinoma (MCF-7), ER^- breast adenocarcinoma (MDA-MB-231), cervix carcinoma (HeLa), melanoma cells (Hs 294T) and against a single normal cell line, foetal lung fibroblasts (MRC-5). Cytotoxic activity was evaluated by using the standard MTT assay, after exposure of cells to the tested compounds for 72 h. (+)-Goniofufurone (**1**), 7-*epi*-(+)-goniofufurone (**2**) and the commercial antitumour agent doxorubicin (DOX) were used as positive controls.

Table 2

According to the recorded IC_{50} values (Table 2), the HL-60, Raji and HeLa cell lines are sensitive to all of the synthesized analogues. Remarkably, in the culture of HL-60 cell line, the majority of synthesized analogues displayed several-fold higher potency when compared to leads **1** and **2**. The highest potency in the culture of these cells was recorded after treatment with **4b** (IC_{50} 0.24 μM), which was approximately 4-fold more active than the commercial drug doxorubicin. All eight (+)-goniofufurone mimics (**3a**–**5d**) demonstrated diverse antiproliferative effects toward HL-60 cells, in contrast to the lead **1**, which was completely inactive against this cell line. With the exception of analogues **6c** and **6d**, all of the remaining 7-*epi*-(+)-goniofufurone mimics were more potent than lead **2**. The most active molecule in the culture of Raji cells is analogue **5a** (IC_{50} 1.01 μM) that exhibited about 18- and 3-fold higher potency than control compounds **1** and DOX, respectively. On the other hand, 7-*epi*-(+)-goniofufurone mimics **4a**, **4b** and **6c** showed similar potency as **2** in this cell line, but were 2- to 3-times more active than the commercial antitumour agent doxorubicin. The most active compound in the culture of HeLa cells is analogue **5a** (IC_{50} 1 nM) that exhibited over 8300- and 65-fold higher potency when compared to control molecules **1** and DOX, respectively. (+)-Goniofufurone mimic **5b** also exhibited a potent growth inhibitory activity against HeLa cell line (IC_{50} 20 nM). It demonstrated over 400- and 3-fold higher activity than lead **1** and DOX (65 nM) in the same cell culture, respectively. The most potent 7-*epi*-(+)-goniofufurone mimic toward the HeLa cells is analogue **6a**, that exhibited a submicromolar antiproliferative activity (IC_{50} 0.23 μM) against these cells, being essentially 4-fold more potent than the parent compound **2**. However, comparing to DOX, this analogue exhibited 3.5-fold lower activity against HeLa cells. The Hs 294T melanoma cells are the least sensitive to most of synthesized lactones, although the analogue **5b** exhibited a potent cytotoxicity (IC_{50} 2 nM) being over 2250-fold more active than DOX. The parent compound **1** was completely inactive, while 7-*epi*-(+)-goniofufurone (**2**) demonstrated a moderate cytotoxicity in the culture of Hs 294T cells. However, the only active analogue of **2** (cinnamate **6a**) exhibited 17- and 1.8-fold higher potency than control compounds **2** and DOX, respectively. As the results in Table 2 further illustrate, analogue **4b** and lead **2** exhibited the most pronounced antiproliferative activities against K562 cells (IC_{50} 23 nM) being approximately10-fold more potent than doxorubicin in the same cell line. Finally, the analogues **3d**, **4a** and **5a**, as well as the natural product **2** displayed significant growth-inhibitory activity against all used tumour cell lines except Hs 294T. Remarkably, none of the synthesized styryl lactones nor the natural products **1** and **2** exhibited toxicity toward the normal MRC-5 cells, in contrast to the

commercial antitumour agent doxorubicin (DOX) that exhibited potent cytotoxic activity (IC_{50} 0.1 μM) against this cell line.

In an attempt to correlate the structures of synthesized goniofufurone mimics with their cytotoxic activities, we first considered the influence of ring insertion in the structures of leads **1** and **2** [21]. As the data in Table 2 reveal the embedment of 1,3-dioxane or 2-substituted 1,3-dioxane rings increases the antitumour potency originally displayed by lead **1**, but decreases the cytotoxicity originally demonstrated by lead **2**. Replacement of the C-7 phenyl group in **3b** and **4b** by a cinnamate moiety caused similar effects. Namely, the cinnamic isosteres of **3b** displayed the increased antitumour potency with respect to that originally displayed by the control molecule **3b**, whereas the same structural changes in **4b** gave less active analogues when compared to the corresponding control. Remarkably, replacement of phenyl ring in compound **3b** with cinnamoyloxy moiety, as in case of compound **5a**, produces the most active analogue in this study which exhibited antitumour activity in a nanomolar range against HeLa cell line (IC_{50} 1 nM). The next round of modifications aimed at improving the activity was made at the phenyl ring. Therefore, keeping intact the 3,6-anhydro-2-deoxy-7-*C*-cinnamoyloxy-5,7-*O*-methylene-D-*ido*-heptono-1,4-lactone scaffold, selected electron-withdrawing, or electron-donating groups were attached in the position C-4 of the aromatic ring. Compounds **5a** and **6a** have been used as control molecules in this SAR analysis. To our disappointment, the introduction of either electron-withdrawing or electron-donating groups in the position of C-4 at the aromatic ring of **5a** did not improve antiproliferative activity. However, the introduction of a fluorine atom in the C-4 position produces the active analogue **5b** which exhibited antitumour activity against Hs 294T melanoma cells in a nanomolar range (IC_{50} 2 nM), whereas the introduction of a methoxy group in the same position of **5a** led to a 120-fold increase in activity against Jurkat cells (IC_{50} 42 nM). We finally wanted to explore the effects of absolute stereochemistry at C-7 to antiproliferative activity of analogues. The importance of this structural feature for the cytotoxic activities was studied by comparing the IC_{50} values of **1** (7*R*) and **2** (7*S*), as well as of seven pairs of analogues (**3a** and **4a**, **3b** and **4b**, **3d** and **4c**, **5a** and **6a**, **5b** and **6b**, **5c** and **6c**, **5d** and **6d**), each of which contains exactly the same substituents and differs only in their absolute stereochemistry at C-7. As the results shown in Table 2 indicate, in most cases, the (7*S*)-configured analogues (**4a**, **4b** and **4c**) show an improved cytotoxicity when compared to the stereoisomers of (7*R*)-series (**3a**, **3b** and **3d**). These results are consistent with our previous findings [32], which indicated that the styryl lactones having the (7*S*)-stereochemistry represent more potent cytotoxic agents with respect to the corresponding (7*R*)-epimers. However, the considerations of the same structural feature in the cinnamic isosteres **5** and **6** reveals that (7*R*)-

stereoisomer **5a** exhibits the higher potency than (7*S*)-epimer **6a** against the majority of tumour cells under evaluation. The remaining (7*R*)-configured cinnamic bioisosteres (**5b**–**d**) show more potent cytotoxicities with respect to their counterparts of (7*S*)-series (**6b**–**d**) against four of eight tested tumour cell lines.

3. Conclusions

In summary, fifteen analogues of natural styryl lactones (+)-goniofufurone (**1**) and 7-*epi*-(+)-goniofufurone (**2**) were designed, synthesized and evaluated in this work. The analogues were designed by combining two different techniques, such as ring insertion and isosterism.

The newly synthesized compounds were tested in vitro toward a panel of human tumour cell lines, and the preliminary structure-activity relationships are briefly discussed. Some of the synthesized compounds showed potent antitumour activity, especially analogues **5a** (IC_{50} 1 nM against HeLa) and **5b** (IC_{50} 2 nM against HS 294T) which displayed the highest activity of all molecules under evaluation.

The preliminary SAR analysis suggested the following general structural requirements for the anti-proliferative action of synthesized (+)-goniofufurone mimics: (A) the presence of an additional 1,3-dioxane or 2-substituted 1,3-dioxane ring increases the antitumour potency originally displayed by lead **1**, but decreases the cytotoxicity originally demonstrated by lead **2**; (B) the replacement of phenyl group at C-7 in **3b** by cinnamoyloxy functionalities increases antitumour potency relative to the control molecule **3b**, whereas the same structural changes in lead **4b** gave less active analogues; (C) the heteroannelated styryl lactones having the (7*S*)-stereochemistry represent more potent cytotoxic agents than the corresponding (7*R*)-epimers, whereas the (7*R*)-configured cinnamic bioisosteres exhibits the increased antitumour potency when compared to the corresponding (7*S*)-isomers.

4. Experimental section

4.1. General experimental procedures

Melting points were determined on a Büchi 510 apparatus and were not corrected. Optical rotations were measured on an Autopol IV (Rudolph Research) polarimeter at room temperature. NMR spectra were recorded on a Bruker AC 250 E instrument and chemical shifts are expressed in ppm downfield from TMS. IR spectra were recorded with an FTIR Nexus 670 spectrophotometer (Thermo-Nicolet). High resolution mass spectra (ESI) of synthesized compounds were acquired on

an Agilent technologies 6210 TOF LC/MS instrument (LC series 1200). Flash column chromatography was performed using Kieselgel 60 (0.040–0.063, E. Merck). All organic extracts were dried with anhydrous Na_2SO_4. Organic solutions were concentrated in a rotary evaporator under reduced pressure at a bath temperature below 30 °C.

*4.1.1. 7-epi-(+)-Goniofufurone (**2**)*

To a cooled (0 °C) and stirred solution of **8** [20] (1.0 g, 2.81 mmol) in dry DMF (20 mL) were added successively 95% NaH (0.202 g, 8.43 mmol) and BnBr (0.44 mL, 3.65 mmol). The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 1.5 h. Absolute MeOH (8 mL) was finally added, and the mixture was stirred at room temperature for the additional 20 min and evaporated. The residue was suspended in water (200 ml) and extracted with EtOAc (3×50 mL). The combined organic solutions were dried and evaporated. The remaining crude **9a** was dissolved in 50% TFA (20 mL) and the resulting solution was stirred for 18 h at room temperature. The mixture was concentrated by co-distillation with toluene and the resulting crude **9b** was dried in vacuum for 2 h. To a solution of crude **9b** in dry DMF (25 mL) was added Meldrum's acid (0.809 g, 5.61 mmol) and dry Et_3N (0.8 mL, 5.8 mmol). The mixture was stirred for 66 h at 44–46 °C and evaporated. The residue was suspended in 10% NaCl (200 ml) and extracted with EtOAc (3×50 mL). The organic solutions were combined, dried and evaporated. A solution of crude **9c** (1.35 g) in MeOH (40 mL) was hydrogenated over 10% Pd/C (0.3 g; the catalyst contained 50% of water). After 24 h an additional amount of catalyst was added (0.3 g) and the hydrogenation was continued for additional 24 h. The mixture was filtered through a Celite pad and the catalyst washed with MeOH. The combined organic solutions were evaporated and the residue was purified by flash chromatography (19:1 CH_2Cl_2/MeOH) to afford pure **2** (0.336 g, 48% from **8**) as a colourless solid. Recrystallization from Me_2CO/hexane gave colourless powder, mp 207–210 °C, $[\alpha]_D^{20}$ +104.7 (*c* 0.75, EtOH), lit. [15] mp 197–200 °C, (from Me_2CO/light petroleum), $[\alpha]_D^{20}$ +108.5 (*c* 0.75, EtOH), lit. [33] mp 200–203 °C, $[\alpha]_D^{20}$ +102.0 (*c* 0.5, EtOH), for (−)-enantiomer: lit. [15] mp 205–206 °C (from EtOAc/hexane), $[\alpha]_D^{20}$ −98.3 (*c* 0.5, acetone), R_f=0.19 (7:3 CH_2Cl_2/EtOAc). IR, ^1H and ^{13}C NMR spectroscopic data of thus prepared natural product **2** matched those previously reported by us [15,21]. HRMS (ESI): *m/z* 268.1177 (M^++NH_4), calcd for $C_{13}H_{18}NO_5$: 268.1180.

*4.1.2. 3,6-Anhydro-2-deoxy-7-C-phenyl-L-ido-hept-7-ulosono-1,4-lactone (**10**)*

To a cooled (0 °C) and stirred solution of **2** (0.04 g, 0.16 mmol) and H_5IO_6 (0.045 g, 0.2 mmol) in anhydrous CH_3CN (5 mL) was added a solution of PCC (0.002 g, 0.009 mmol) in anhydrous

CH_3CN (1 mL) over a period of 1 min. The mixture was stirred at 0 °C for 2 h, then poured into 10% aq NaCl (75 mL) and extracted with EtOAc (3×25 mL). The combined organic solutions were evaporated and the residue was purified by flash column chromatography (47:2:1 CH_2Cl_2/MeOH/Me_2CO) to afford pure **10** (0.038 g, 96%) as a colourless solid. Recrystallization from Me_2CO/hexane gave colourless crystals, mp 198−201°C, $[\alpha]_D^{20}$ +31.2 (*c* 0.5, Me_2CO); R_f=0.46 (EtOAc). IR ($CHCl_3$): ν_{max} 3411 (OH), 1798 (C=O, lactone), 1681 (PhC=O), 1600 (Ph). ^{1}H NMR (acetonitrile-d_3): δ 2.98 (m, 2 H, OH and H-2a), 3.01 (dd, 1 H, $J_{2a,2b}$=18.6, $J_{2b,3}$=5.6 Hz, H-2b), 4.97 (br d, 2 H, H-4 and H-5), 5.20 (dd, 1 H, $J_{3,4}$=4.4, $J_{2b,3}$=5.1 Hz, H-3), 5.69 (t, 1 H, $J_{5,6}$=$J_{6,7}$=4.4 Hz, H-6), 7.56–7.56 (m, 5 H, Ph). ^{13}C NMR (acetonitrile-d_3): δ 36.8 (C-2), 76.5 (C-5), 78.8 (C-3), 85.2 (C-6), 89.3 (C-4), 128.9, 129.6, 134.3, 136.8 (Ph), 176.7 (C-1), 196.1 (Ph*C*=O). HRMS (ESI): *m/z* 271.0572 (M^++Na), calcd for $C_{13}H_{12}NaO_5$: 271.0577.

*4.1.3. (+)-Goniofufurone (**1**)*

To a suspension of L-tartaric acid (0.324 g, 0.22 mmol) in dry THF (6 mL) was added $NaBH_4$ (0.084 g, 2.22 mmol) in two equal portions and the suspension was heated at reflux for 2 h before being cooled to −18 °C. A solution of ketone **10** (0.108 g, 0.42 mmol) in dry THF (10 mL) was added in two equal portions and the mixture was stirred at −18 °C for 20 h. The mixture was evaporated with silica gel and the residue was purified on a column of flash silica (Et_2O for **1**, then EtOAc for **2**). Eluted first was pure (+)-goniofufurone (0.088 g, 81%) isolated as a colourless solid. Recrystallization from CH_2Cl_2/hexane gave colourless powder, mp 149–151 °C, $[\alpha]_D^{20}$ +52.8 (*c* 0.5, $CHCl_3$), lit. [15] mp 154–155 °C (from EtOAc/hexane), $[\alpha]_D^{20}$ +39.2 (*c* 0.9, $CHCl_3$), R_f=0.19 (7:3 CH_2Cl_2/EtOAc). IR, ^{1}H and ^{13}C NMR spectroscopic data of thus prepared natural product **1** matched those previously reported by us [15,21]. HRMS (ESI): *m/z* 251.0912 (M^++H), calcd for $C_{13}H_{15}O_5$: 251.0914; *m/z* 273.0736 (M^++Na), calcd for $C_{13}H_{14}NaO_5$: 273.0733; *m/z* 251.0912 (M^++H), calcd for $C_{13}H_{15}O_5$: 251.0914. Eluted second was the minor stereoisomer **2** (0.019 g, 17%).

*4.1.4. General procedure for O-isopropylidenation of **1** and **2***

To a solution of lactones **1** or **2** (1 equiv) in dry Me_2CO (0.02 M) was added 2,2′-dimethoxypropane (7 equiv) and TsOH×H_2O (0.01 equiv). The mixture was stirred at room temperature until the starting materials were consumed (TLC, 3.5 h for **1**, 4.5 h for **2**). The mixture was neutralized with 10% aq $NaHCO_3$ and evaporated with silica gel. The residue was purified by flash column chromatography (1:1 Et_2O/hexane).

*4.1.4.1. 3,6-Anhydro-2-deoxy-5,7-O-isopropylidene-7-C-phenyl-D-glycero-D-ido-heptono-1,4-lactone (**3a**)*

Yield 95%. Colourless needles, mp 165–166 °C (Et_2O/hexane), $[\alpha]_D^{20}$ +89.6 (*c* 0.5, MeOH), lit. [24] mp 165–166 °C, $[\alpha]_D^{20}$ +80.0 (*c* 0.05, MeOH); R_f=0.33 (1:1 Et_2O/hexane). IR (KBr): ν_{max} 1785 (C=O), 1607 (Ph). For ^1H and ^{13}C NMR data, see Table S5 in the Supplementary data. HRMS (ESI): *m/z* 291.1228 (M^++H), calcd for $C_{16}H_{19}O_5$: 291.1227.

*4.1.4.2. 3,6-Anhydro-2-deoxy-5,7-O-isopropylidene-7-C-phenyl-L-glycero-D-ido-heptono-1,4-lactone (**4a**)*

Yield 95%. Colourless powder (Et_2O/hexane, at −10 °C), mp 85 °C (Et_2O/light petroleum), $[\alpha]_D^{20}$ +44.6 (*c* 0.5, MeOH); R_f=0.33 (3:2 Et_2O/hexane). IR ($CHCl_3$): ν_{max} 1789 (C=O), 1499 (Ph). ^1H NMR ($CDCl_3$): δ 2.58 (dd, 1 H, $J_{2a,3}$=1.5, $J_{2a,2b}$=18.8 Hz, H-2a), 2.67 (dd, 1 H, $J_{2b,3}$=5.2, $J_{2a,2b}$=18.8 Hz, H-2b), 4.08 (t, 1 H**,** $J_{5,6}$=$J_{6,7}$=2.1 Hz, H-6), 4.67 (br s, 1 H, H-5), 4.69 (d, 1 H, $J_{3,4}$=4.3 Hz, H-4), 5.00 (m, 1 H, $J_{2b,3}$=5.4, $J_{2a,3}$=1.6, $J_{3,4}$=4.1 Hz, H-3), 5.11 (d, 1 H, $J_{6,7}$=1.8 Hz, H-7), 7.28–7.54 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$): δ 29.2 and 29.3 (C*Me*$_2$) 35.8 (C-2), 70.2 (C-7), 73.2 (C-5), 74.0 (C-6), 77.1 (C-3), 86.4 (C-4), 98.8 (*C*Me$_2$), 126.3, 127.7, 128.2, 137.9 (Ph), 175.3 (C-1). HRMS (ESI): *m/z* 291.1218 (M^++H), calcd for $C_{16}H_{19}O_5$: 291.1227.

*4.1.5. General procedure for O-methylidenation of **1** and **2***

Procedure A [25]. To a solution of **1** or **2** (1 equiv) in dry CH_3CN (0.02–0.03 M) was added paraformaldehyde (3 equiv) and TsOH×H_2O (0.5 equiv). The mixture was stirred at room temperature (20 h for **1**, 72 h for **2**) then neutralized with solid $NaHCO_3$ and evaporated with silica gel. The residue was purified by flash column chromatography (99:1 CH_2Cl_2/Me_2CO).

Procedure B [26]. To a stirred solution of **1** or **2** (1 equiv) in dry DMSO (0.06 M) was added $SOCl_2$ (14 equiv). The mixture was stirred at 65 °C for 1.5 h, then poured into 10% aq NaCl and extracted with EtOAc. The combined organic solutions were dried and evaporated and the residue was purified by flash column chromatography (99:1 CH_2Cl_2/Me_2CO).

*4.1.5.1. 3,6-Anhydro-2-deoxy-5,7-O-methylidene-7-C-phenyl-D-glycero-D-ido-heptono-1,4-lactone (**3b**)*

Yield: 48% (Procedure A); 38% (Procedure B). Colourless needles, mp 125 °C (CH_2Cl_2/hexane), $[\alpha]_D^{20}$ +182 (*c* 0.2, $CHCl_3$); R_f=0.32 (2:3 light petroleum/Et_2O). IR (film): ν_{max} 1789 (C=O), 1497

(Ph). ^{1}H NMR ($CDCl_3$): δ 2.77 (br d, 1 H, $J_{2a,2b}$=18.7 Hz, H-2a), 2.85 (dd, 1 H, $J_{2a,2b}$=18.8, $J_{2b,3}$=5.1 Hz, H-2b), 4.47 (t, 1 H, $J_{5,6}$=$J_{6,7}$=2.3 Hz, H-6), 4.53 (br s, 1 H, H-5), 4.83 and 4.89 (2×d, 1 H each, J_{gem}=6.1 Hz, CH_2), 4.99 (d, 1 H, $J_{3,4}$=4.3 Hz, H-4), 5.10–5.22 (m, 2 H, H-7 and H-3), 7.31–7.51 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$): δ 35.9 (C-2), 73.8 (C-7), 75.2 (C-3), 76.5 (C-6), 77.1 (C-5), 86.1 (C-4), 86.8 (*C*H_2), 127.5, 128.3, 128.8 and 136.5 (Ph), 175.0 (C-1). HRMS (ESI): *m/z* 280.1175 (M^++NH_4), calcd for $C_{14}H_{18}NO_5$: 280.1180.

*4.1.5.2. 1,3,5-Trioxaepane **3c***

Yield: 49% (Procedure A); 51% (Procedure B). Colourless needles, mp 188 °C (CH_2Cl_2/hexane), $[\alpha]_D^{20}$ −65.0 (*c* 0.1, $CHCl_3$); R_f=0.27 (2:3 light petroleum/Et_2O). IR (film): ν_{max} 1775 (C=O), 1603 and 1495 (Ph). ^{1}H NMR ($CDCl_3$): δ 2.57 (br d, 1 H, $J_{2a,2b}$=18.2 Hz, H-2a), 2.68 (dd, 1 H, $J_{2a,2b}$=18.6, $J_{2b,3}$=4.7 Hz, H-2b), 4.26 (dd, 1 H, $J_{5,6}$=3.4, $J_{6,7}$=9.1 Hz, H-6), 4.62 (d, 1 H, $J_{5,6}$=3.4 Hz, H-5), 4.67 (d, 1 H, $J_{6,7}$=9.1 Hz, H-7), 4.77 and 4.82 (2×d, 1 H each, J_{gem}=6.8 Hz , CH_2-a), 4.92–5.03 (m, 2 H, H-3 and H-4), 5.06 and 5.11 (2×d, 1 H each, J_{gem}=6.8 Hz , CH_2-b), 7.29–7.46 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$): δ 36.1 (C-2), 77.8 (C-7), 78.0 (C-3), 81.4 (C-5), 83.3 (C-6), 86.9 (C-4), 94.8 and 94.9 (2×*C*H_2), 127.0, 128.2, 128.4 and 139.5 (Ph), 174.9 (C-1). HRMS (ESI): *m/z* 310.1278 (M^++NH_4), calcd for $C_{15}H_{20}NO_6$: 310.1285.

*4.1.5.3. 3,6-Anhydro-2-deoxy-5,7-O-methylidene-7-C-phenyl-L-glycero-D-ido-heptono-1,4-lactone (**4b**)*

Yield: 82% (Procedure A); 95% (Procedure B). Colourless needles, mp 195 °C (CH_2Cl_2/hexane), $[\alpha]_D^{20}$ +72.0 (*c* 0.1, $CHCl_3$); R_f=0.3 (1:2 light petroleum/Et_2O). IR (film): ν_{max} 1789 (C=O), 1497 (Ph). ^{1}H NMR ($CDCl_3$): δ 2.60 (dd, 1 H, $J_{2a,2b}$=18.8, $J_{2a,3}$=1.1 Hz, H-2a), 2.18 (dd, 1 H, $J_{2a,2b}$=18.9, $J_{2b,3}$=5.6 Hz, H-2b), 4.18 (t, 1 H, $J_{5,6}$=$J_{6,7}$=1.9 Hz, H-6), 4.55 (br s, 1 H, H-5), 4.89 (d, 1 H, $J_{6,7}$=1.7 Hz, H-7), 4.93 (d, 1 H, J_{gem}=6.6 Hz, CH_2-a), 4.95 (d, 1 H, $J_{3,4}$=4.7 Hz, H-4), 5.19 (m, 1 H, H-3), 5.24 (d, 1 H, J_{gem}=6.5 Hz, CH_2-b), 7.48–7.29 (m, 5 H, Ph). *NOE* contact: H-4 and H-5; *NOE* contact: H-7 and H-6. ^{13}C NMR ($CDCl_3$): δ 35.7 (C-2), 75.6 (C-6), 77.2 (C-7), 77.6 (C-3), 77.7 (C-5), 85.3 (C-4), 92.2 (*C*H_2), 126.0, 128.0, 128.3 and 137.1 (Ph), 175.2 (C-1). HRMS (ESI): *m/z* 280.1175 (M^++NH_4), calcd for $C_{14}H_{18}NO_5$: 280.1180.

*4.1.6. General procedure for the preparation of cyclic carbonates **4c** and **3d***

To a solution of **1** or **2** (1 equiv) in dry CH_3CN (0.03 M) was added 1,1′-carbonyldiimidazole (2 equiv) and the mixture was stirred at 46–48 °C (1.5 h for **1**, 2 h for **2**). After the mixture cooled to

room temperature it was concentrated and the residue purified by flash chromatography (24:1 CH_2Cl_2/Me_2CO for **3d**, 24:1 CH_2Cl_2/Me_2CO for **4c**).[†]

*4.1.6.1. 3,6-Anhydro-2-deoxy-5,7-O-carbonyl-7-C-phenyl-D-glycero-D-ido-heptono-1,4-lactone (**3d**)*

Yield 96%. Colourless needles, mp 165 °C (CH_2Cl_2/hexane), $[\alpha]_D^{20}$ +159.0 (*c* 0.1, CH_2Cl_2); R_f=0.48 (24:1 CH_2Cl_2/Me_2CO). IR (KBr): ν_{max} 1815 (C=O, cyclic carbonate), 1759 (C=O, lactone), 1499 (Ph). ^{1}H NMR ($CDCl_3$): δ 2.78 (d, 1 H, $J_{2a,2b}$=18.7 Hz, H-2a), 2.89 (dd, 1 H, $J_{2a,2b}$=18.9, $J_{2a,3}$=6.4 Hz, H-2b), 4.50 (t, 1 H, $J_{5,6}$=$J_{6,7}$=2.9 Hz, H-6), 4.97 (d, 1 H, $J_{5,6}$=2.9 Hz, H-5), 5.11 (d, 1 H, $J_{3,4}$=4.3 Hz, H-4), 5.18 (m, 1 H, H-3), 5.70 (d, 1 H, $J_{6,7}$=2.3 Hz, H-7), 7.23–7.58 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$): δ 35.5 (C-2), 75.2 (C-6), 77.9 (C-3), 79.6 (C-5), 79.7 (C-7), 84.8 (C-4), 124.9, 129.4, 134.5, 135.2 (Ph), 146.9 (*C*=O, cyclic carbonate), 173.6 (C-1). HRMS (ESI): *m/z* 294.0971 (M^++NH_4), calcd for $C_{14}H_{16}NO_6$: 294.0972.

*4.1.6.2. 3,6-Anhydro-2-deoxy-5,7-O-carbonyl-7-C-phenyl-L-glycero-D-ido-heptono-1,4-lactone (**4c**)*

Yield 73%. Colourless needles, mp 223 °C (CH_2Cl_2/$CHCl_3$), $[\alpha]_D^{20}$ +85.0 (*c* 0.1, CH_2Cl_2); R_f=0.32 (24:1 CH_2Cl_2/Me_2CO). IR (KBr): ν_{max} 1794 (C=O, cyclic carbonate), 1732 (C=O, lactone), 1502 (Ph). ^{1}H NMR (DMSO-d_6): δ 2.52 (d, 1 H, $J_{2a,2b}$=18.7 Hz, H-2a), 2.92 (dd, 1 H, $J_{2a,2b}$=18.9, $J_{2a,3}$=6.6 Hz, H-2b), 4.77 (br s, 1 H, H-6), 5.01 (m, 1 H, H-3), 5.17 (d, 1 H, $J_{3,4}$=4.5 Hz, H-4), 5.37 (d, 1 H, $J_{4,5}$=3.1 Hz, H-5), 5.90 (br s, 1H, H-7) and 7.30–7.56 (m, 5 H, Ph). ^{13}C NMR (DMSO-d_6): δ 35.3 (C-2), 72.8 (C-6), 77.2 (C-7), 78.0 (C-3), 81.8 (C-5), 84.7 (C-4), 126.7, 128.5, 128.7, 135.2 (Ph), 146.9 (*C*=O, cyclic carbonate), 175.1 (C-1). HRMS (ESI): *m/z* 294.0970 (M^++NH_4), calcd for $C_{14}H_{16}NO_5$: 294.0972.

*4.1.7. (7S)-3,6-anhydro-2-deoxy-7-C-hydroxy-5,7-O-methylene-D-ido-heptono-1,4-lactone (**12**)*

A solution of **11** [29] (0.33 g, 1.62 mmol) and H_5IO_6 (0.331 g, 1.45 mmol) in dry CH_3CN (30 mL) was stirred at room temperature for 20 h. The mixture was evaporated, and the residue purified by flash column chromatography (9:1 CH_2Cl_2/Me_2CO). Pure **12** (0.26 g, 80%) was isolated as a white glassy solid. Recrystallization from Me_2CO/hexane gave cloudy needles, mp 152–153 °C, $[\alpha]_D^{20}$ +130.0 (*c* 0.25, Me_2CO); R_f=0.31 (9:1 CH_2Cl_2/Me_2CO). IR (KBr): ν_{max} 3338 (OH), 1763 (C=O). ^{1}H

[†] Anhydrous solvents must be used as eluents for flash column chromatography. Otherwise, it may cause a significant drop in yield.

NMR ($CDCl_3$): δ 2.53 (dd, 1 H, $J_{2a,2b}$=18.7, $J_{2a,3}$=1.4 Hz, H-2a), 2.92 (dd, 1 H, $J_{2a,2b}$=18.7, $J_{2b,3}$=6.1 Hz, H-2b), 3.71 (d, 1 H, $J_{5,6}$=2.7 Hz, H-6), 4.48 (br s, 1 H, H-5), 4.61 (d, 1 H, J_{gem}=6.3 Hz, CH_2-a), 4.92 (d, 1 H, $J_{3,4}$=4.1 Hz, H-4), 5.02 (m, 1 H, H-3), 5.15–5.25 (m, 2 H, H-7 and CH_2-b), 5.95 (d, 1 H, $J_{7,OH}$=4.3 Hz, OH). ^{13}C NMR ($CDCl_3$): δ 36.1 (C-2), 75.9 (C-5), 76.1 (C-6), 78.5 (C-3), 83.6 (*C*H_2), 86.3 (C-4), 90.2 (C-7), 175.8 (C-1). HRMS (ESI): *m/z* 220.0816 (M^++NH_4), calcd for $C_8H_{14}NO_6$: 220.0816.

*4.1.8. (7S)- (**5a**) and (7R)-3,6-anhydro-2-deoxy-7-C-cinnamoyloxy-5,7-O-methylene-D-ido-heptono-1,4-lactone (**6a**)*

To a cooled (0 °C) and stirred solution of **12** (0.12 g, 0.59 mmol) and *trans*-cinnamoyl chloride (0.148 g, 0.89 mmol) in dry CH_3CN (5 mL) was added DMAP (0.145 g, 1.19 mmol). The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 2 h. The mixture was poured into 5% aq NaCl (100 mL) and extracted with CH_2Cl_2 (2×30 mL) and EtOAc (30 mL). The combined organic solutions were dried and evaporated and the residue was purified by flash column chromatography (9:1 toluene/EtOAc). Eluted first was pure **5a** (0.12 g, 61%) isolated as a colourless solid. Recrystallization from CH_2Cl_2/hexane gave colourless needles, mp 180 °C, $[\alpha]_D^{20}$ +205.8 (*c* 0.5, $CHCl_3$); R_f=0.33 (4:1 toluene/EtOAc). IR (film): ν_{max} 1793 (C=O, lactone), 1724 (C=O, cinnamate), 1636 (C=C, cinnamate), 1578 and 1497 (Ph). ^{1}H NMR ($CDCl_3$): δ 2.70 (br d, 1 H, $J_{2a,2b}$=18.2 Hz, H-2a), 2.82 (dd, 1 H, $J_{2a,2b}$=18.9, $J_{2b,3}$=5.4 Hz, H-2b), 3.90 (br s, 1 H, H-6), 4.65 (br s, 1 H, H-5), 4.82 (d, 1 H, J_{gem}=6.5 Hz, CH_2-a), 4.96 (d, 1 H, $J_{3,4}$=4.2 Hz, H-4), 5.12 (m, 2 H, H-3 and CH_2), 5.29 (s, 2 H, CH_2Cl_2), 6.32 (s, 1 H, H-7), 6.46 (d, 1 H, $J_{2',3'}$=16.1 Hz, H-2′), 7.33–7.61 (m, 5 H, Ph), 7.77 (d, 1 H, $J_{2',3'}$=16.1 Hz, H-3′). ^{13}C NMR ($CDCl_3$): δ 35.6 (C-2), 53.5 (CH_2Cl_2), 73.5 (C-6), 75.5 (C-5), 77.8 (C-3), 85.2 (*C*H_2), 85.4 (C-4), 88.2 (C-7), 116.5 (C-2′), 128.3, 129.0, 130.9, 133.8 (Ph), 147.0 (C-3′), 164.4 (*C*=O, cinnamate), 174.6 (C-1). HRMS (ESI): *m/z* 371.0545 (M^++K), calcd for $C_{17}H_{16}KO_7$: 371.0528.

Eluted second was pure **6a** (0.05 g, 25%). Recrystallization from CH_2Cl_2/hexane gave colourless powder, mp 176–177 °C, $[\alpha]_D^{20}$ +6.8 (*c* 0.25, Me_2CO); R_f=0.27 (4:1 toluene/EtOAc). IR (KBr): ν_{max} 1793 (C=O, lactone), 1732 (C=O, cinnamate), 1636 (C=C, cinnamate), 1578 and 1497 (Ph). ^{1}H NMR ($CDCl_3$): δ 2.81 (d, 2 H, $J_{2,3}$=3.4 Hz, H-2), 4.18 (t, 1 H, $J_{5,6}$=$J_{6,7}$=1.8 Hz, H-6), 4.61 (br s, 1 H, H-5), 4.91–4.98 (m, 2 H, H-4 and CH_2), 5.12 (d, 1 H, J_{gem}=6.9 Hz, CH_2), 5.20 (m, 1 H, H-3), 6.15 (d, 1 H, $J_{6,7}$=1.6 Hz, H-7), 6.54 (d, 1 H, $J_{2',3'}$=16.0 Hz, H-2′),7.59–7.32 (m, 5 H, *J*=8.8 Hz, Ph), 7.82 (d, 1 H, $J_{2',3'}$=16.1 Hz, H-3′). ^{13}C NMR ($CDCl_3$): δ 35.6 (C-2), 73.9 (C-6), 78.3 (C-5), 78.6 (C-3),

84.7 (C-4), 90.2 (*C*H_2), 90.6 (C-7), 116.2 (C-2′), 128.3, 128.9, 130.9, 133.8 (Ph), 147.5 (C-3′), 164.6 (C-1′), 174.6 (C-1). HRMS (ESI): *m/z* 350.1236 (M^++NH_4), calcd for $C_{17}H_{20}NO_7$: 350.1234.

*4.1.9. (7S)- (**5b**) and (7R)-3,6-anhydro-2-deoxy-7-C-(trans-4-fluorocinnamoyloxy)-5,7-O-methylene-D-ido-heptono-1,4-lactone (**6b**)*

Procedure A. To a stirred solution of **12** (0.065 g, 0.32 mmol) in dry CH_2Cl_2 (7 mL) were added successively *trans*-4-fluorocinnamic acid (0.123 g, 0.74 mmol), DCC (0.161 g, 0.78 mmol) and DMAP (0.181 g, 1.48 mmol). The mixture was stirred at room temperature for 24 h, then poured in water (100 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined extracts were washed with 10% aq NaCl (100 mL), dried and evaporated. Flash column chromatography (9:1 toluene/EtOAc) of the residue afforded pure **5b** (0.068 g, 60%) as a colourless glassy solid.

Procedure B. To a cooled (0 °C) and stirred solution of **12** (0.075 g, 0.37 mmol), Ph_3P (0.214 g, 0.82 mmol) and *trans*-4-fluorocinnamic acid (0.117 g, 0.7 mmol) in dry CH_3CN (10 mL) was added 40% DEAD in toluene (0.32 mL, 0.74 mmol). The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 1 h. The mixture was concentrated and the residue purified on a column of flash silica (22:3 toluene/EtOAc). Eluted first was pure **5b** (0.026 g, 20%), which crystallized from CH_2Cl_2/hexane in the form of colourless needles, mp 190–191 °C, $[\alpha]_D^{20}$ +221.4 (*c* 0.5, Me_2CO); R_f=0.37 (4:1 toluene/EtOAc). IR (KBr): ν_{max} 1789 (C=O, lactone), 1725 (C=O, cinnamate), 1638 (C=C, cinnamate), 1600 (Ph). ^{1}H NMR ($CDCl_3$): δ 2.71 (br d, 1 H, $J_{2a,2b}$=18.6 Hz, H-2a), 2.82 (dd, 1 H, $J_{2a,2b}$=18.9, $J_{2b,3}$=5.4 Hz, H-2b), 3.89 (br s, 1 H, H-6), 4.65 (br s, 1 H, H-5), 4.83 (d, 1 H, J_{gem}=6.5 Hz, C*H*$_2$-a), 4.97 (d, 1 H, $J_{3,4}$=4.2 Hz, H-4), 5.07–5.17 (m, 2 H, H-3 and C*H*$_2$-b), 6.31 (s, 1 H, H-7), 6.39 (d, 1 H, $J_{2',3'}$=16.0 Hz, H-2′), 7.11 and 7.55 (2×m, 4 H, Ph), 7.73 (d, 1 H, $J_{2',3'}$=16.0 Hz, H-3′). ^{13}C NMR ($CDCl_3$): δ 35.6 (C-2), 73.5 (C-6), 75.5 (C-5), 77.7 (C-3), 85.1 (*C*H_2), 85.4 (C-4), 88.3 (C-7), 116.4 (C-2′), 116.0, 116.2, 116.4, 130.1, 130.2, 130.3, 162.2, 166.2 (Ph), 145.6 (C-3′), 164.7 (C-1′), 174.6 (C-1). HRMS (ESI): *m/z* 368.1147 (M^++NH_4), calcd for $C_{17}H_{19}FNO_7$: 368.1140. Eluted second was pure **6b** (0.059 g, 45%). Crystallization from CH_2Cl_2/hexane gave colourless powder, mp 194–195 °C, $[\alpha]_D^{20}$ +10.4 (*c* 0.25, Me_2CO); R_f=0.30 (4:1 toluene/EtOAc). IR (KBr): ν_{max} 1792 (C=O, lactone), 1732 (C=O, cinnamate), 1637 (C=C, cinnamate), 1600 (Ph). ^{1}H NMR ($CDCl_3$): δ 2.81 (d, 2 H, $J_{2,3}$=3.3 Hz, H-2), 4.17 (br s, 1 H, H-6), 4.61 (br s, 1 H, H-5), 4.89–5.00 (m, 2 H, H-4 and C*H*$_2$-a), 5.12 (d, 1 H, J_{gem}=6.8 Hz, C*H*$_2$-b), 5.20 (m, 1 H, H-3), 6.14 (d, 1 H, $J_{6,7}$=1.4 Hz, H-7), 6.45 (d, 1 H, $J_{2',3'}$=16.0 Hz, H-2′), 7.09 and 7.53 (2×m, 4 H, Ph), 7.78 (d, 1 H, $J_{2',3'}$=16.0 Hz, H-3′). *NOE* contact: H-5 and H-7. ^{13}C NMR ($CDCl_3$): δ 35.6 (C-2), 73.9 (C-6), 78.5 (C-5), 78.6 (C-3), 84.7 (C-4), 90.2 (*C*H_2), 90.6 (C-7), 116.3 (C-2′), 115.88, 115.91, 116.0, 130.0,

130.1, 130.2, 130.4, 162.2, 166.2 (Ph), 146.1 (C-3′), 164.5 (C-1′), 174.6 (C-1). HRMS (ESI): *m/z* 368.1133 (M^++NH_4), calcd for $C_{17}H_{19}FNO_7$: 368.1140.

*4.1.10. (7S)- (**5c**) and (7R)-3,6-anhydro-2-deoxy-7-C-(trans-4-nitrocinnamoyloxy)-5,7-O-methylene-D-ido-heptono-1,4-lactone (**6c**)*

To a cooled (0 °C) and stirred solution of **12** (0.115 g, 0.57 mmol) and *trans*-4-nitrocinnamoyl chloride (0.157 g, 0.74 mmol) in dry CH_3CN (5 mL) was added DMAP (0.108 g, 0.88 mmol). The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 1.5 h. A new portion of *trans*-4-nitrocinnamoyl chloride (0.157 g, 0.74 mmol) and DMAP (0.108 g, 0.88 mmol) was added and stirring at room temperature was continued for additional 1 h. The mixture was poured into 5% aq NaCl (100 mL) and extracted with EtOAc (3×30 mL). The combined organic solutions were dried and evaporated and the residue purified by flash column chromatography (49:1 CH_2Cl_2/Me_2CO). Eluted first was pure **5c** (0.136 g, 63%). Recrystallization from CH_2Cl_2/hexane gave white flakes, mp 198–200 °C, $[\alpha]_D^{20}$ +225.8 (*c* 0.5, Me_2CO); R_f=0.32 (4:1 toluene/EtOAc). IR (KBr): ν_{max} 1780 (C=O, lactone), 1717 (C=O, cinnamate), 1633 (C=C, cinnamate), 1604 (Ph), 1514 (NO_2). ^{1}H NMR ($CDCl_3$): δ 2.72 (d, 1 H, $J_{2a,2b}$=17.8 Hz, H-2a), 2.84 (dd, 1 H, $J_{2a,2b}$=17.9, $J_{2b,3}$=5.4 Hz, H-2b), 3.90 (br s, 1 H, H-6), 4.66 (br s, 1 H, H-5), 4.85 (d, 1 H, J_{gem}=6.5 Hz, CH_2-a), 4.98 (d, 1 H, $J_{3,4}$=4.1 Hz, H-4), 5.11 (d, 1 H, J_{gem}=6.6 Hz, C*H*$_2$-b), 5.15 (m, 1 H, H-3), 6.33 (s, 1 H, H-7), 6.59 (d, 1 H, $J_{2',3'}$=16.0 Hz, H-2′), 7.72 and 8.27 (2×d, 4 H, *J*=8.8 Hz, Ph), 7.79 (d, 1 H, $J_{2',3'}$=16.1 Hz, H-3′). ^{13}C NMR ($CDCl_3$): δ 35.6 (C-2), 73.4 (C-6), 75.5 (C-5), 77.8 (C-3), 85.2 (*C*H_2), 85.4 (C-4), 88.7 (C-7), 120.8 (C-2′), 124.2, 128.9, 139.8, 148.8 (Ph), 143.9 (C-3′), 163.5 (C-1′), 174.6 (C-1). HRMS (ESI): *m/z* 395.1085 (M^++NH_4), calcd for $C_{17}H_{19}N_2O_9$: 395.1085. Eluted second was the minor stereoisomer **6c** (0.07 g, 33%). Recrystallization from CH_2Cl_2/hexane gave colourless powder, mp 232–233 °C, $[\alpha]_D^{20}$ −1.6 (*c* 0.5, Me_2CO); R_f=0.22 (4:1 toluene/EtOAc). IR (KBr): ν_{max} 1794 (C=O, lactone), 1745 (C=O, cinnamate), 1640 (C=C, cinnamate), 1522 (NO_2), 1603 (Ph). ^{1}H NMR ($CDCl_3$): δ 2.82 (d, 2 H, $J_{2,3}$=4.4 Hz, H-2), 4.18 (t, 1 H, $J_{5,6}$=$J_{6,7}$=1.9 Hz, H-6), 4.63 (br s, 1 H, H-5), 4.94 (d, 1 H, J_{gem}=6.9 Hz, C*H*$_2$-a), 4.97 (dd, 1 H, $J_{3,4}$=4.3, $J_{4,5}$=0.6 Hz, H-4), 5.13 (d, H, J_{gem}=6.9 Hz, C*H*$_2$-b), 5.21 (m, 1 H, H-3), 6.15 (d, 1 H, $J_{6,7}$=1.7 Hz, H-7), 6.65 (d, 1 H, $J_{2',3'}$=16.0 Hz, H-2′), 7.70 and 8.261 (2×d, 4 H, *J*=8.8 Hz, Ph), 7.84 (d, 1 H, $J_{2',3'}$=16.1 Hz, H-3′). *NOE* contact: H-5 and H-7. ^{13}C NMR ($CDCl_3$): δ 35.6 (C-2), 73.8 (C-6), 78.4 (C-5), 78.6 (C-3), 84.7 (C-4), 90.3 (**C**H_2), 91.0 (C-7), 120.6 (C-2′), 124.2, 128.9, 139.8 (Ph), 144.3 (C-3′), 163.7 (C-1′), 174.5 (C-1). HRMS (ESI): *m/z* 400.0639 (M^++Na), calcd for $C_{17}H_{15}NNaO_9$: 400.0639.

*4.1.11. (7S)- (**5d**) and (7R)-3,6-anhydro-2-deoxy-7-C-(trans-4-methoxycinnamoyloxy)-5,7-O-*

*methylene-D-ido-heptono-1,4-lactone (**6d**)*

Procedure A. To a stirred solution of **12** (0.125 g, 0.62 mmol) in dry CH_2Cl_2 (15 mL) were added successively *trans*-4-methoxycinnamic acid (0.23 g, 1.29 mmol), DCC (0.323 g, 1.57 mmol) and DMAP (0.32 g, 2.61 mmol). The mixture was stirred at room temperature for 20 h, then suspended in water (100 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic solutions were washed with 10% aq NaCl (100 mL), dried and evaporated. Flash column chromatography (9:1 toluene/EtOAc) of the residue gave pure **5d** (0.135 g, 60%) as a colourless solid. Recrystallization from CH_2Cl_2/hexane gave colourless needles, mp 182–183 °C, $[\alpha]_D^{20}$ +303.6 (*c* 0.25, Me_2CO); R_f=0.33 (4:1 toluene/EtOAc).

Procedure B. To a cooled (0 °C) and stirred solution of **12** (0.08 g, 0.39 mmol), Ph_3P (0.285 g, 1.09 mmol) and *trans*-4-methoxycinnamic acid (0.167 g, 0.94 mmol) in dry CH_3CN (12 mL) was added 40% DEAD in toluene (0.43 mL, 0.99 mmol). The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 1 h. The mixture was evaporated and the residue purified by flash column chromatography (99:1 → 49:1 CH_2Cl_2/Me_2CO). Eluted first was pure **5d** (0.015 g, 10%) as a colourless glassy solid. Recrystallization from CH_2Cl_2/hexane gave colourless needles, mp 181–182 °C, $[\alpha]_D^{20}$ +254.4 (*c* 0.25, Me_2CO); R_f=0.33 (4:1 toluene/EtOAc). IR (KBr): ν_{max} 1773 (C=O, lactone), 1710 (C=O, cinnamate), 1633 (C=C, cinnamate), 1604 (Ph). ^{1}H NMR ($CDCl_3$): δ 2.71 (br d, 1 H, $J_{2a,2b}$=18.5 Hz, H-2a), 2.82 (dd, 1 H, $J_{2a,2b}$=18.9, $J_{2b,3}$=5.4 Hz, H-2b), 3.84 (s, 3 H, CH_3), 3.89 (br s, 1 H, H-6), 4.65 (br s, 1 H, H-5), 4.83 (d, 1 H, J_{gem}=6.5 Hz, CH_2-a), 4.96 (d, 1 H, $J_{3,4}$=4.2 Hz, H-4), 5.07–5.17 (m, 2 H, H-3 and CH_2-b), 6.31 (s, 1 H, H-7), 6.32 (d, 1 H, $J_{2',3'}$=16.0 Hz, H-2′), 6.93 and 7.51 (2×d, 4 H, Ph), 7.73 (d, 1 H, $J_{2',3'}$=15.9 Hz, H-3′). ^{13}C NMR ($CDCl_3$): δ 35.6 (C-2), 55.4 (OCH_3), 73.6 (C-6), 75.5 (C-5), 77.7 (C-3), 85.1 (CH_2), 85.4 (C-4), 88.1 (C-7), 113.8 (C-2′), 114.4, 126.6, 130.1, 161.9 (Ph), 146.7 (C-3′), 164.7 (C-1′), 174.6 (C-1). HRMS (ESI): *m/z* 380.1339 (M^++NH_4), calcd for $C_{18}H_{22}NO_8$: 380.1340. Eluted second was pure **6d** (0.05 g, 35%). Recrystallization from CH_2Cl_2/hexane gave pure **6d** as colourless needles, mp 184 °C, $[\alpha]_D^{20}$ −0.8 (*c* 0.25, Me_2CO); R_f=0.23 (4:1 toluene/EtOAc). IR (KBr): ν_{max} 1788 (C=O, lactone), 1731 (C=O, cinnamate), 1632 (C=C, cinnamate), 1602 (Ph). ^{1}H NMR ($CDCl_3$): δ 2.82 (d, 2 H, $J_{2,3}$=3.4 Hz, H-2), 3.84 (s, 3 H, OCH_3), 4.17 (t, 1 H, $J_{5,6}$=$J_{6,7}$=1.8 Hz, H-6), 4.60 (br s, 1 H, H-5), 4.93 (d, 1 H, J_{gem}=6.9 Hz, CH_2-a), 4.95 (br d, 1 H, $J_{3,4}$=4.4 Hz, H-4), 5.11 (d, 1 H, J_{gem}=6.9 Hz, CH_2-b), 5.20 (m, 1 H, H-3), 6.14 (d, 1 H, $J_{6,7}$=1.6 Hz, H-7), 6.65 (d, 1 H, $J_{2',3'}$=15.9 Hz, H-2′), 6.91 and 7.50 (2×d, 4 H, *J*=8.7 Hz, Ph), 7.78 (d, 1 H, $J_{2',3'}$=15.9 Hz, H-3′). *NOE* contact: H-5 and H-7. ^{13}C NMR ($CDCl_3$): δ 35.6 (C-2), 55.4 (OCH_3), 74.0 (C-6), 78.3 (C-5), 78.5 (C-3), 84.7 (C-4), 90.2 (CH_2), 90.5 (C-7),

113.8 (C-2′), 114.4, 126.6, 130.1, 161.8 (Ph), 147.2 (C-3′), 165.0 (C-1′), 174.6 (C-1). HRMS (ESI): *m/z* 380.1339 (M^++NH_4), calcd for $C_{18}H_{22}NO_8$: 380.1340.

4.2. MTT assay

The colorimetric MTT assay was carried out following the procedure recently reported by us [34]**.**

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Appendix A. Supplementary material

CCDC 979783 contains the supplementary crystallographic data for structure **3a**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033).

Appendix B. Supplementary data

These data include modified experimental procedures for preparation of starting compounds (**7** and **8**), and copies of ^{1}H, and ^{13}C NMR spectra of the most important compounds described in this article. Additional crystallographic results are also included in this section. Supplementary data associated with this article can be found in online version.

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Captions

Figure 1. ORTEP presentation of compound **3a**.

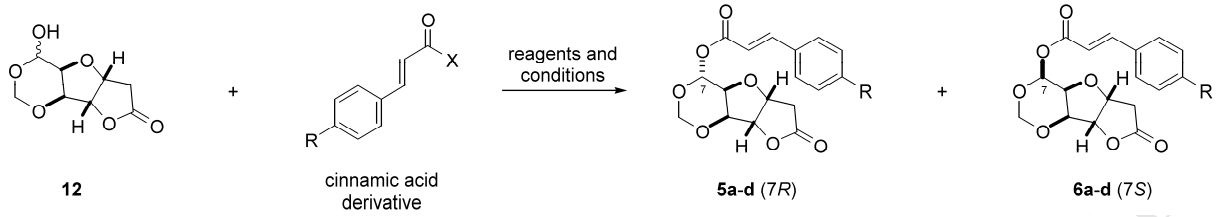
Scheme 1. Design of conformationally constrained (+)-goniofufurone and 7-*epi*-(+)-goniofufurone mimics **3** and **4**, as well as the corresponding cinnamic isosteres **5** and **6**, respectively.

Scheme 2. Reagents and conditions: (a) BnBr, NaH, DMF, 0 ºC for 0.5 h, then rt for 1.5 h; (b) 50% aq TFA, rt, 18 h; (c) Meldrum's acid, Et_3N, DMF, 44–46 ºC, 66 h; (d) H_2-Pd/C, MeOH, rt, 48 h, 39% from **7**, 48% from **8**; (e) H_5IO_6, PCC (cat), MeCN, 0 ºC, 2 h, 96%; (f) $NaBH_4$, L-tartaric acid, THF, reflux for 2 h, then cooled to −18 ºC added **10** and stirred for 20 h, 81% of **1**, 17% of **2**.

Scheme 3. Reagents and conditions: (a) $Me_2C(OMe)_2$, TsOH, Me_2CO, rt, 3.5 h for **1**, 4.5 h for **2**, 95% of **3a**, 95% of **4a**; (b) paraformaldehyde, TsOH, MeCN, rt, 20 h for **1**, 48% of **3b**, 49% of **3c**, 72 h for **2**, 82% of **4b**; (c) $SOCl_2$, DMSO, 65 ºC, 1.5 h, 38% of **3b**, 51% of **3c**, 95% of **4b**; (d) Imd_2CO, MeCN, 46–48 ºC, 1.5 h for **1**, 96% of **3d**, 2 h for **2**, 73% of **4c**.

Scheme 4. Reagents and conditions: (a) see references [27] and [28]; (b) H_5IO_6, MeCN, rt, 20 h, 80%.

Table 1. Preparation of (+)-goniofufurone and 7-*epi*-(+)-goniofufurone mimics **5a**–**d** and **6a**–**d**, respectively



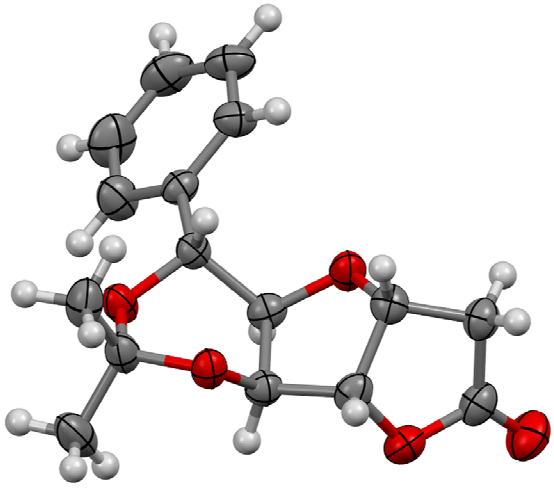
Entry	Cinnamic acid derivative	Reagents and conditions	Major product (isolated yield, %)	Minor product (isolated yield, %)
1	R = H, X = Cl	DMAP, MeCN, 0 °C for 0.5 h, then rt for 2 h	**5a** R = H (61)	**6a** R = H (25)
2	R = F, X = OH	DCC, DMAP, CH_2Cl_2, rt for 24 h	**5b** R = F (60)	—
3	R = F, X = OH	Ph_3P, DEAD, MeCN, 0 °C for 0.5 h, then rt for 1 h	**6b** R = F (45)	**5b** R = F (20)
4	R = NO_2, X = Cl	DMAP, MeCN, 0 °C for 0.5 h, then rt for 2.5 h	**5c** R = NO_2 (63)	**6c** R = NO_2 (33)
5	R = OMe, X = OH	DCC, DMAP, CH_2Cl_2, rt for 20 h	**5d** R = OMe (60)	—
6	R = OMe, X = OH	Ph_3P, DEAD, MeCN, 0 °C for 0.5 h, then rt for 1 h	**6d** R = OMe (35)	**5d** R = OMe (10)

Table 2. In vitro cytotoxicity of (+)-goniofufurone (**1**), 7-*epi*-(+)-goniofufurone (**2**), the corresponding mimics **3a–d**, **4a–c**, **5a–d**, **6a–d** and DOX

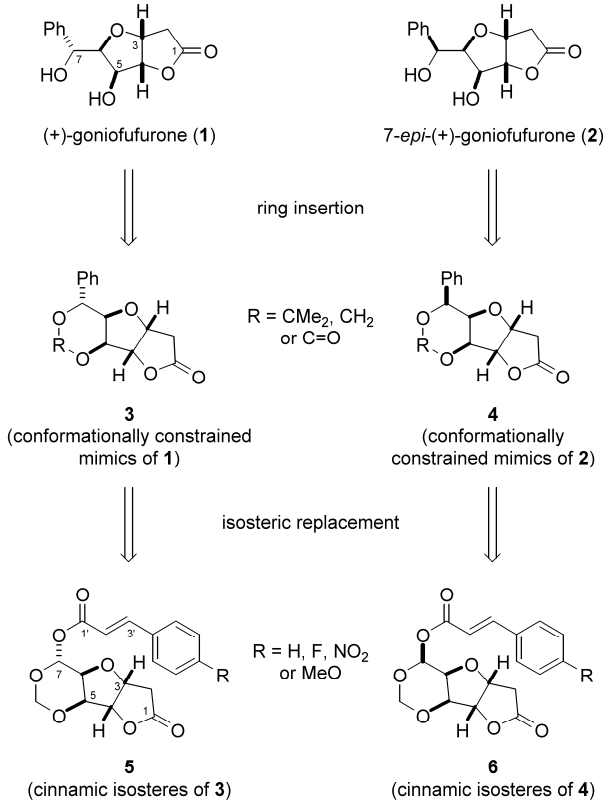
Compounds	IC_{50} (μM)[a]								
	K562	HL-60	Jurkat	Raji	MCF-7	MDA-MB 231	HeLa	Hs 294T	MRC-5
1	0.41	>100	32.45	18.45	16.59	75.34	8.32	>100	>100
3a	16.59	2.36	34.15	3.25	87.45	5.27	1.64	>100	>100
3b	>100	10.08	18.21	17.89	23.45	>100	18.87	35.64	>100
3c	>100	14.34	13.64	12.45	27.79	>100	12.36	45.32	>100
3d	5.59	33.78	11.52	25.31	1.01	2.37	14.26	>100	>100
5a	3.16	8.08	5.06	1.01	27.32	4.08	0.001	>100	>100
5b	>100	2.36	>100	5.78	>100	>100	0.02	0.002	>100
5c	>100	6.37	>100	20.01	3.64	1.01	8.79	>100	>100
5d	8.77	1.24	0.042	4.32	>100	>100	12.51	89.74	>100
2	0.028	22.02	18.64	1.25	9.24	58.7	0.89	43.58	>100
4a	0.17	1.25	22.51	1.01	1.06	24.89	9.75	>100	>100
4b	0.023	0.24	3.33	1.01	8.08	>100	3.02	>100	>100
4c	4.46	12.85	7.89	15.78	32.45	>100	5.67	>100	>100
6a	>100	8.45	>100	7.56	>100	2.36	0.23	2.53	>100
6b	4.32	12.07	15.47	87.23	32.22	5.69	11.69	>100	>100
6c	>100	35.38	>100	1.32	>100	>100	1.01	>100	>100
6d	3.68	25.61	12.01	69.24	51.79	3.03	2.21	>100	>100
DOX	0.25	0.92	0.03	2.98	0.20	0.09	0.065	4.50	0.10

[a] IC_{50} is the concentration of compound required to inhibit the cell growth by 50% compared to an untreated control. Values are means of three independent experiments. Coefficients of variation were less than 10%.

Figure 1.



Scheme 1.



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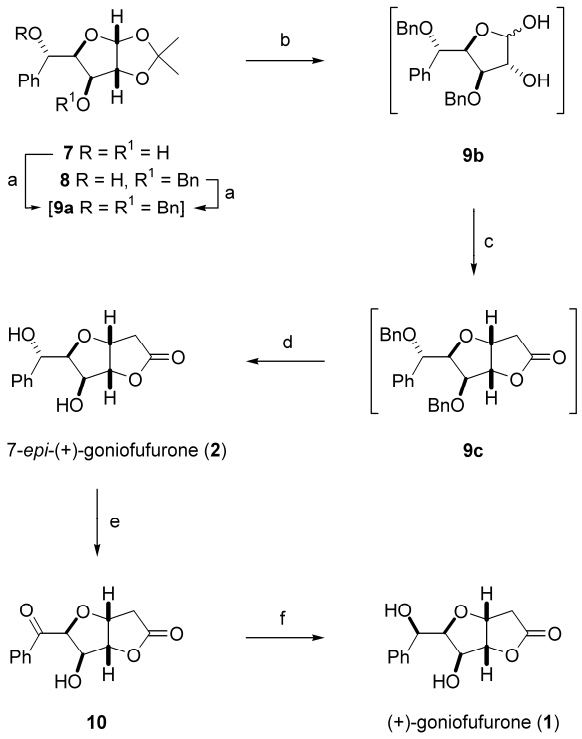

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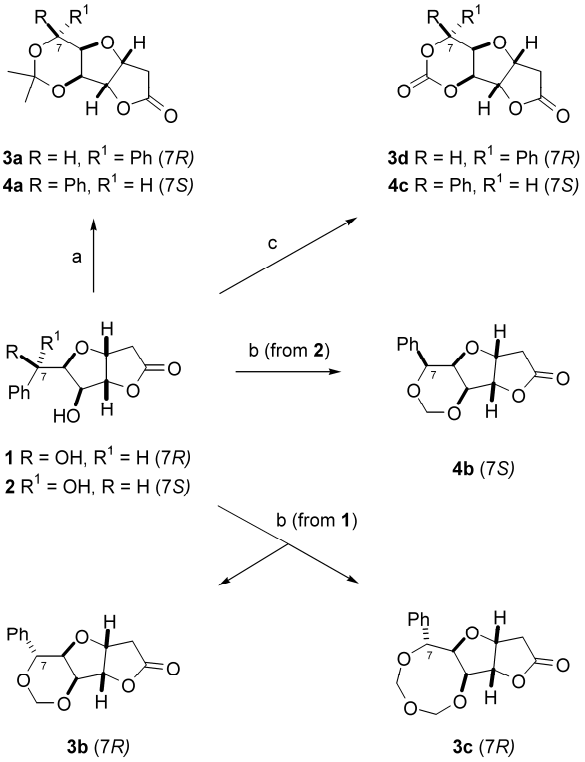

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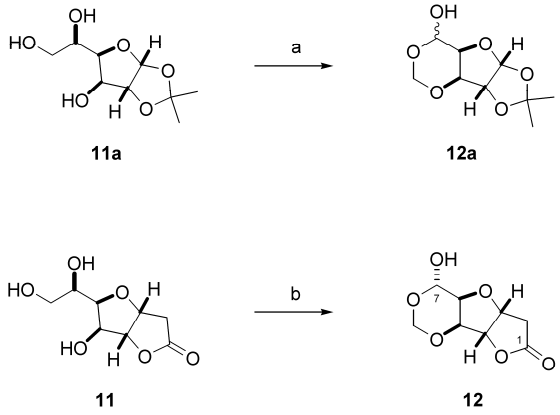
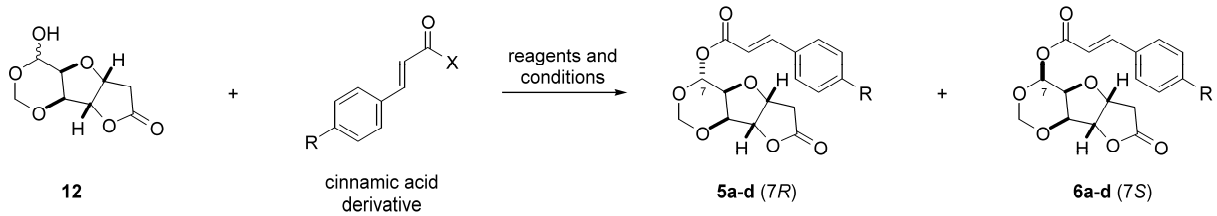


Table 1. Preparation of (+)-goniofufurone and 7-*epi*-(+)-goniofufurone mimics **5a**–**d** and **6a**–**d**, respectively



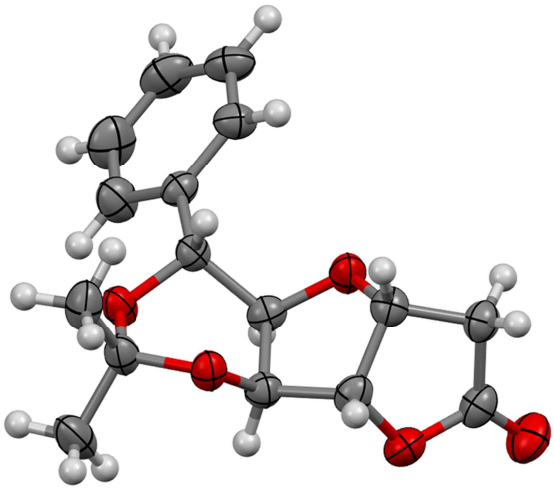
12 **5a-d** (7*R*) **6a-d** (7*S*)

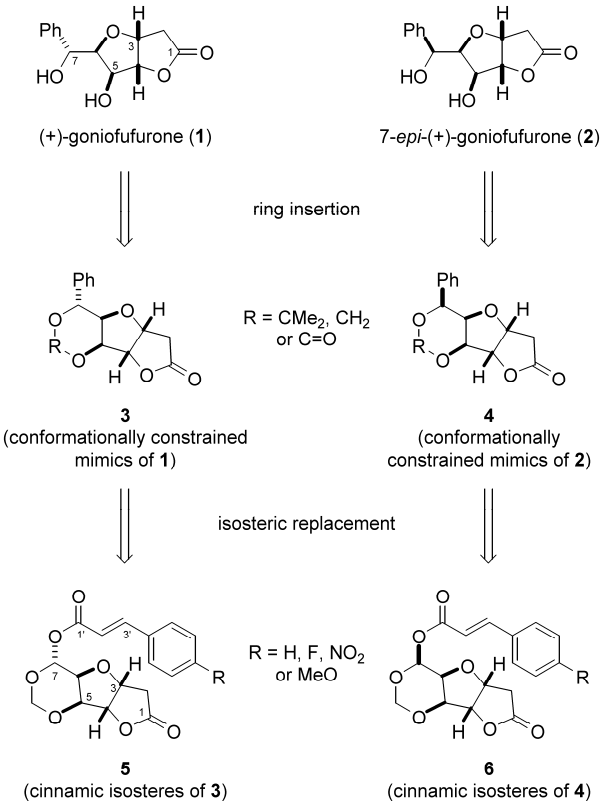
Entry	Cinnamic acid derivative	Reagents and conditions	Major product (isolated yield, %)	Minor product (isolated yield, %)
1	R = H, X = Cl	DMAP, MeCN, 0 °C for 0.5 h, then rt for 2 h	**5a** R = H (61)	**6a** R = H (25)
2	R = F, X = OH	DCC, DMAP, CH_2Cl_2, rt for 24 h	**5b** R = F (60)	—
3	R = F, X = OH	Ph_3P, DEAD, MeCN, 0 °C for 0.5 h, then rt for 1 h	**6b** R = F (45)	**5b** R = F (20)
4	R = NO_2, X = Cl	DMAP, MeCN, 0 °C for 0.5 h, then rt for 2.5 h	**5c** R = NO_2 (63)	**6c** R = NO_2 (33)
5	R = OMe, X = OH	DCC, DMAP, CH_2Cl_2, rt for 20 h	**5d** R = OMe (60)	—
6	R = OMe, X = OH	Ph_3P, DEAD, MeCN, 0 °C for 0.5 h, then rt for 1 h	**6d** R = OMe (35)	**5d** R = OMe (10)

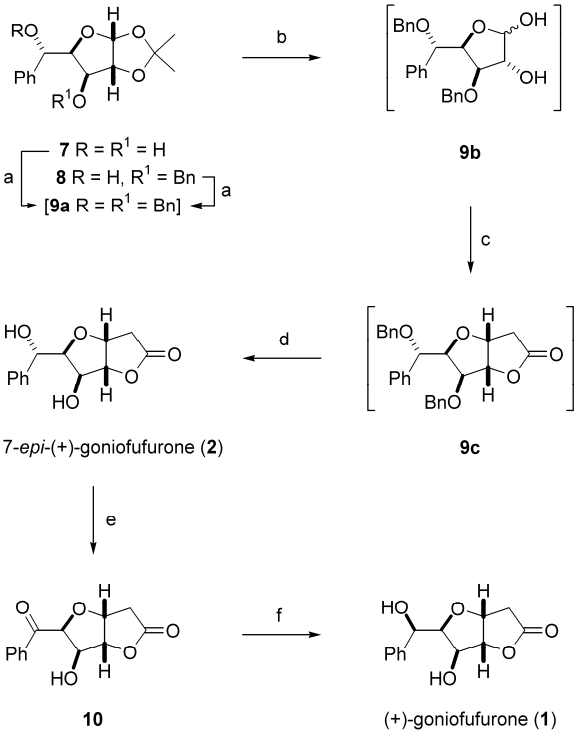
Table 2. In vitro cytotoxicity of (+)-goniofufurone (**1**), 7-*epi*-(+)-goniofufurone (**2**), the corresponding mimics **3a**–**d**, **4a**–**c**, **5a**–**d**, **6a**–**d** and DOX

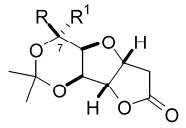
Compounds	IC_{50} (μM)[a]								
	K562	HL-60	Jurkat	Raji	MCF-7	MDA-MB 231	HeLa	Hs 294T	MRC-5
1	0.41	>100	32.45	18.45	16.59	75.34	8.32	>100	>100
3a	16.59	2.36	34.15	3.25	87.45	5.27	1.64	>100	>100
3b	>100	10.08	18.21	17.89	23.45	>100	18.87	35.64	>100
3c	>100	14.34	13.64	12.45	27.79	>100	12.36	45.32	>100
3d	5.59	33.78	11.52	25.31	1.01	2.37	14.26	>100	>100
5a	3.16	8.08	5.06	1.01	27.32	4.08	0.001	>100	>100
5b	>100	2.36	>100	5.78	>100	>100	0.02	0.002	>100
5c	>100	6.37	>100	20.01	3.64	1.01	8.79	>100	>100
5d	8.77	1.24	0.042	4.32	>100	>100	12.51	89.74	>100
2	0.028	22.02	18.64	1.25	9.24	58.7	0.89	43.58	>100
4a	0.17	1.25	22.51	1.01	1.06	24.89	9.75	>100	>100
4b	0.023	0.24	3.33	1.01	8.08	>100	3.02	>100	>100
4c	4.46	12.85	7.89	15.78	32.45	>100	5.67	>100	>100
6a	>100	8.45	>100	7.56	>100	2.36	0.23	2.53	>100
6b	4.32	12.07	15.47	87.23	32.22	5.69	11.69	>100	>100
6c	>100	35.38	>100	1.32	>100	>100	1.01	>100	>100
6d	3.68	25.61	12.01	69.24	51.79	3.03	2.21	>100	>100
DOX	0.25	0.92	0.03	2.98	0.20	0.09	0.065	4.50	0.10

[a] IC_{50} is the concentration of compound required to inhibit the cell growth by 50% compared to an untreated control. Values are means of three independent experiments. Coefficients of variation were less than 10%.

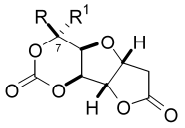








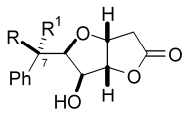
3a R = H, R^1 = Ph (7*R*)
4a R = Ph, R^1 = H (7*S*)



3d R = H, R^1 = Ph (7*R*)
4c R = Ph, R^1 = H (7*S*)

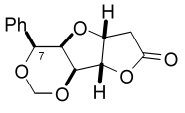
a

c



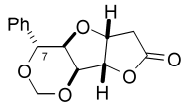
1 R = OH, R^1 = H (7*R*)
2 R^1 = OH, R = H (7*S*)

b (from **2**)

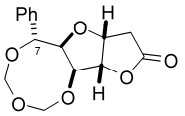


4b (7*S*)

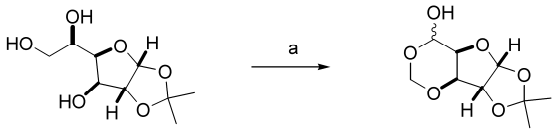
b (from **1**)



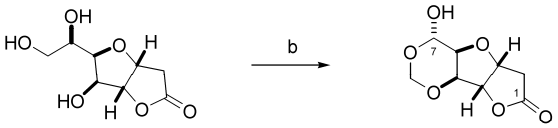
3b (7*R*)



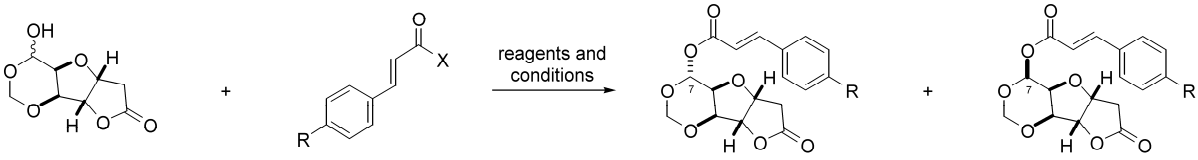
3c (7*R*)



11a **12a**



11 **12**



12 cinnamic acid derivative **5a-d** (7*R*) + **6a-d** (7*S*)

Highlights

► A series of conformationally constrained goniofufurone mimics were designed and synthesized.

► The in vitro antitumour activities were further evaluated.

► Some members showed high antitumor activity when compared to (+)-goniofufurone or 7-*epi*-goniofufurone as references.

SUPPLEMENTARY DATA

for

Conformationally constrained goniofufurone mimics as inhibitors of tumour cells growth: design, synthesis and SAR study

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[b] *Oncology Institute of Vojvodina, Put doktora Goldmana 4, 21204 Sremska Kamenica, Serbia*

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TABLE OF CONTENTS

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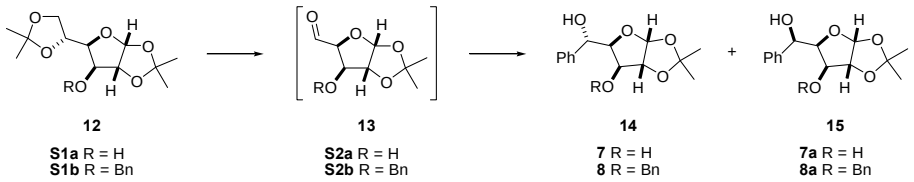
I. GENERAL PROCEDURE FOR THE PREPARATION OF 7 AND 8



To a solution of diacetonides **S1a** or **S1b** (1 equiv) in dry EtOAc (0.03–0.04 mmol) was added H_5IO_6 (1 equiv). The mixture was stirred at room temperature until the starting materials were consumed (TLC, 3.5 h for **S1a**, 6 h for **S1b**). The mixtures were filtered and evaporated and the remaining crude aldehydes **S2a** or **S2b** were dried in a vacuum dessicator for 2 h. To a stirred and cooled (0 °C) solution of **S2** in dry ether (0.03–0.04 mmol) was added a 3 M etheral solution of PhMgBr (10 equiv for **S2a**, 3 equiv for **S2b**). The mixture was stirred for 5 h at 0 °C, in an atmosphere of nitrogen, then allowed to worm up to room temperature, then poured into 10% aq NH_4Cl and extracted first with ether, then with EtOAc. The combined extracts were washed with 10% aq NaCl, organic phase was dried and evaporated and the residue purified by flash column chromatography.

1,2-*O*-Isopropylidene-5-*C*-phenyl-β-L-*ido*-pentofuranose (7)

Yield 60% (from **S1a**). Solvent for column chromatography: 2:1 Et_2O/light petroleum → Et_2O. Colorless needles, mp 166–168 °C (EtOH), $[\alpha]_D^{20}$ +14.9 (*c* 1.0, $CHCl_3$), lit.[1] mp 162–165 °C (EtOH), lit.[2] $[\alpha]_D^{20}$ +25.0 (*c* 1.1, $CHCl_3$); R_f=0.25 (1:1 toluene/EtOAc). IR (KBr): ν_{max} 3343 (OH), 1496 (Ph). ^{1}H and ^{13}C NMR spectral data in Table S1. HRMS (ESI): *m/z* 284.1488 (M^++NH_4), calcd for $C_{14}H_{22}NO_5$: 284.1492; *m/z* 289.1042 (M^++Na), calcd for $C_{14}H_{18}NaO_5$: 289.1046; *m/z* 305.0784 (M^++K), calcd for $C_{14}H_{18}KO_5$: 305.0786.

1,2-*O*-Isopropylidene-5-*C*-phenyl-α-D-*gluco*-pentofuranose (7a)

Yield 19% (from **S1a**). Solvent for column chromatography: 2:1 Et_2O/light petroleum → Et_2O. Colorless needles, mp 106–107 °C (Me_2CO/light petroleum), $[\alpha]_D^{20}$ −28.6 (*c* 0.5, $CHCl_3$), lit.[1] tt 104–106 °C (EtOH), lit.[2] $[\alpha]_D^{20}$ −26.0 (*c* 0.8, $CHCl_3$); R_f=0.32 (1:1 toluene/EtOAc). IR (film): ν_{max} 3407 (OH), 1496 (Ph). ^{1}H and ^{13}C NMR spectral data in Table S2. HRMS (ESI): *m/z* 284.1488 (M^++NH_4), calcd for $C_{14}H_{22}NO_5$: 284.1492; *m/z* 289.1042 (M^++Na), calcd for $C_{14}H_{18}NaO_5$: 289.1046; *m/z* 305.0785 (M^++K), calcd for $C_{14}H_{18}KO_5$: 305.0786.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*C*-phenyl-β-L-*ido*-pentofuranose (8)

Yield 68% (from **S1b**). Solvent for column chromatography: 3:1 → 1:1 Et_2O/light petroleum. Colorless oil, $[\alpha]_D^{20}$ −40.7 (*c* 1.0, $CHCl_3$), lit.[2] $[\alpha]_D^{20}$ −33.5 (*c* 2.0, $CHCl_3$); R_f=0.23 (3:2 light petroleum/Et_2O). IR (film): ν_{max} 3497 (OH). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.33 and 1.52 (2×s, 3 H each, C**Me**$_2$), 3.36 (br. s, 1 H, OH), 3.62 (d, 1 H, $J_{3,4}$=3.1 Hz, H-3), 4.26 and 4.52 (2×d, 1 H each, J_{gem}=11.5 Hz, PhC**H**$_2$), 4.39 (dd, 1 H, $J_{3,4}$=3.1, $J_{4,5}$=7.8 Hz, H-4), 4.61 (d, 1 H, $J_{1,2}$=3.8 Hz, H-2), 5.09 (d, 1 H, $J_{4,5}$=7.8 Hz, H-5), 6.04 (d, 1 H, $J_{1,2}$=3.8 Hz, H-1), 7.28–7.48 (m, 10 H, 2×Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 25.9 and 26.4 (2×C**Me**$_2$), 71.3 (Ph**C**H_2), 71.9 (C-5), 81.6 (C-2), 81.7 (C-3), 84.3 (C-4), 104.8 (C-1), 111.4

[1] R. Bruns, A. Wernicke, P. Köll, Tetrahedron 55 (1999) 9793–9800.
[2] T.D. Inch, Carbohydr. Res. 5 (1967) 45–52.

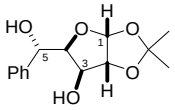
(**C**Me_2), 126.8, 127.3, 127.6, 127.7, 127.9, 128.1, 136.8, 139.6 (2×Ph). HRMS (ESI): *m/z* 374.1953 (M^++NH_4), calcd for $C_{21}H_{28}NO_5$: 374.1962; *m/z* 379.1509 (M^++Na), calcd for $C_{21}H_{24}NaO_5$: 379.1516; *m/z* 395.1252 (M^++K), calcd for $C_{21}H_{24}KO_5$: 395.1255.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*C*-phenyl-α-D-*gluco*-pentofuranose (8a)

Yield 2% (from **S1b**). Solvent for column chromatography: 3:1 → 1:1 Et_2O/light petroleum. Colorless oil, $[\alpha]_D^{20}$ −83.1 (*c* 1.0, $CHCl_3$), lit.[2] $[\alpha]_D^{20}$ −76.0 (*c* 1.0, $CHCl_3$); R_f=0.46 (3:2 light petroleum/Et_2O). IR (film): ν_{max} 3481 (OH). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.32 and 1.48 (2×s, 3 H svaki, C**Me**$_2$), 3.14 (br. s, 1 H, OH), 4.04 (d, 1 H, $J_{3,4}$=3.2 Hz, H-3), 4.35 (dd, 1 H, $J_{3,4}$=3.2, $J_{4,5}$=6.5 Hz, H-4), 4.49 i 4.69 (2×d, 1 H svaki, J_{gem}=11.5 Hz, PhC**H**$_2$), 4.63 (d, 1 H, $J_{1,2}$=3.9 Hz, H-2), 5.10 (d, 1 H, $J_{4,5}$=6.5 Hz, H-5), 6.03 (d, 1 H, $J_{1,2}$=3.9 Hz, H-1), 7.25–7.43 (m, 10 H, 2×Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 26.0 and 26.6 (2×C**Me**$_2$), 71.7 (C-5), 72.1 (Ph**C**H_2), 81.6 (C-2), 82.4 (C-4), 82.5 (C-3), 105.0 (C-1), 111.5 (**C**Me_2), 126.0, 127.5, 127.8, 128.17, 128.2, 128.6, 136.7, 141.3 (2×Ph). HRMS (ESI): *m/z* 374.1955 (M^++NH_4), calcd for $C_{21}H_{28}NO_5$: 374.1962; *m/z* 379.1508 (M^++Na), calcd for $C_{21}H_{24}NaO_5$: 379.1516; *m/z* 395.1251 (M^++K), calcd for $C_{21}H_{24}KO_5$: 395.1255.

II. COMPARISON OF NMR DATA OF KNOWN COMPOUNDS WITH REPORTED VALUES

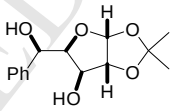
Table S1. NMR spectral data ($CDCl_3$) for 1,2-*O*-isopropylidene-5-*C*-phenyl-β-L-*ido*-pentofuranose (**7**)



7

C/H	This work		R. Bruns, A. Wernicke, P. Köll, Tetrahedron 55 (1999) 9793.	
	δ_H (*J*)	δ_C	δ_H (*J*)	δ_C
1	6.01 d (3.6)	104.9	5.97 d (3.8)	105.0
2	4.50 d (3.6)	85.4	4.47 d (3.8)	85.4
3	4.09 d (2.6)	76.0	4.05 d (2.5)	76.0
4	4.33 dd (2.7, 4.8)	82.6	4.30 dd (2.5, 5.1)	82.8
5	5.05 d (4.9)	72.6	5.11 d (5.1)	72.6
Me$_2$C	1.31 s and 1.47 s	26.2 and 26.8	1.28 s and 1.44 s	26.2 and 26.8
Me$_2$**C**		112.0		112.0
Ph	7.30–7.55	126.8, 128.3, 128.7, 140.0	7.27–7.47	126.8, 128.2, 128.6, 140.0

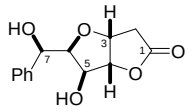
Table S2. NMR spectral data ($CDCl_3$) for 1,2-*O*-isopropylidene-5-*C*-phenyl-α-D-*gluco*-pentofuranose (**7a**)



7a

C/H	This work		R. Bruns, A. Wernicke, P. Köll, Tetrahedron 55 (1999) 9793.	
	δ_H (*J*)	δ_C	δ_H (*J*)	δ_C
1	6.01 d (3.6)	104.9	5.97 d (3.8)	104.8
2	4.48 d (3.6)	85.0	4.44 d (3.8)	84.9
3	4.14–4.22 m	75.3	4.14 d (2.5)	75.1
4		82.0	4.15 d (2.5)	82.1
5	5.25 d (3.9)	73.5	5.20 d (2.8)	73.1
Me$_2$C	1.29 s and 1. 45 s	26.1 and 26.6	1.26 s and 1. 42 s	25.9 i 26.6
Me$_2$**C**		111.7		111.6
Ph	7.28–7.51	125.9, 128.2, 128.7, 139.1	7.27–7.43	126.0, 128.1, 128.5, 139.6

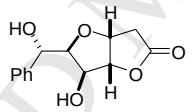
Table S3. NMR spectral data ($CDCl_3$) of (+)-goniofufurone (**1**)



1

C/H	This work		V. Popsavin, et al. Tetrahedron 65 (2009) 10596.	
	δ_H (*J*)	δ_C	δ_H (*J*)	δ_C
1		175.8		175.4
2a	2.63 d (18.8)	36.0	2.61 d (18.7)	36.1
2b	2.75 dd (18.8, 5.5)		2.74 dd (18.7, 5.6)	
3	5.11 dd (5.5, 4.3)	77.0	5.08 dd (5.6, 4.2)	77.3
4	4.85 d (4.3)	87.4	4.87 d (4.2)	87.4
5	4.45 d (2.6)	74.2	4.43 d (2.7)	74.4
6	4.02 dd (2.6, 5.3)	82.9	4.05 dd (2.7, 5.3)	82.9
7	5.14 d (5.3)	72.9	5.12 d (5.3)	73.5
Ph	7.32–7.46 m	126.0, 128.3, 128.6, 139.3	7.30–7.44 m	125.8, 128.5, 128.8, 138.8

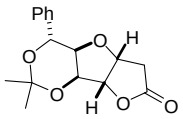
Table S4. NMR spectral data (DMSO-d_6) for 7-*epi*-(+)-goniofufurone (**2**)



2

C/H	This work		V. Popsavin, et al. Tetrahedron 65 (2009) 10596.	
	δ_H (*J*)	δ_C	δ_H (*J*)	δ_C
1		177.4		178.3
2a	2.53 d (18.7)	36.4	2.50 d (18.6)	36.7
2b	2.85 dd (18.7, 6.5)		2.85 dd (18.6, 6.4)	
3	4. 94 dd (4.7, 6.5)	77.4	4.93 dd (4.6, 6.4)	77.8
4	4.78 d (4.7)	88.5	4.78 d (4.6)	88.8
5	3.60 d (2.8)	73.5	3.59 d (2.8)	73.6
6	3.84 dd (2.8, 8.3)	85.4	3.82 dd (2.8, 7.9)	85.5
7	4.73 d (8.3)	72.2	4.73 d (7.9)	72.6
Ph	7.23–7.41 m	127.6, 128.3, 129.0, 141.4	7.20–7.38 m	127.9, 129.0, 129.4, 142.3

Table S5. NMR spectral data ($CDCl_3$) for 3,6-anhydro-2-deoxy-5,7-*O*-isopropylidene-7-*C*-phenyl-D-*glycero*-D-*ido*-heptono-1,4-lactone (**3a**)



3a

C/H	This work		S. Wang, et al. Chin. Chem. Lett. 12 (2001) 787.	
	δ_H (*J*)	δ_C	δ_H (*J*)	δ_C
1		174.5		174.5
2	2.72 d (2.8)	36.4	2.71 d (3.0)	36.5
3	5.07 m	78.3	5.06 m	78.3
4	4.96 d (3.7)	87.1	4.95 d (3.5)	87.0
5	4.67 d (4.6)	74.8	4.56 dd (8.0) [a]	74.8
6	4.45 dd (4.6, 8.1)	84.8	4.44 dd (4.5, 8.0)	84.9
7	4.57 d (8.1)	72.0	4.65 d (4.5) [a]	72.0
Me$_2$C	1.47 s and 1.49 s	24.0 and 24.4	1.46 s and 1.47 s	23.9 and 24.4
Me$_2$*C*		101.3		101.8
Ph	7.30–7.49 m	126.3, 128.0, 128.5, 139.2	7.31–7.41 m	126.3, 128.0, 128.5, 139.2

[a] The assignment of these signals should be mutually interchanged.

III. X-RAY CRYSTAL STRUCTURE DETERMINATION

Single crystals of the synthesized compounds were selected and glued on glass fiber. Diffraction data were collected on an Oxford Diffraction KM4 Gemini S four-circle goniometer equipped with Sapphire CCD detector. The frame widths of 1° in ω were used to acquire each frame. The crystal to detector distance was 45.0 mm and a graphite monochromated MoKα (λ = 0.71073 Å) X-radiation was employed. More than a hemisphere of three-dimensional data was collected in all measurements. The data were reduced using the Oxford Diffraction program *CrysAlisPro*. A semiempirical absorption-correction based upon the intensities of equivalent reflections was applied, and the data were corrected for Lorentz, polarization, and background effects. Scattering curves for neutral atoms, together with anomalous-dispersion corrections, were taken from *International Tables for X-ray Crystallography*.[3] The structures were solved by direct methods,[4] and the figures were drawn using *MERCURY*.[5] Refinements were based on F^2 values and done by full-matrix least-squares[6] methods. The middle stages of refinement included atomic positional and displacement parameters for all non-hydrogen atoms anisotropically. The positions of hydrogen atoms were found from the inspection of the difference Fourier maps. However, at the final stage of the refinement, H atoms belonging to molecules were positioned geometrically (O−H = 0.82 and C−H = 0.93–0.97 Å) and refined using a riding model with fixed isotropic displacement parameters.

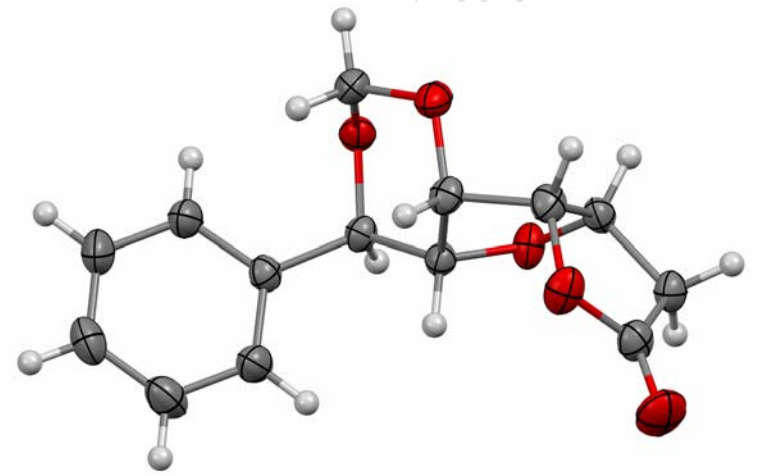


Figure S1. ORTEP presentation of compound **3b** [7]

[3] J.A. Ibers, W.C. Hamilton, *International Tables for X-ray Crystallography*, Kynoch Press, Birmingham: Birmingham, 1974.
[4] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, J. Appl. Cryst. 26 (1993) 343.
[5] C.F. Macrae, P.R. Edgington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler, J. Van de Streek, J. Appl. Cryst. 39 (2006) 453.
[6] G.M. Sheldrick, *SHELXL 97, Program for Refinement of Crystal Structures*; University of Göttingen: Göttingen, 1997.
[7] Crystallographic data for **3b** are deposited at the Cambridge Crystallographic Data Centre, the deposition number: CCDC 979780.

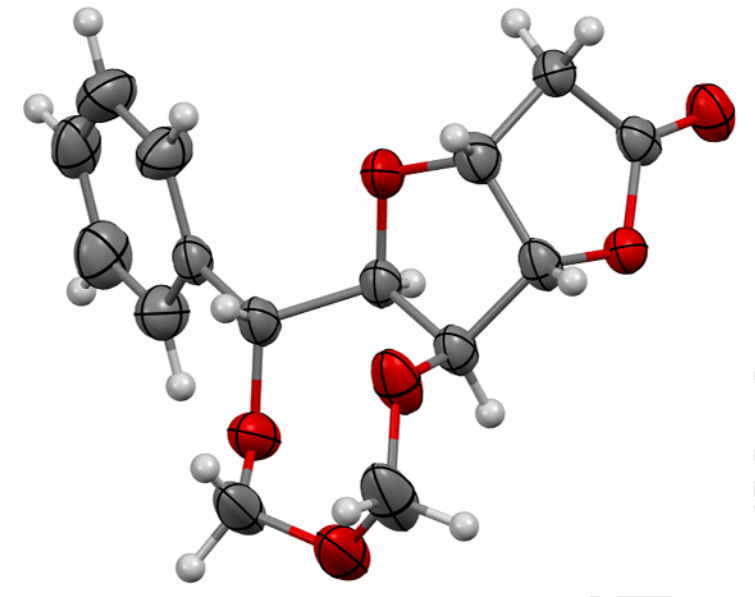


Figure S2. ORTEP presentation of compound **3c** [8]

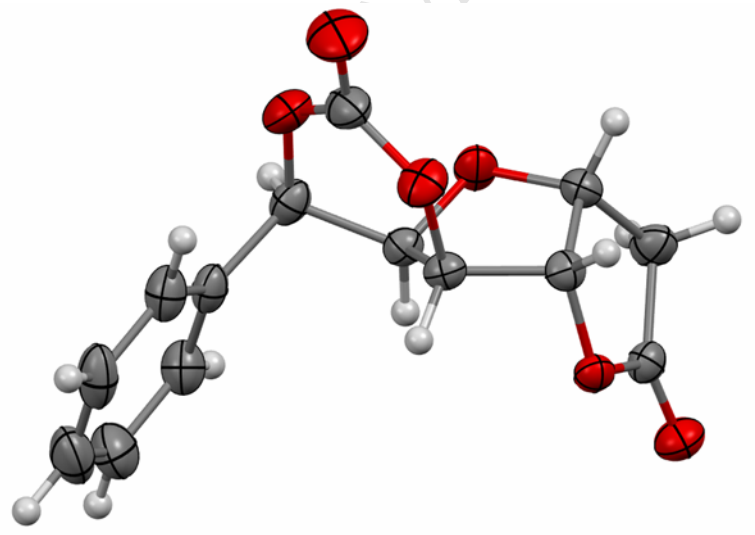


Figure S3. ORTEP presentation of compound **3d** [8]

[8] Crystallographic data for **3c** and **3d** are deposited at the Cambridge Crystallographic Data Centre, the deposition numbers: CCDC 979781 and CCDC 979779, respectively.

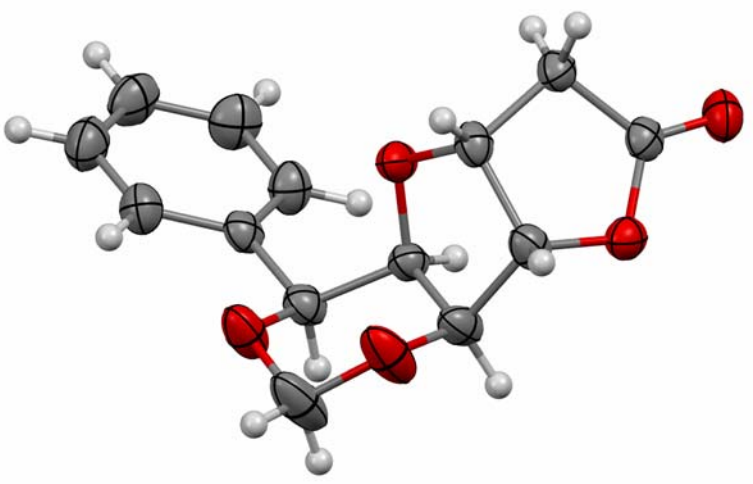


Figure S4. ORTEP presentation of compound **4b** [9]

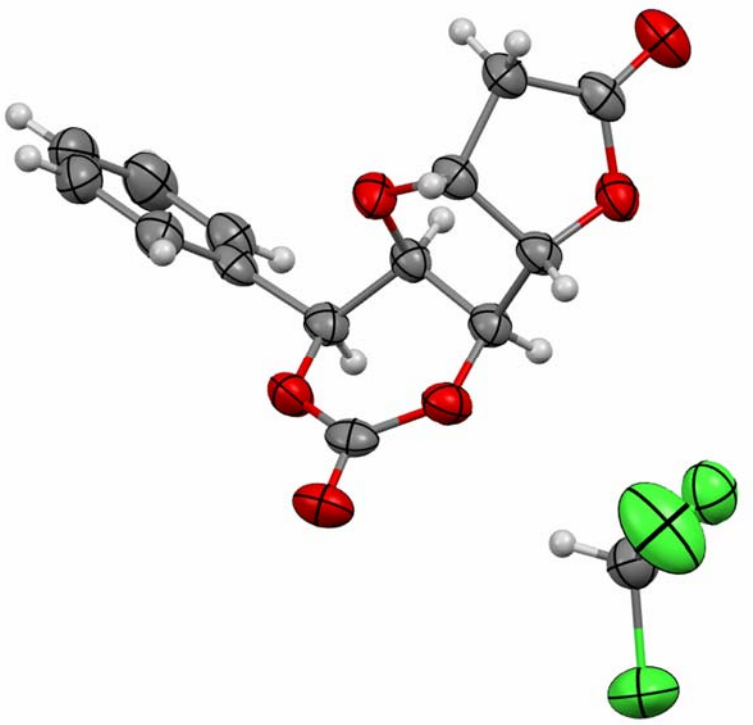


Figure S5. ORTEP presentation of compound **4c** [9]

[9] Crystallographic data for **4b** and **4c** are deposited at the Cambridge Crystallographic Data Centre, the deposition numbers: CCDC 979782 and CCDC 979778, respectively.

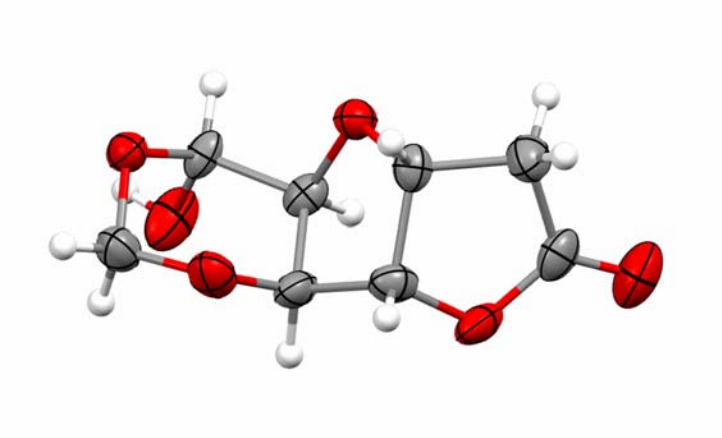


Figure S6. ORTEP presentation of compound **12** [10]

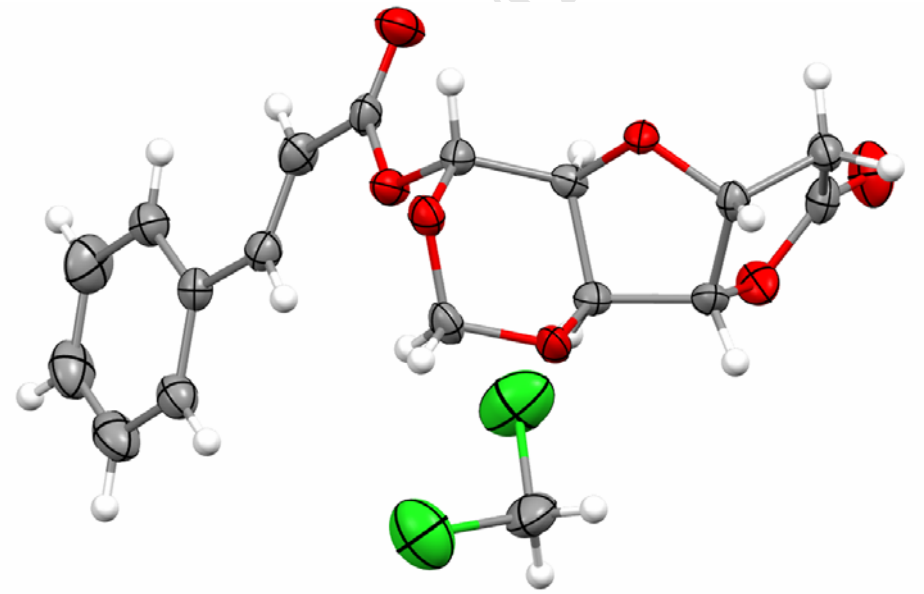


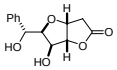
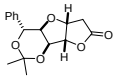
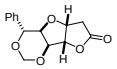
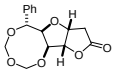
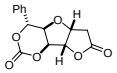
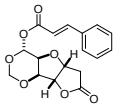
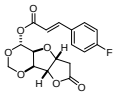
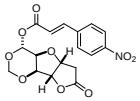
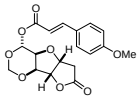
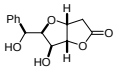
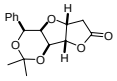
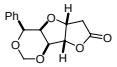
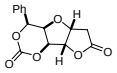
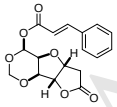
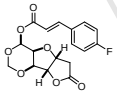
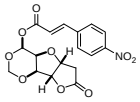
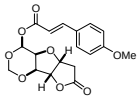
Figure S7. ORTEP presentation of compound **5a** [10]

[10] Crystallographic data for **12** and **5a** are deposited at the Cambridge Crystallographic Data Centre, the deposition numbers: CCDC 979776 and CCDC 979777, respectively.

IV. SAR STUDIES

The structures and the corresponding cytotoxicity data for establishing the SAR are given in Table S6.

Table S6. Cytotoxicity data for SAR studies

Compds	Structures	IC_{50}, μM (72 h)							
		K562	HL-60	Jurkat	Raji	MCF-7	MDA-MB 231	HeLa	Hs249T
1		0.41	558.32	32.45	18.45	16.59	75.34	8.32	4665.49
3a		16.59	2.36	34.15	3.25	87.45	5.27	1.64	857.01
3b		476.09	10.08	18.21	17.89	23.45	1123.69	18.87	35.64
3c		367.29	14.34	13.64	12.45	27.79	367.19	12.36	45.32
3d		5.59	33.78	11.52	25.31	1.01	2.37	14.26	6012.85
5a		3.16	8.08	5.06	1.01	27.32	4.08	0.001	364.58
5b		559.36	2.36	589.36	5.78	289.21	975.31	0.02	0.002
5c		599.01	6.37	201.59	20.01	3.64	1.01	8.79	3815.28
5d		8.77	1.24	0.042	4.32	156.32	582.31	12.51	89.74
2		0.028	22.02	18.64	1.25	9.24	58.70	0.89	43.58
4a		0.17	1.25	22.51	1.01	1.06	24.89	9.75	5024.23
4b		0.023	0.24	3.33	1.01	8.08	558.28	3.02	3159.46
4c		4.46	12.85	7.89	15.78	32.45	639.19	5.67	4682.25
6a		798.05	8.45	2056.34	7.56	101.36	2.36	0.23	2.53
6b		4.32	12.07	15.47	87.23	32.22	5.69	11.69	2285.22
6c		423.25	35.38	433.55	1.32	1479.21	648.22	1.01	2239.14
6d		3.68	25.61	12.01	69.24	51.79	3.03	2.21	6745.29

The structure-activity relationships were accessed as follows: the IC_{50} values of two compounds were compared, and the Δ log IC_{50} was calculated (Δ log IC_{50} is a difference between the log IC_{50} values of an analogue and the corresponding control compound). Positive Δ log IC_{50} values show a decrease of antiproliferative activity, whereas negative values indicate an increase in the activity upon the structural modification being considered. The results are presented in Figure S8.

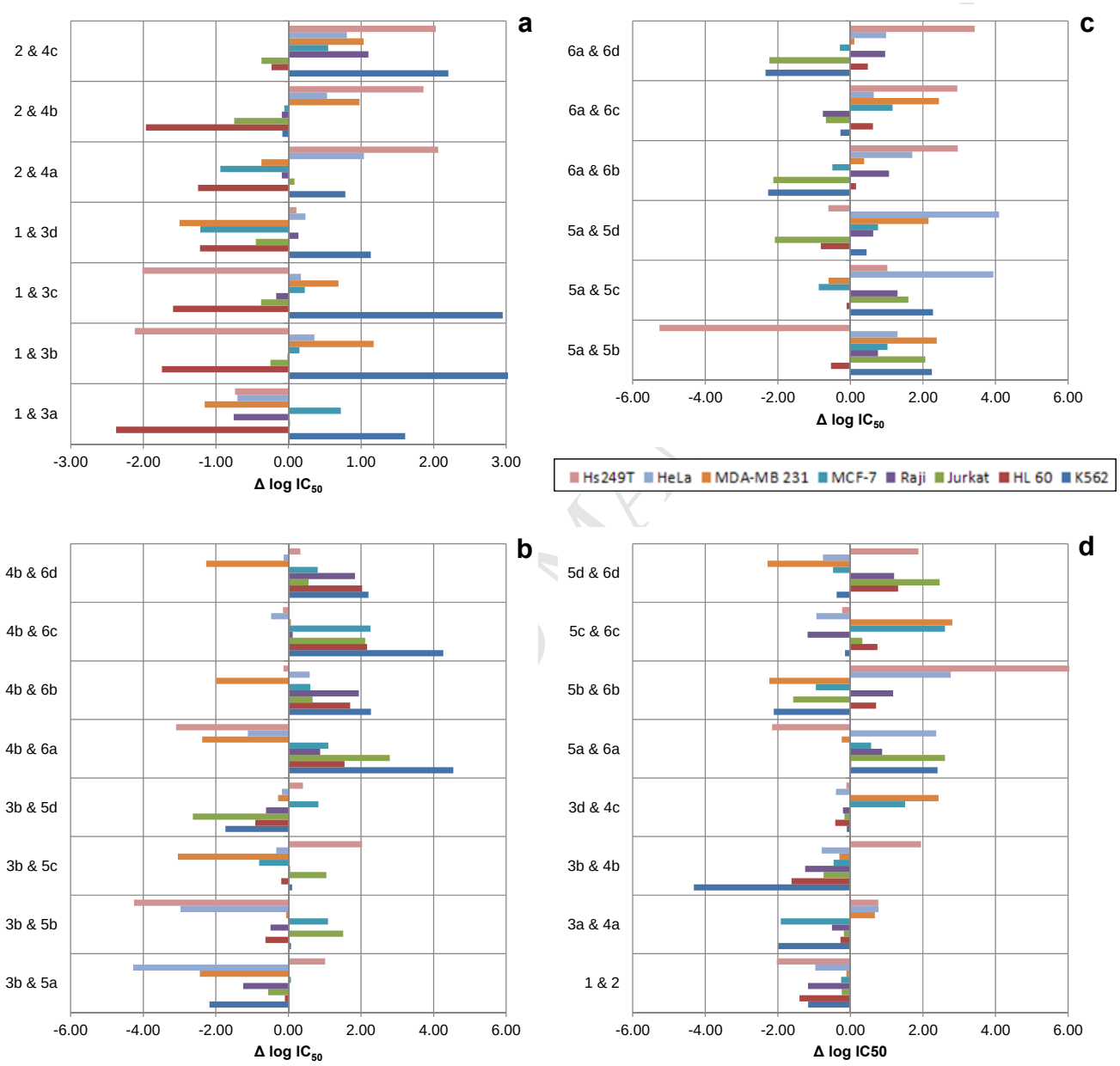
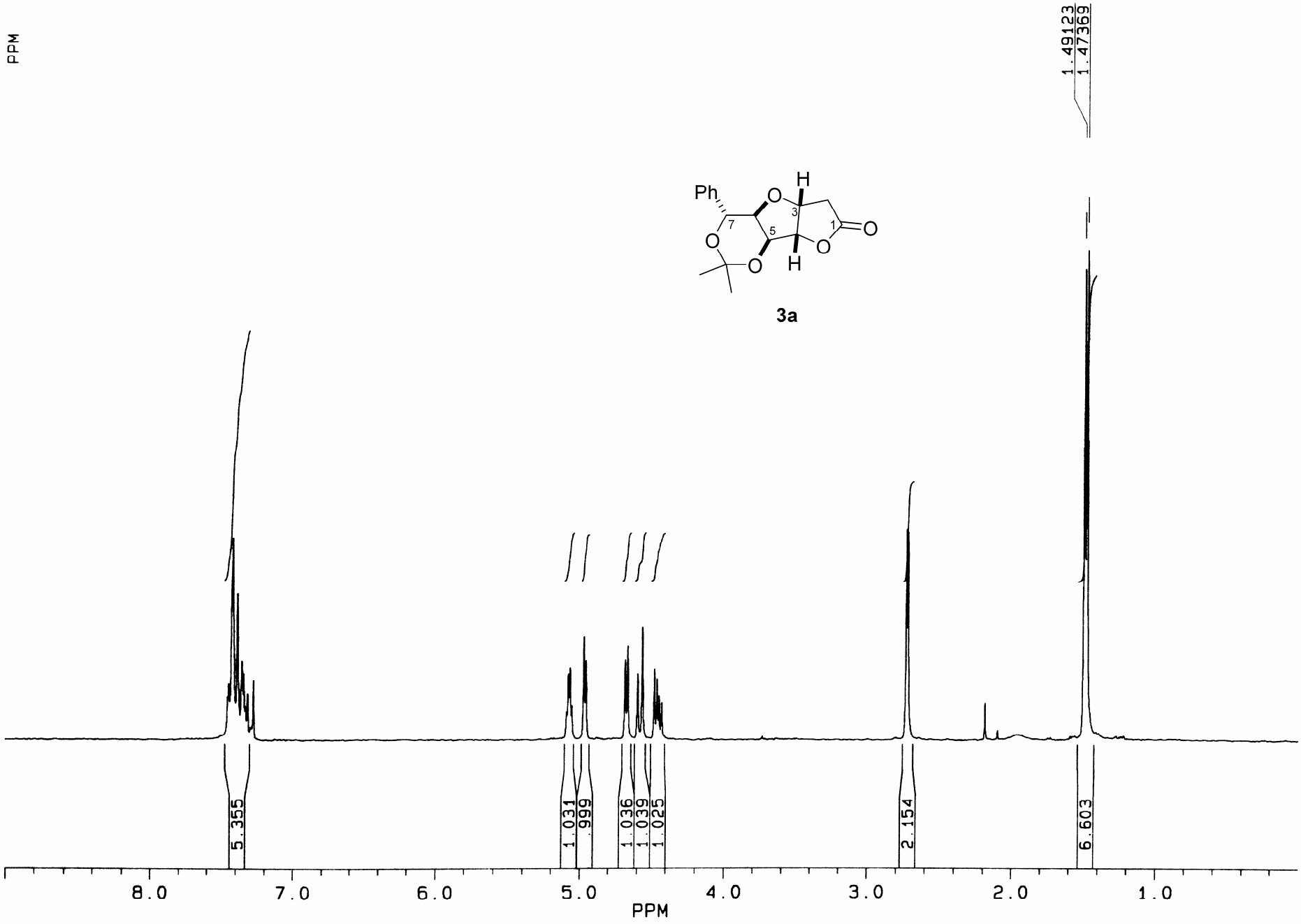


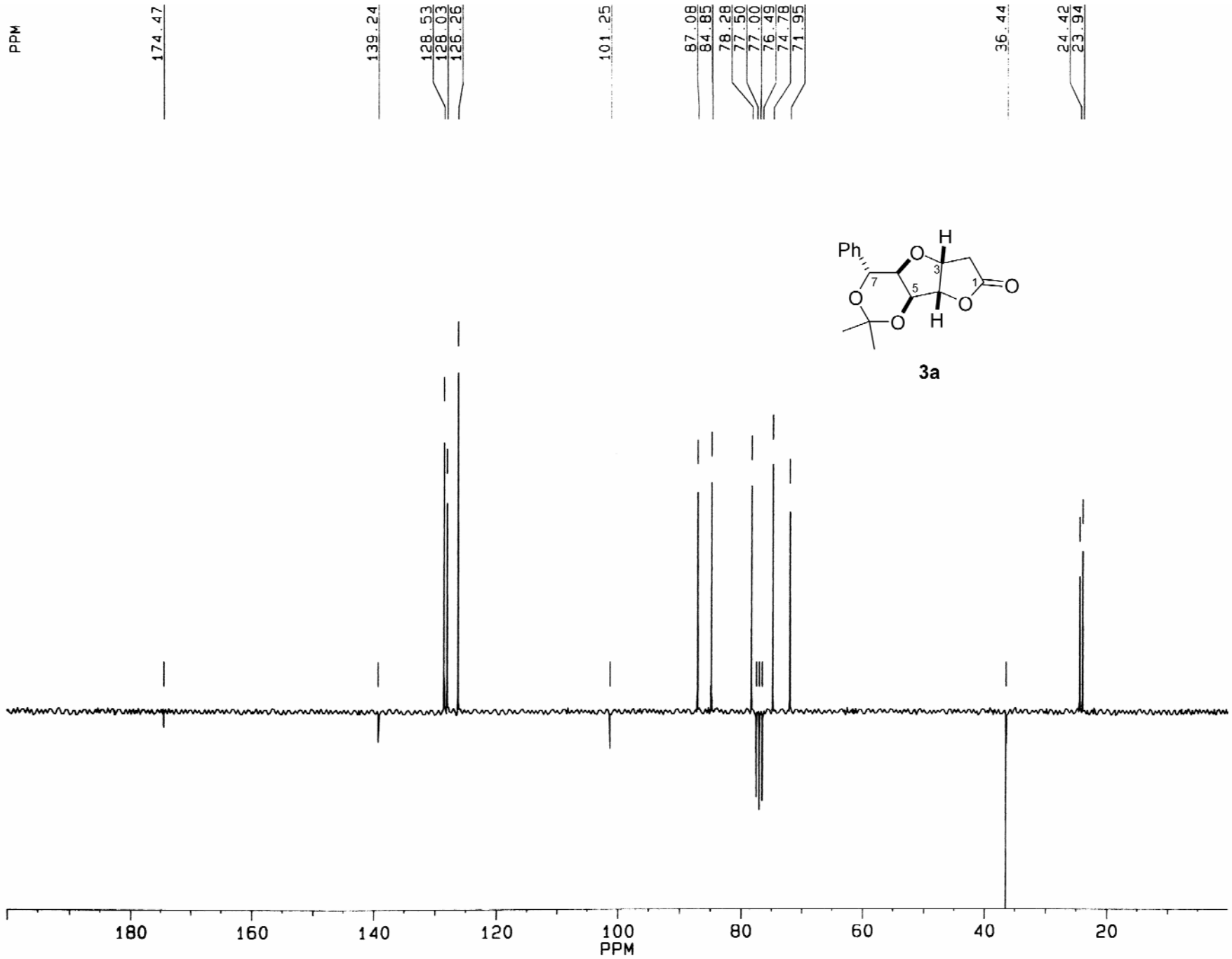
Figure S8. Contributions of selected structural features to the antiproliferative activities. The influence of: (a) addition of a six-membered ring, (b) Ph → cinnamate replacement, (c) isosteric replacement at the C-4 position of cinnamate moiety (H → F, NO_2 or OMe), (d) stereochemistry at the C-7 position.

V. COPIES OF NMR SPECTRA OF FINAL PRODUCTS

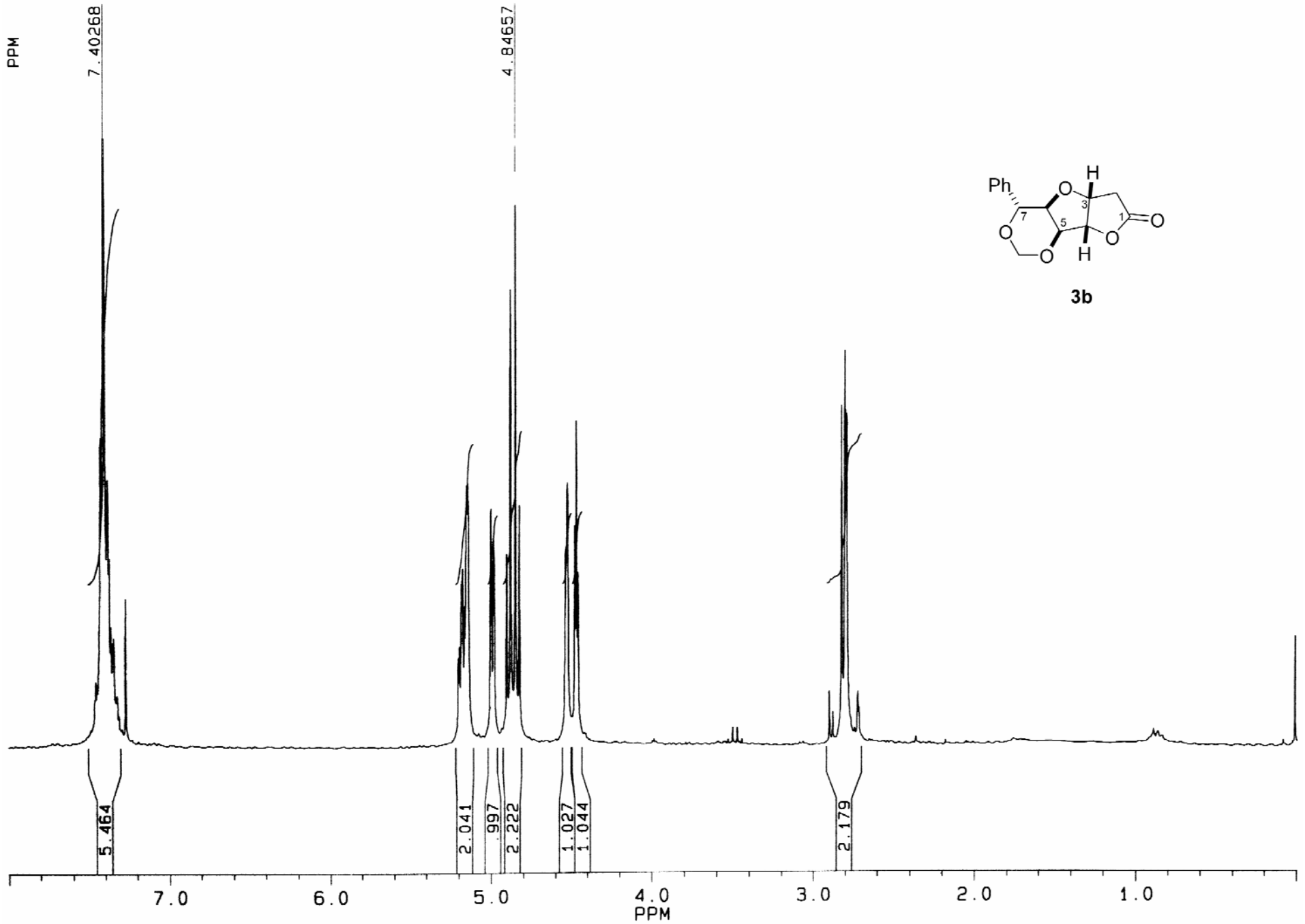
^{1}H NMR Spectrum of Compound 3a (250 MHz, $CDCl_3$)



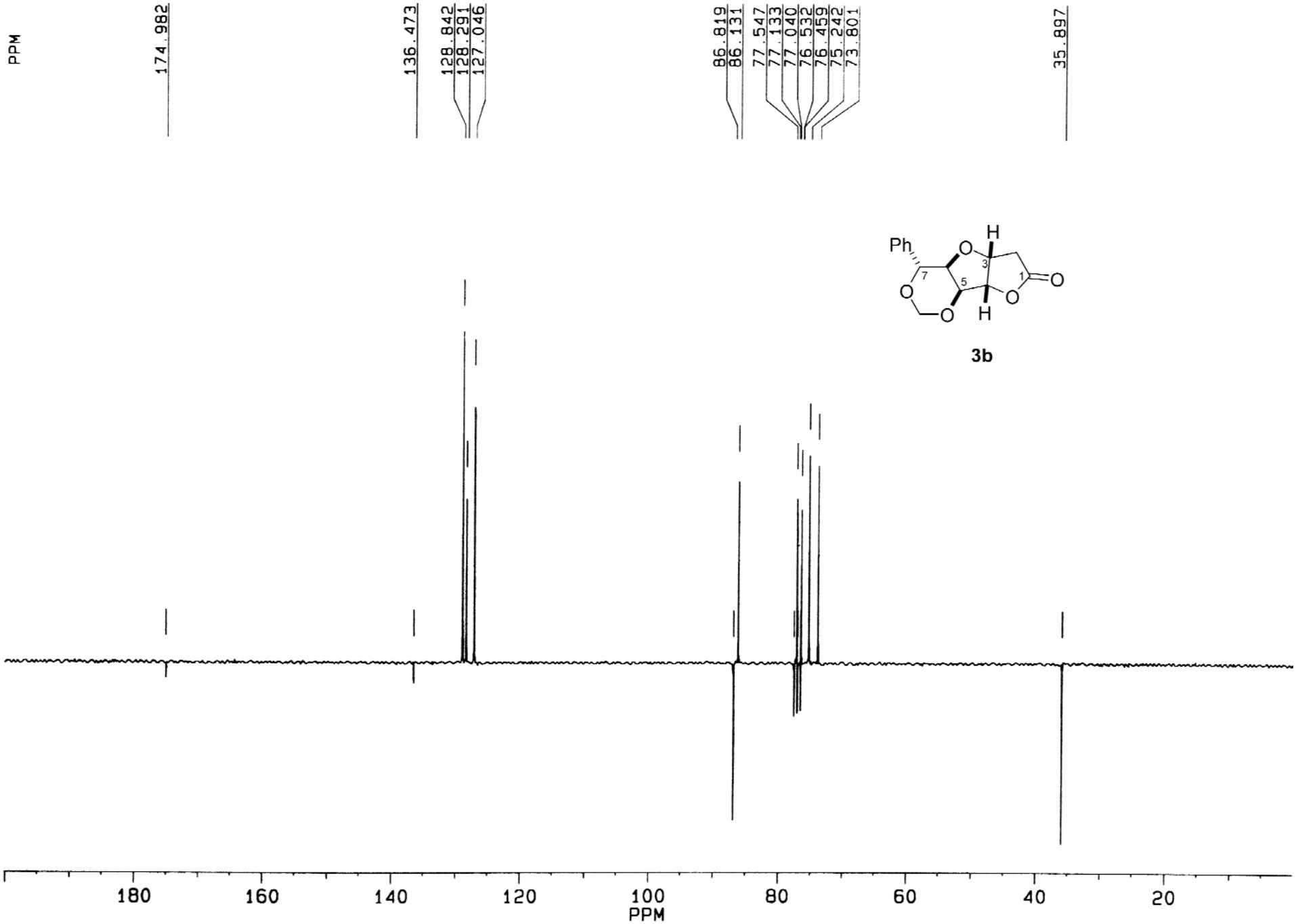
^{13}C NMR Spectrum of Compound 3a (62.9 MHz, $CDCl_3$)



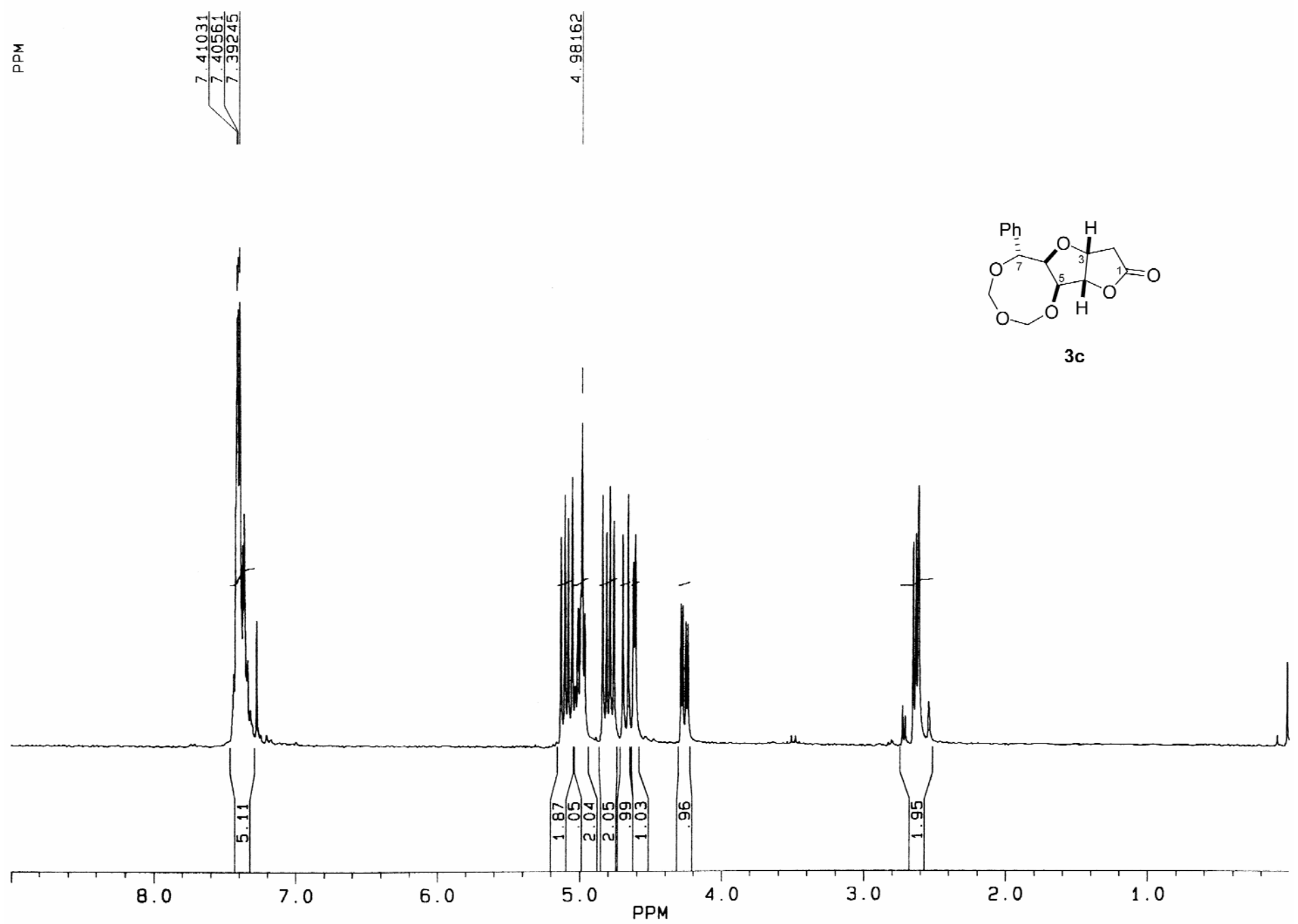
^{1}H NMR Spectrum of Compound 3b (250 MHz, $CDCl_3$)



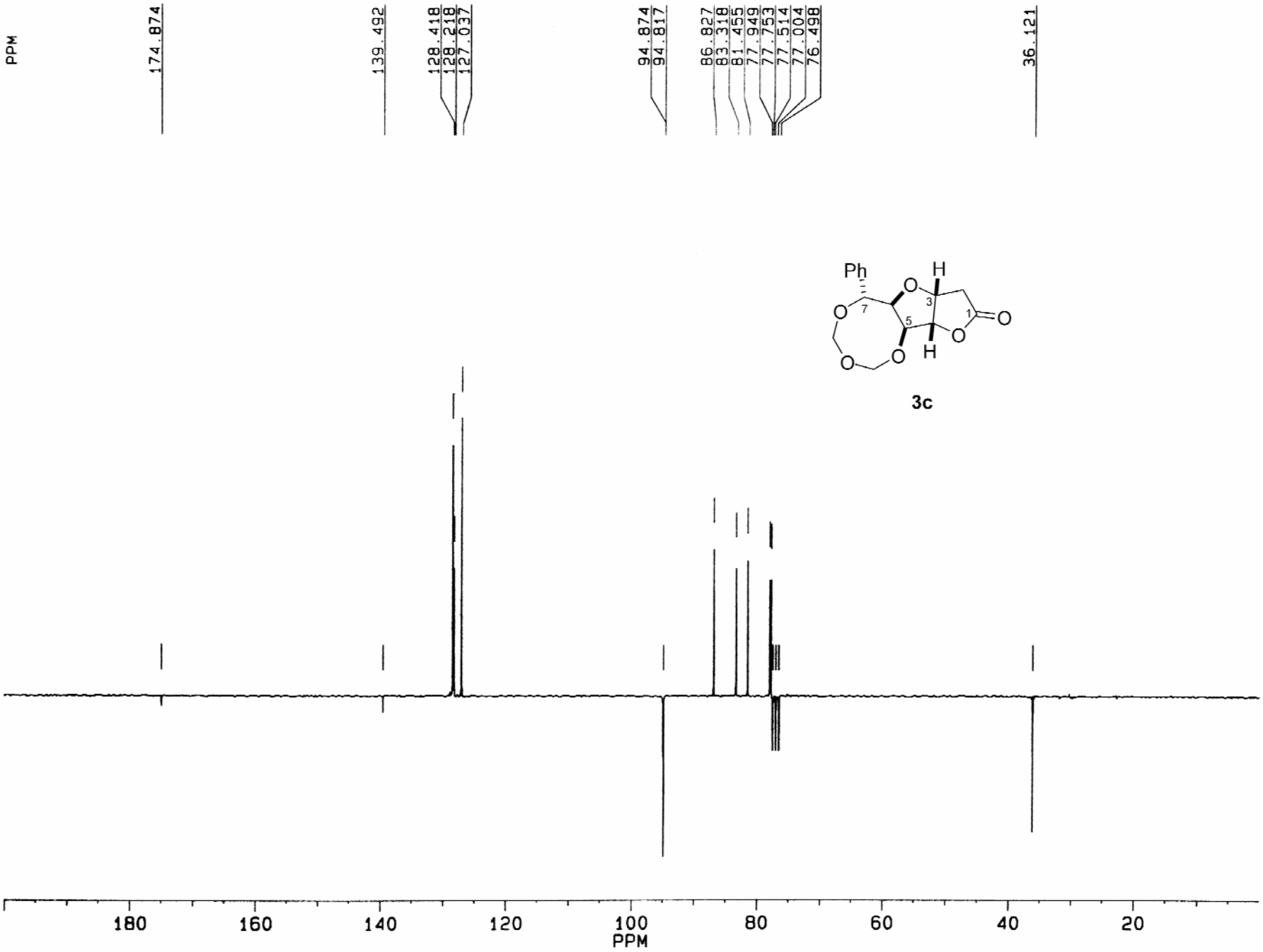
^{13}C NMR Spectrum of Compound 3b (62.9 MHz, $CDCl_3$)



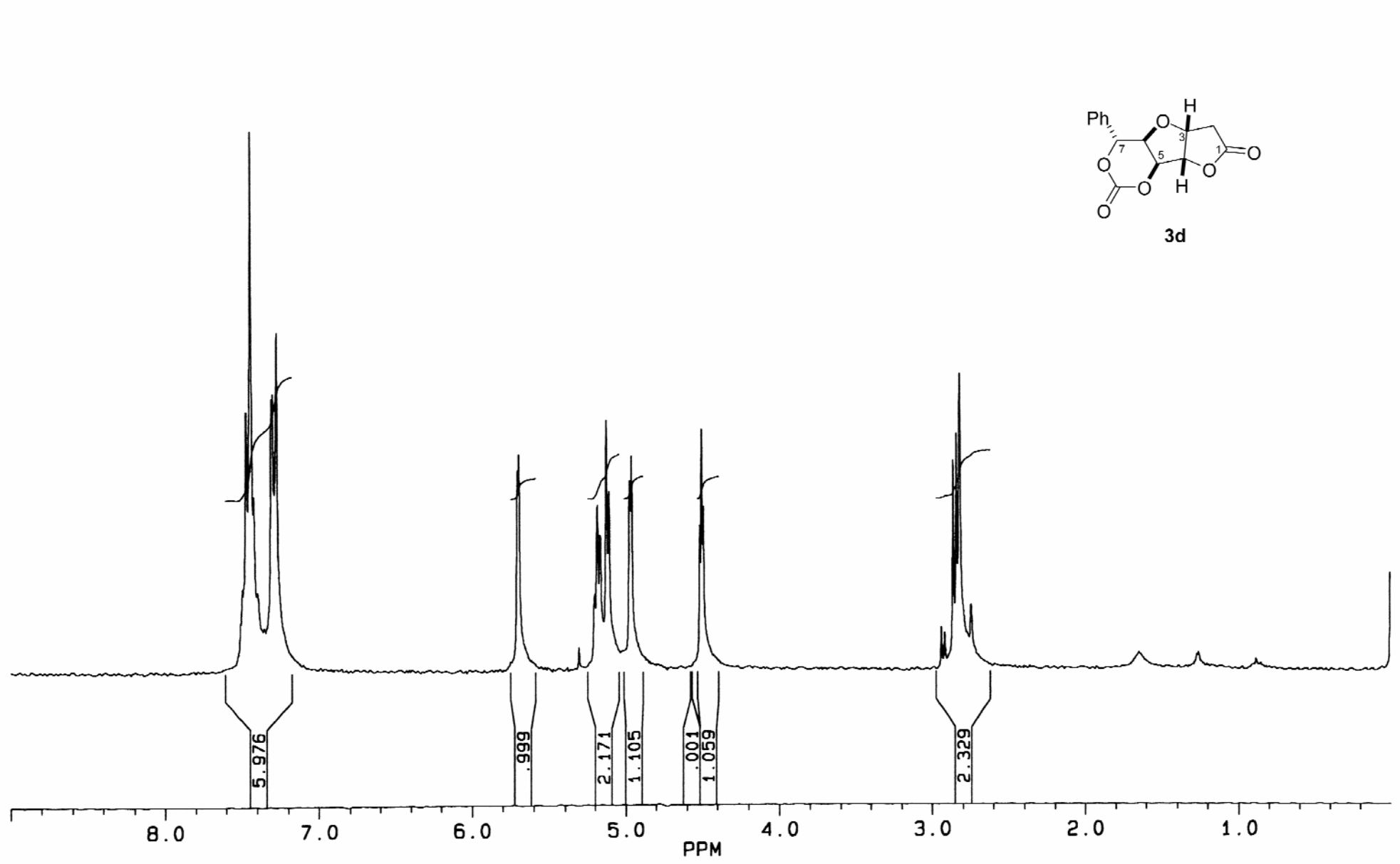
^{1}H NMR Spectrum of Compound 3c (250 MHz, $CDCl_3$)



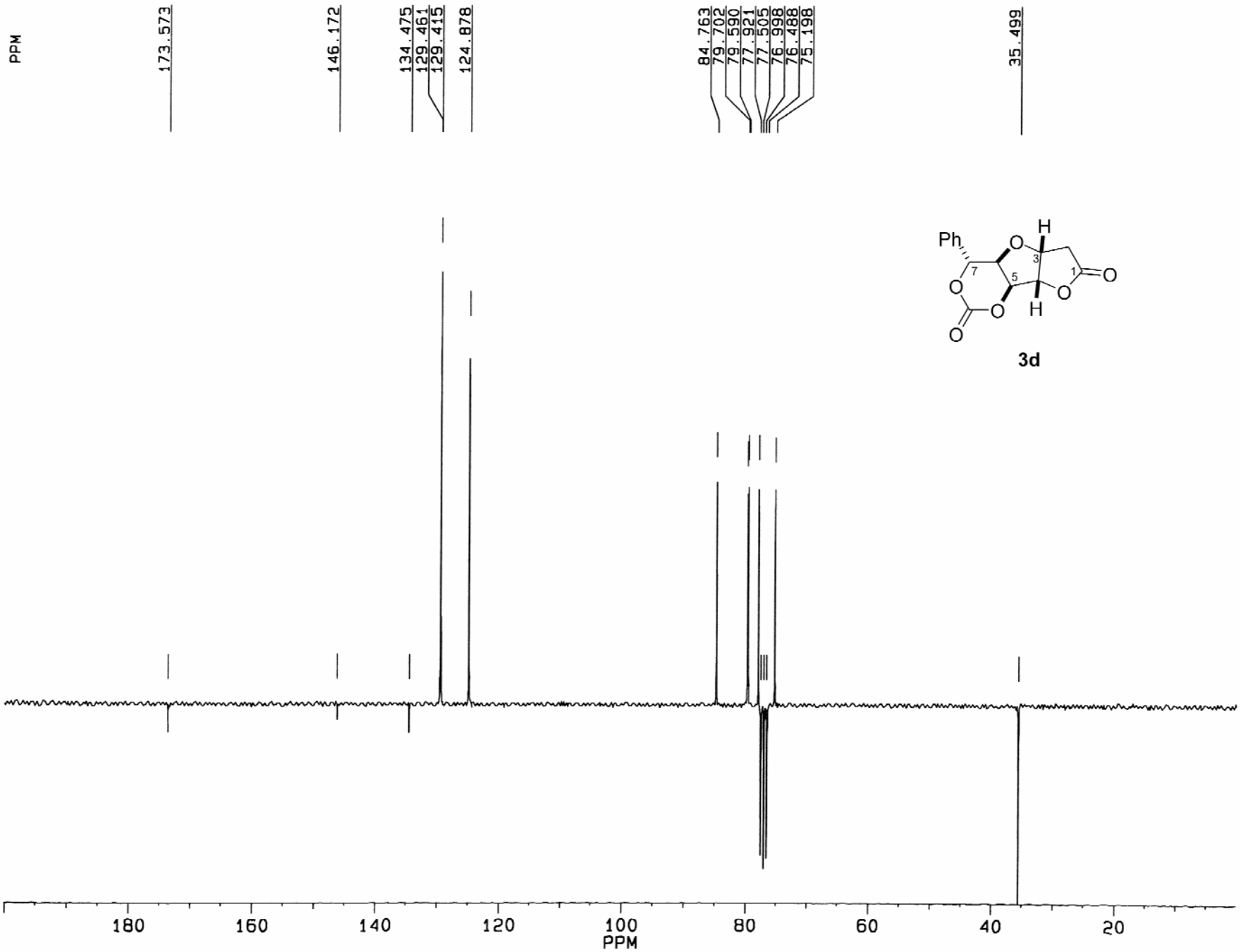
^{13}C NMR Spectrum of Compound 3c (62.9 MHz, $CDCl_3$)



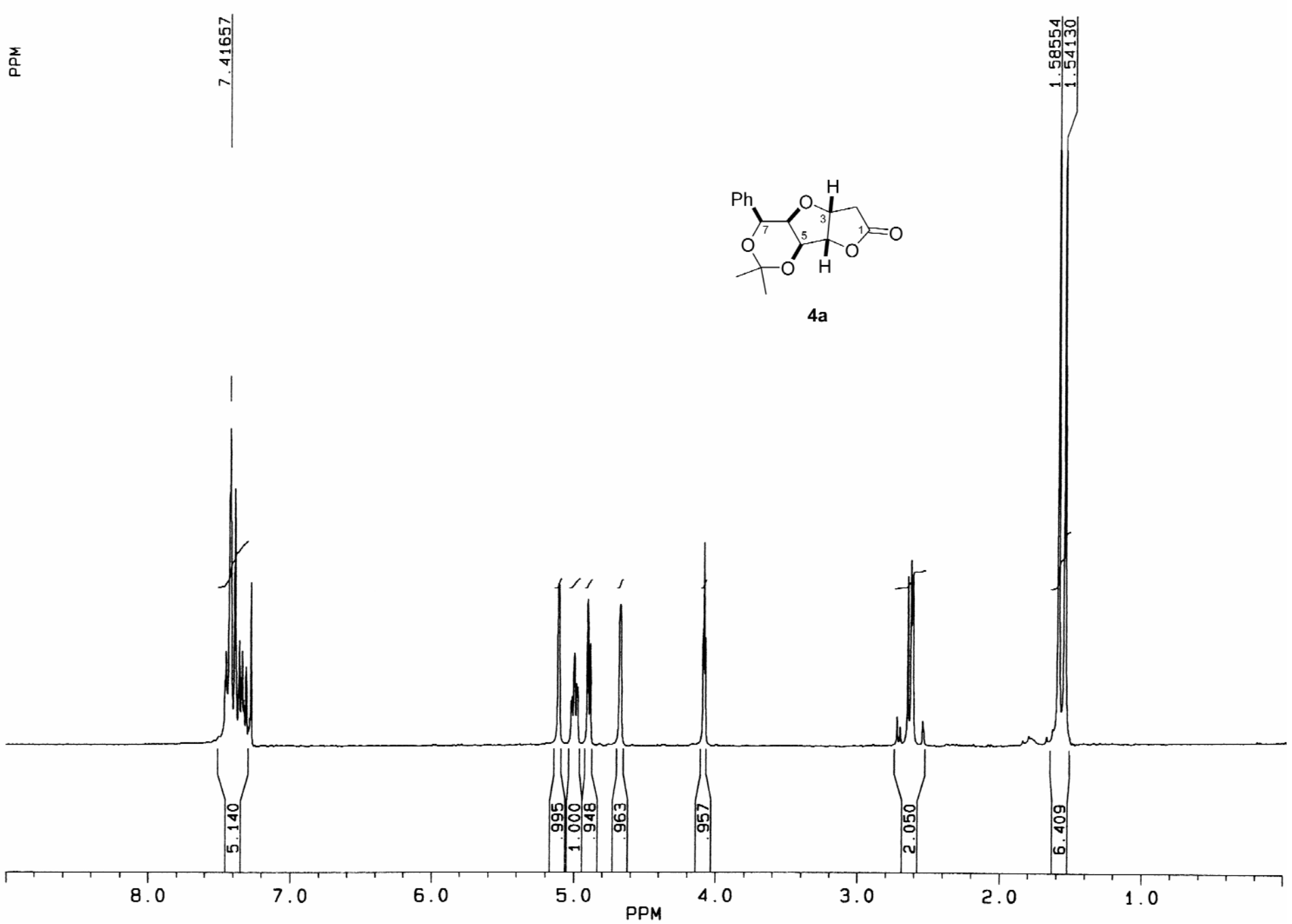
^{1}H NMR Spectrum of Compound 3d (250 MHz, $CDCl_3$)



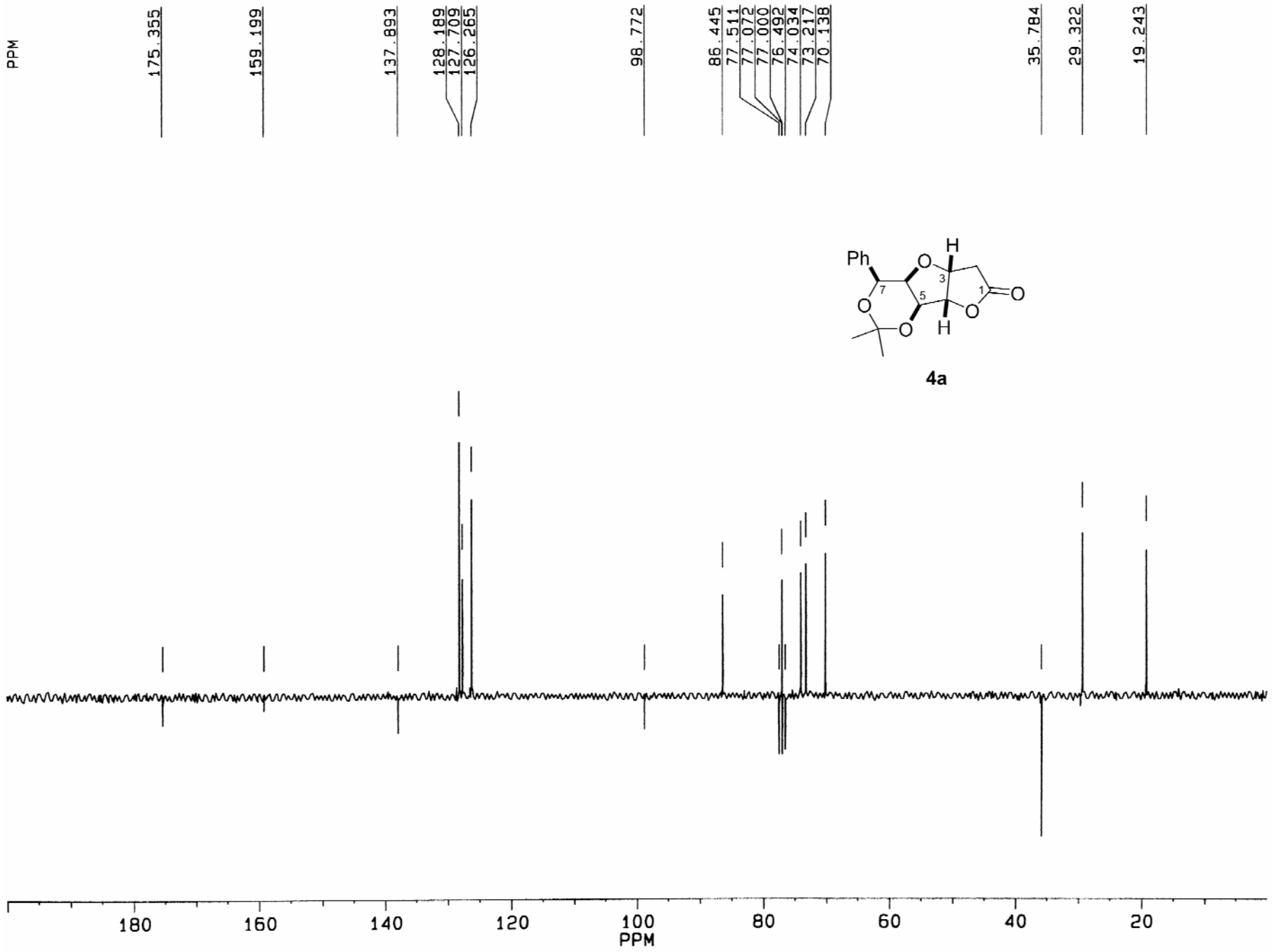
^{13}C NMR Spectrum of Compound 3d (62.9 MHz, $CDCl_3$)



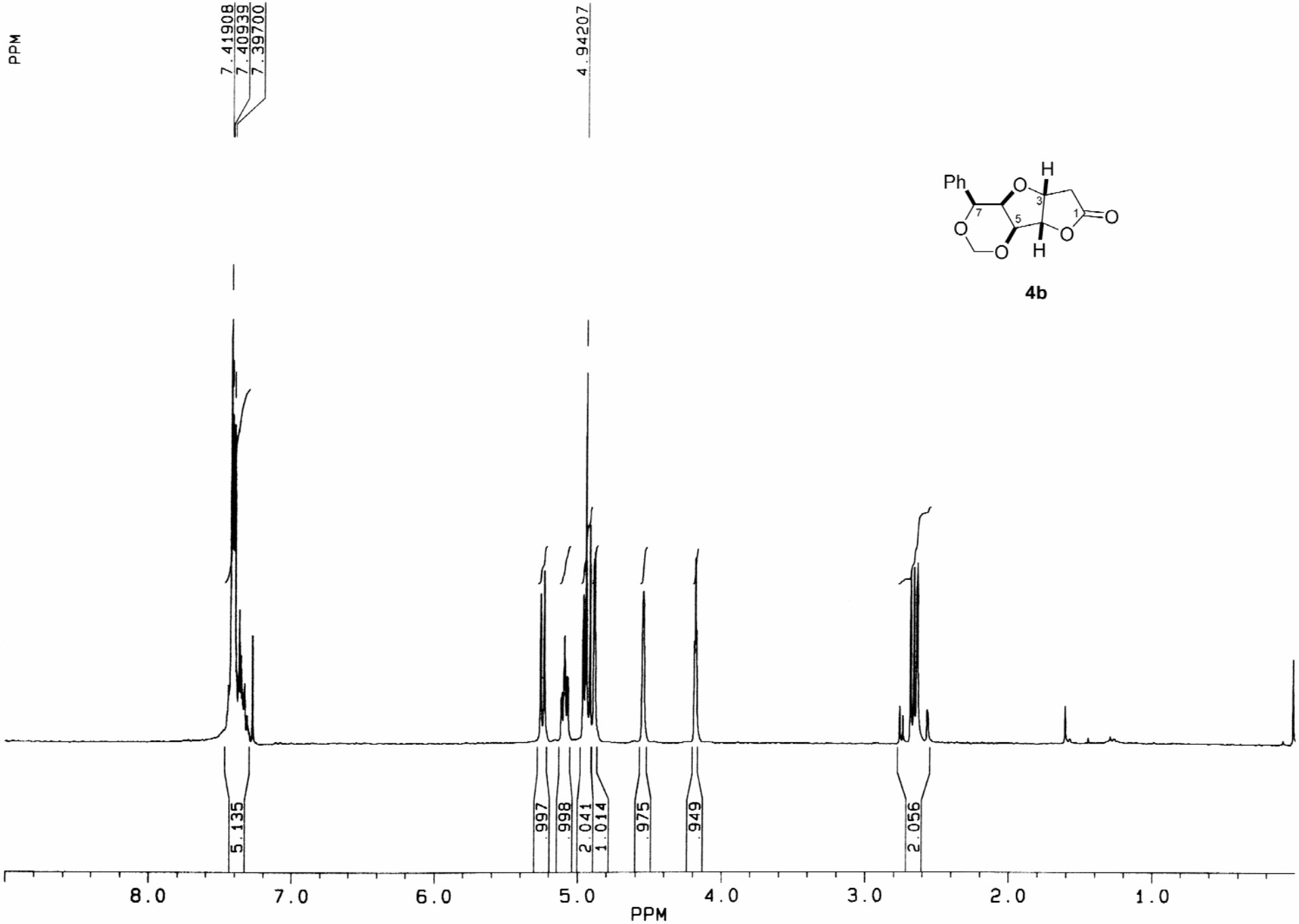
^{1}H NMR Spectrum of Compound 4a (250 MHz, $CDCl_3$)



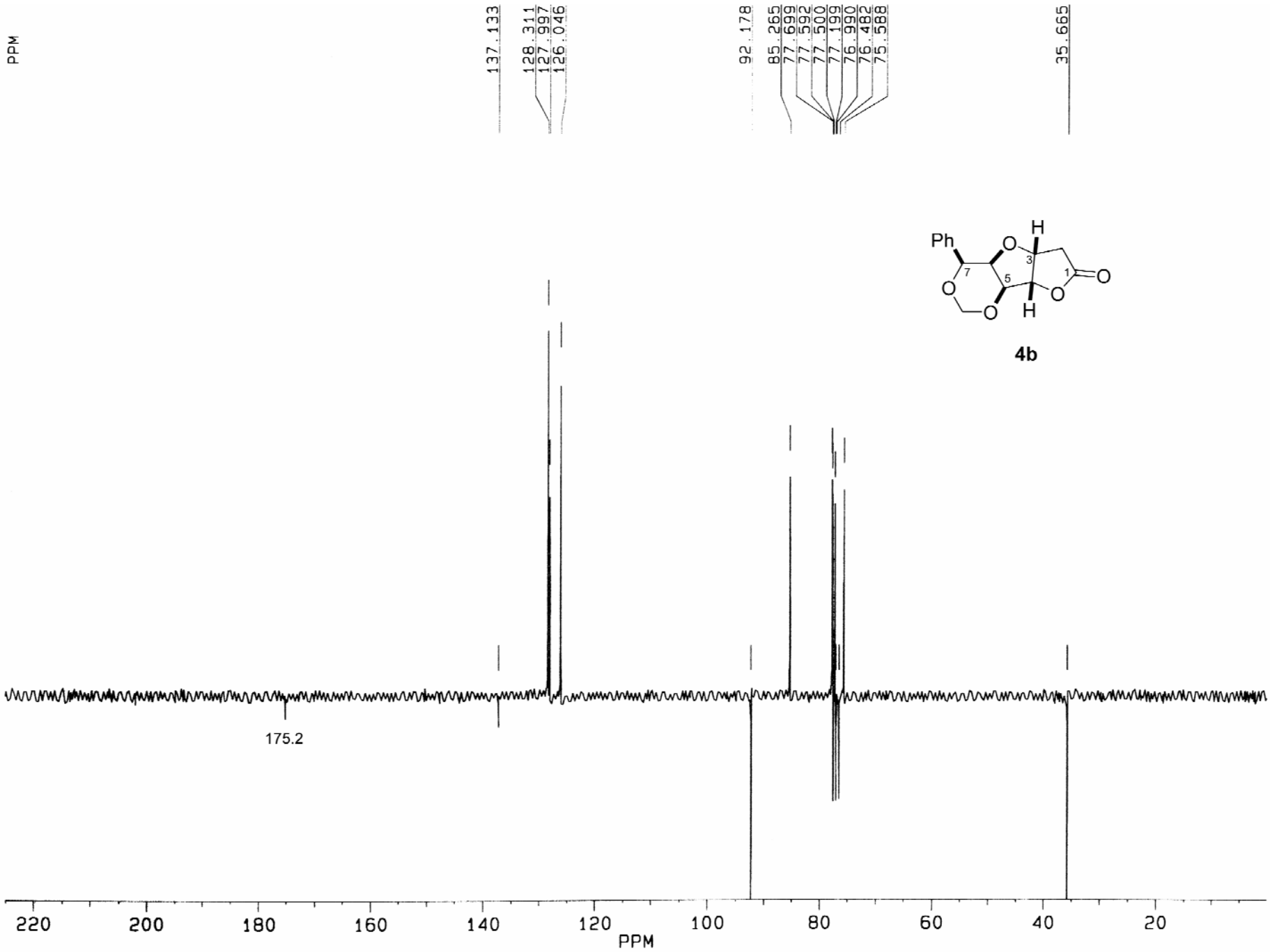
^{13}C NMR Spectrum of Compound 4a (62.9 MHz, $CDCl_3$)



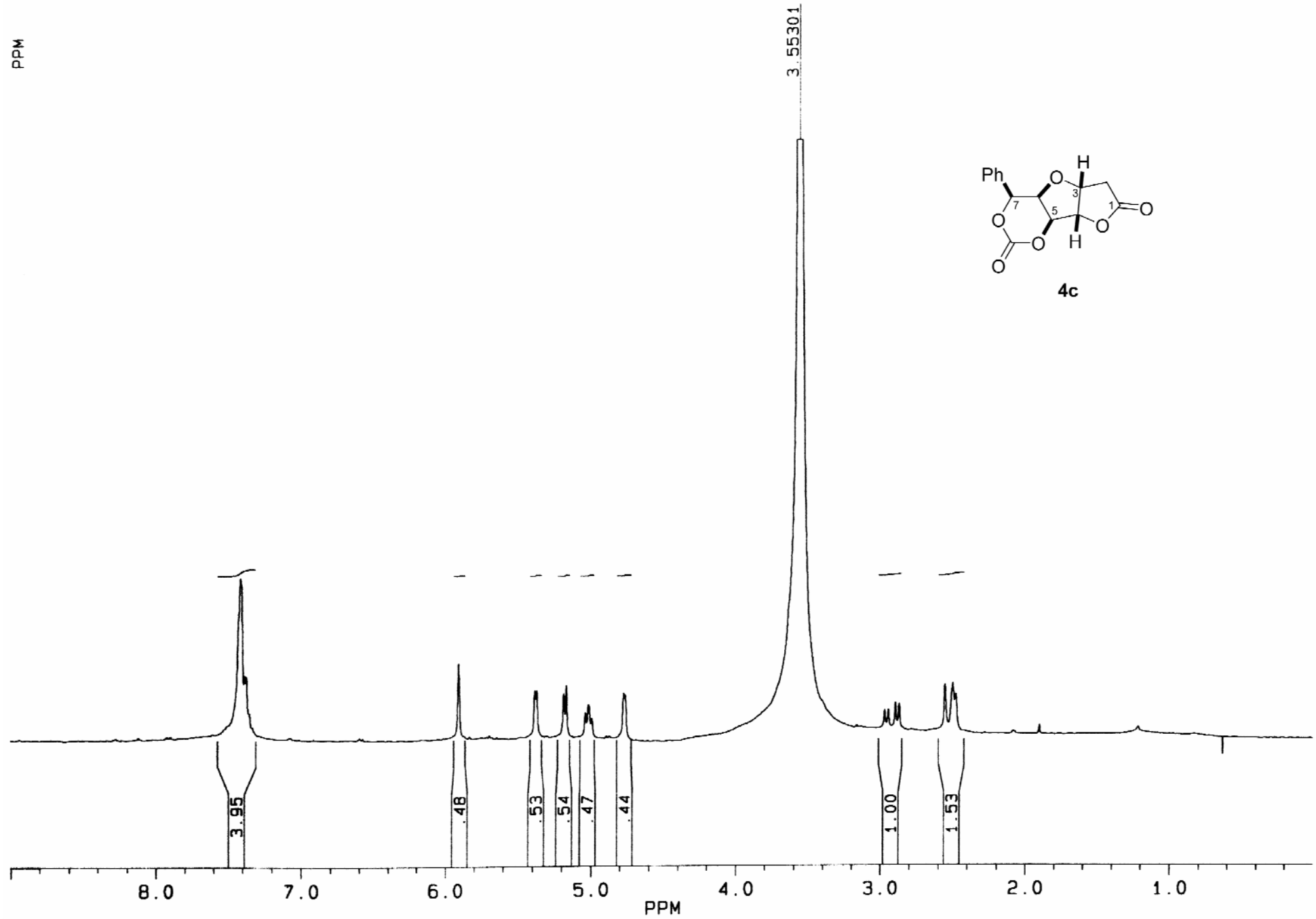
^{1}H NMR Spectrum of Compound 4b (250 MHz, $CDCl_3$)



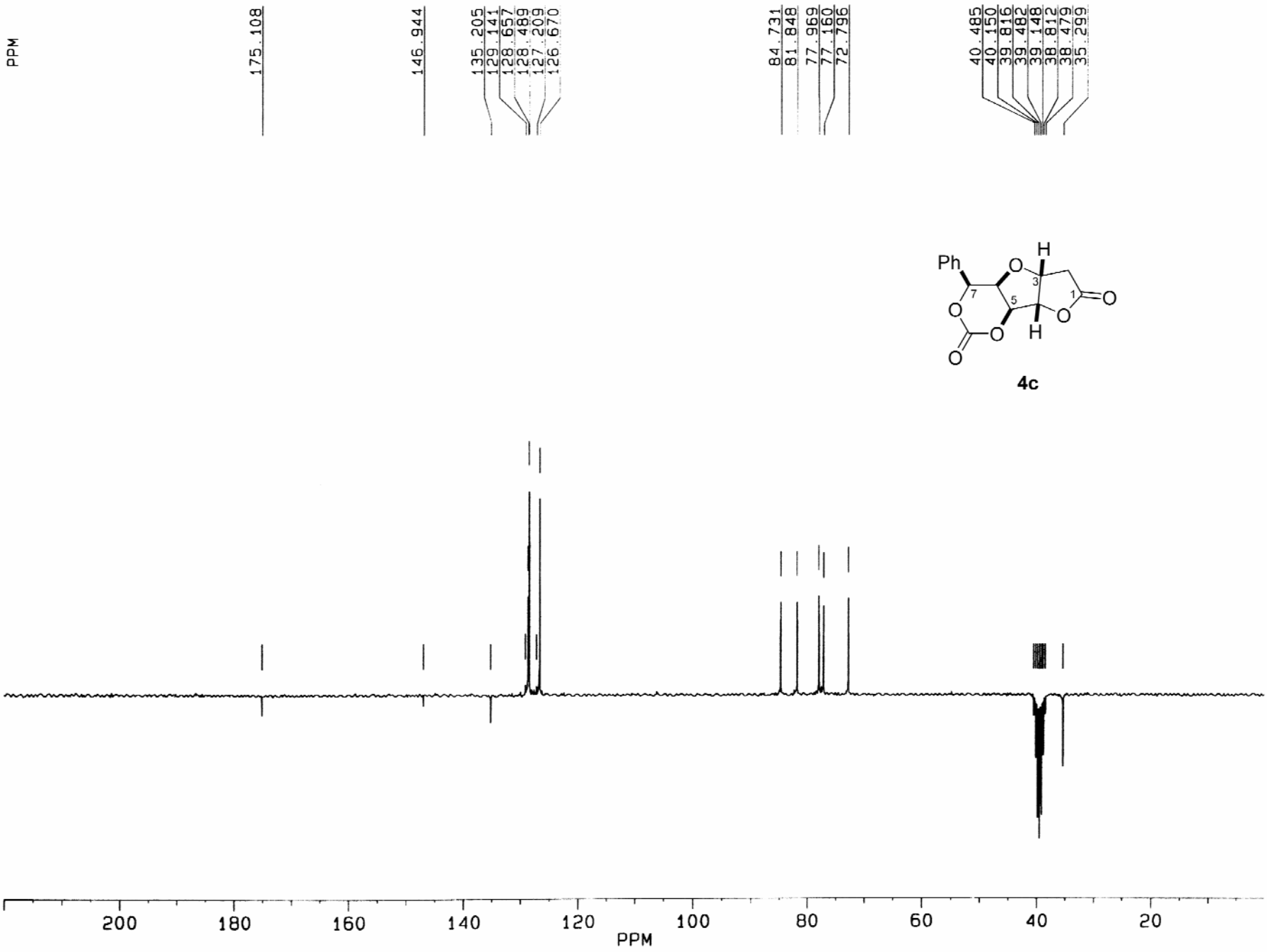
^{13}C NMR Spectrum of Compound 4b (62.9 MHz, $CDCl_3$)



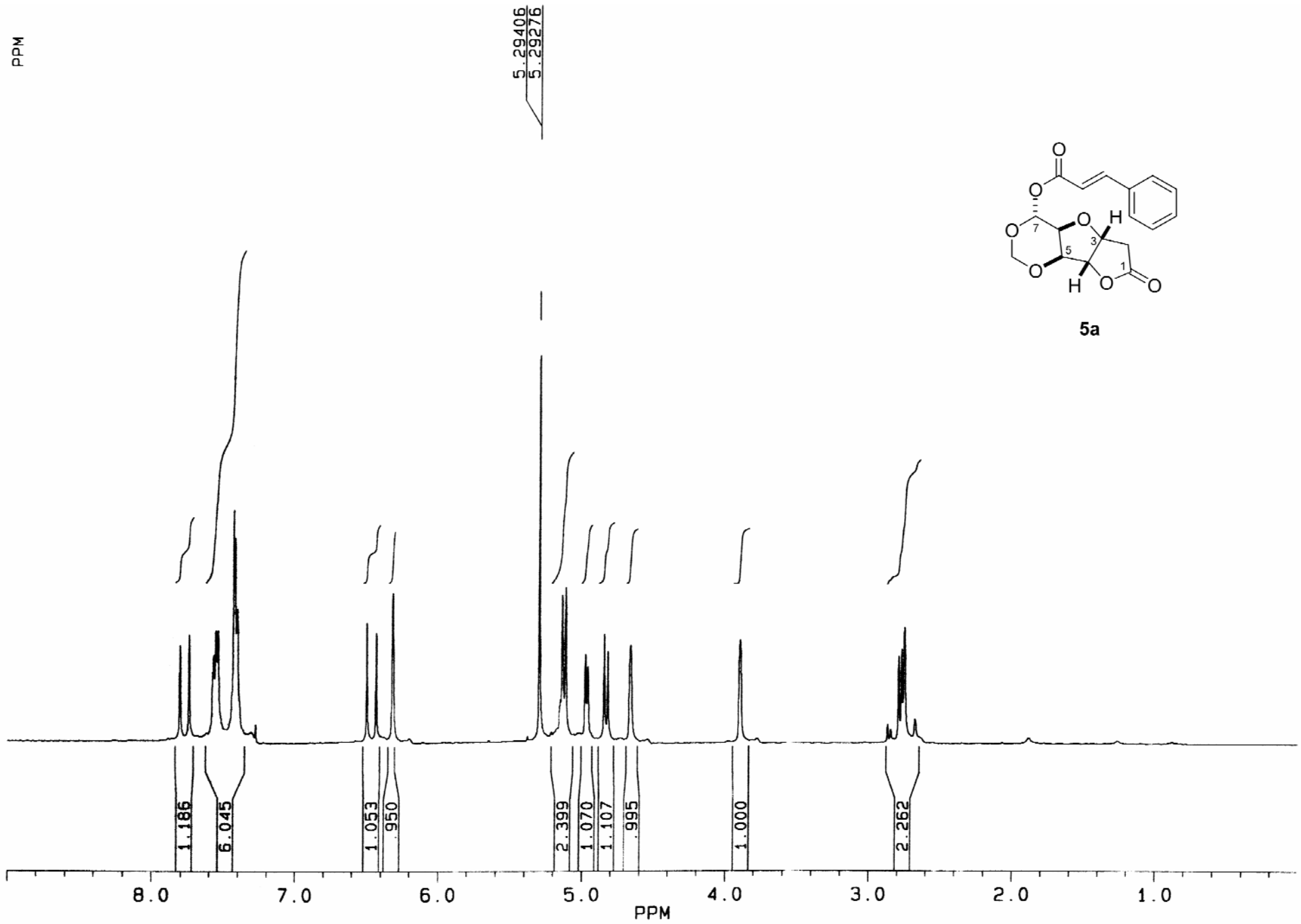
^{1}H NMR Spectrum of Compound 4c (250 MHz, DMSO-d_6)



^{13}C NMR Spectrum of Compound 4c (62.9 MHz, DMSO-d_6)

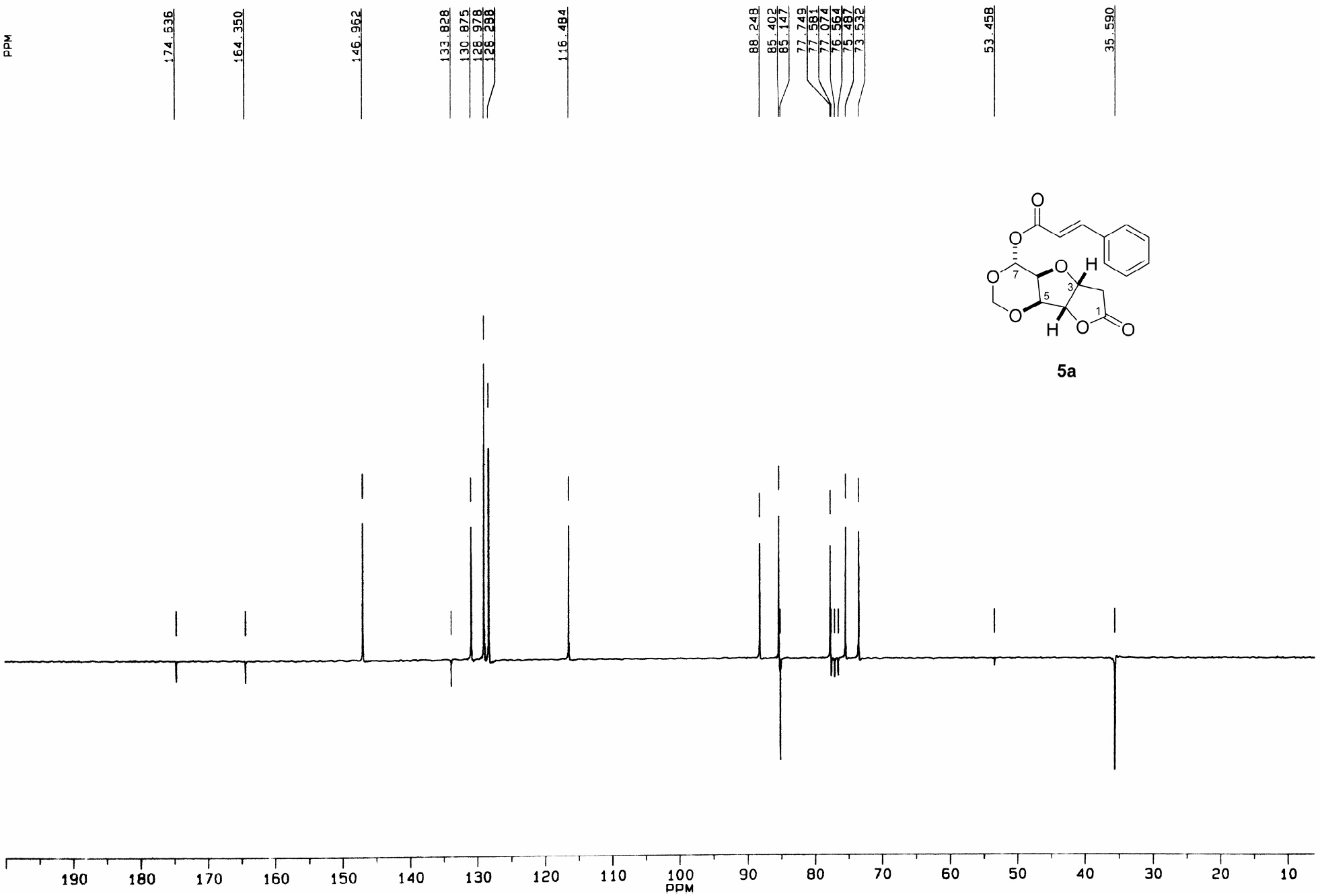


^{1}H NMR Spectrum of Compound 5a (250 MHz, $CDCl_3$)

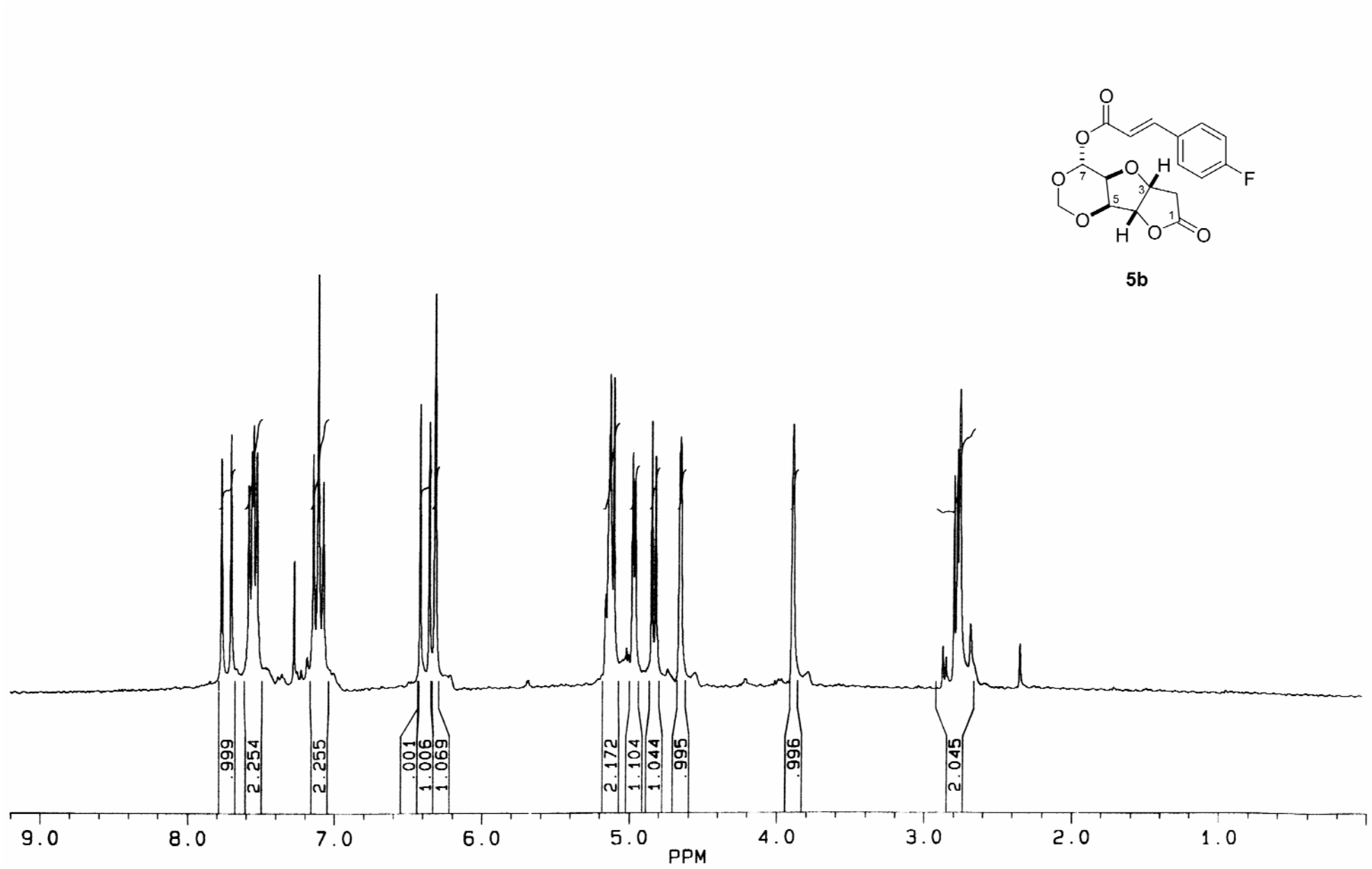


5a

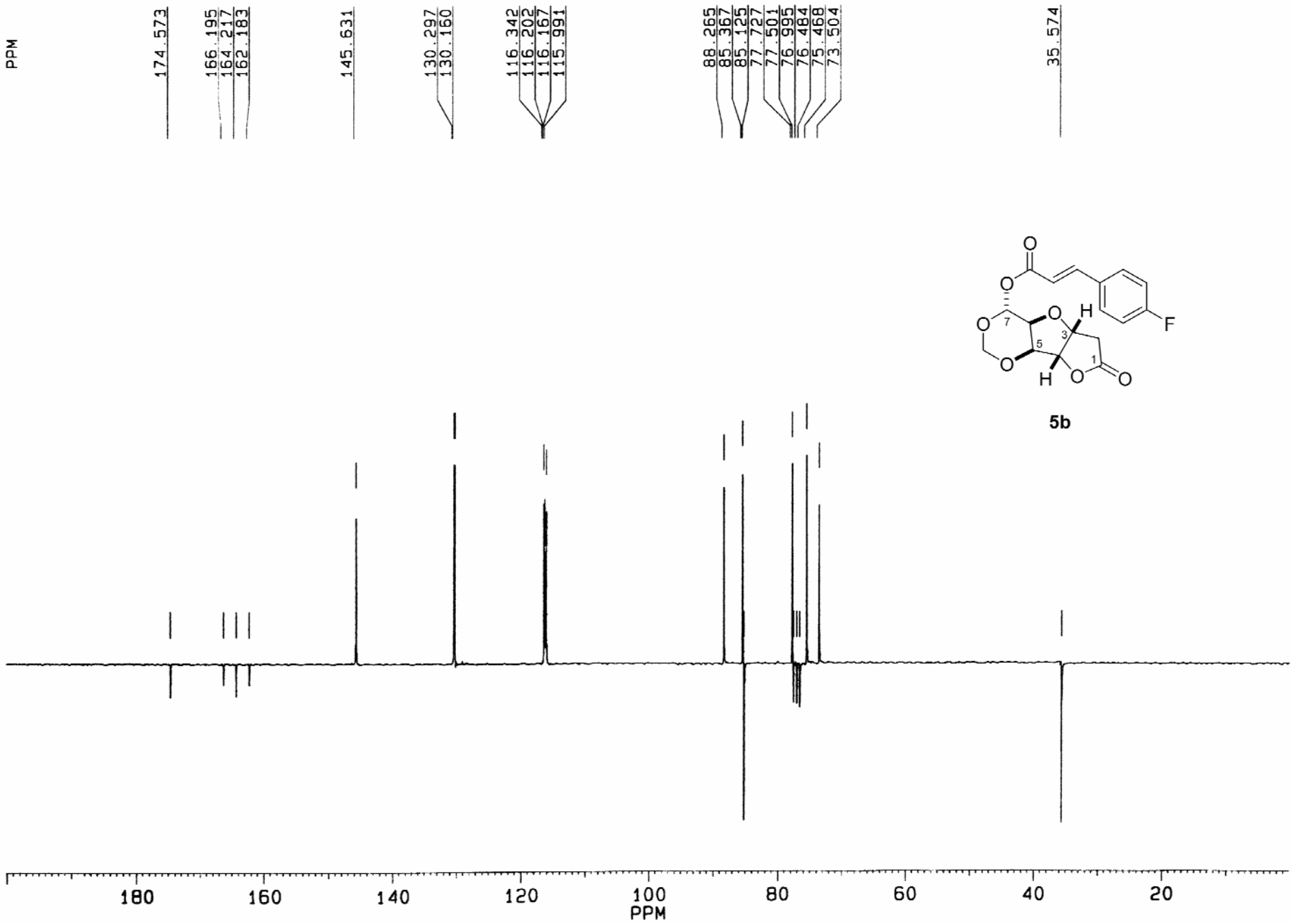
^{13}C NMR Spectrum of Compound 5a (62.9 MHz, $CDCl_3$)



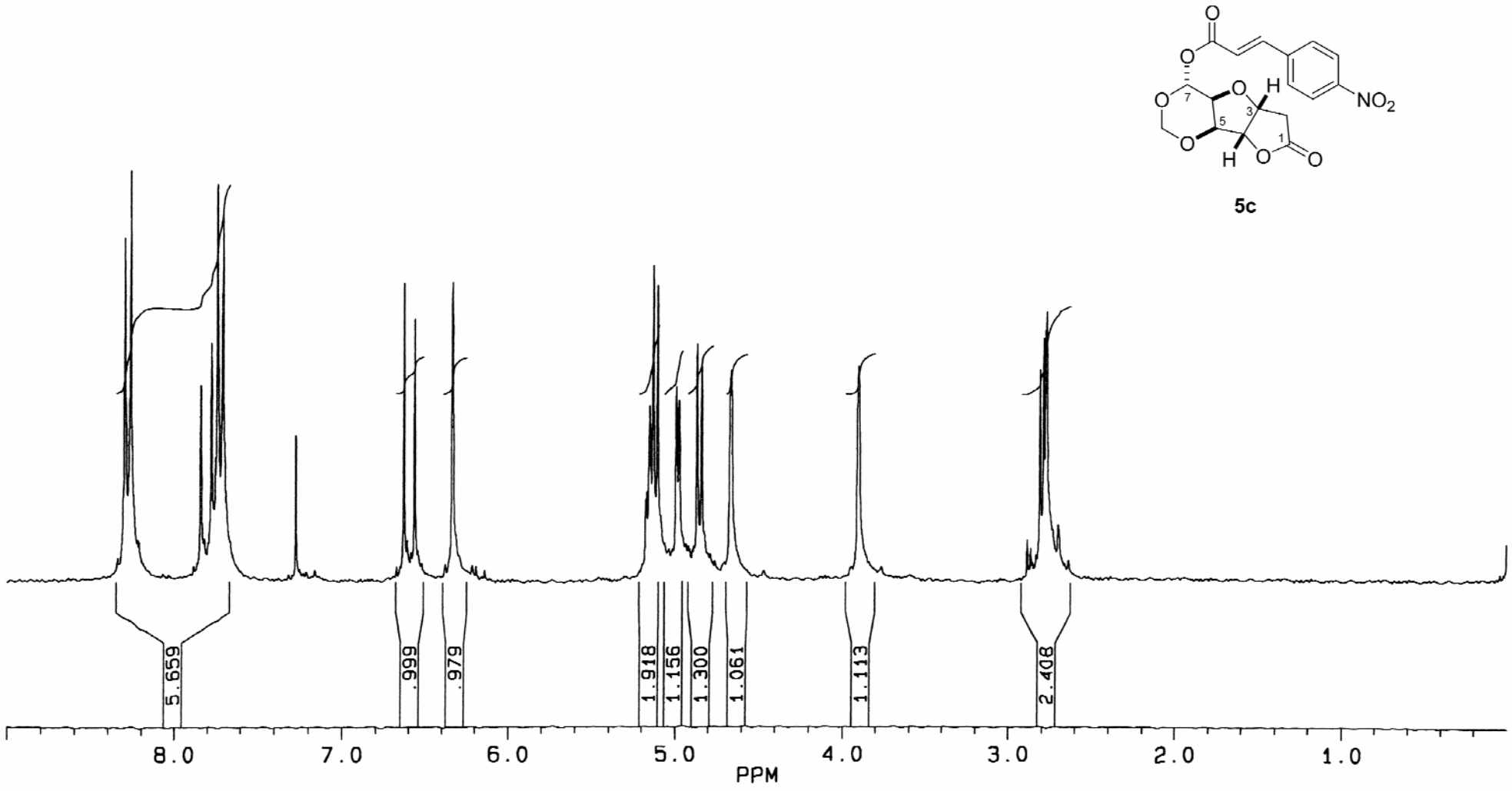
^{1}H NMR Spectrum of Compound 5b (250 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound 5b (62.9 MHz, $CDCl_3$)

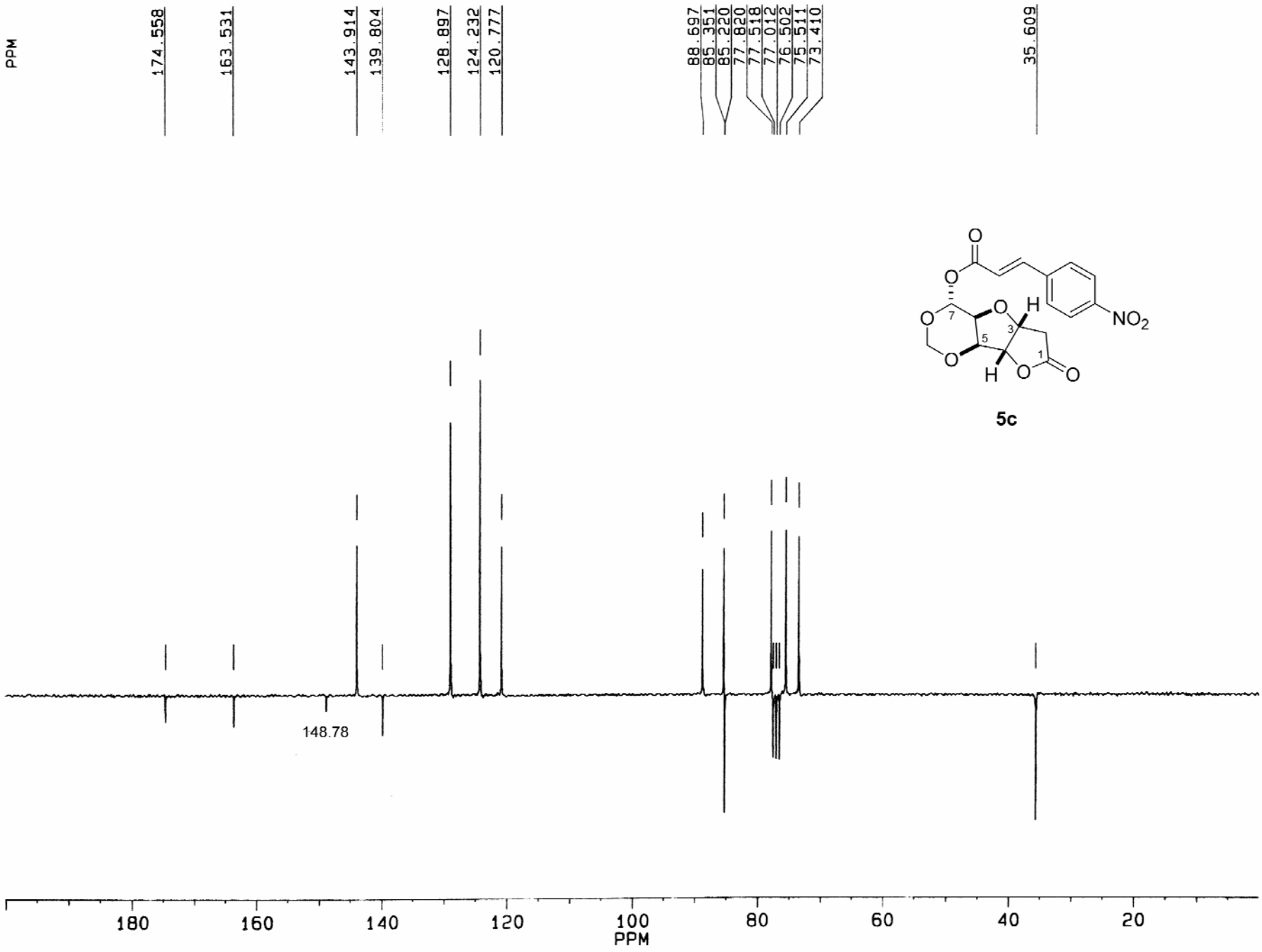


^{1}H NMR Spectrum of Compound 5c (250 MHz, $CDCl_3$)



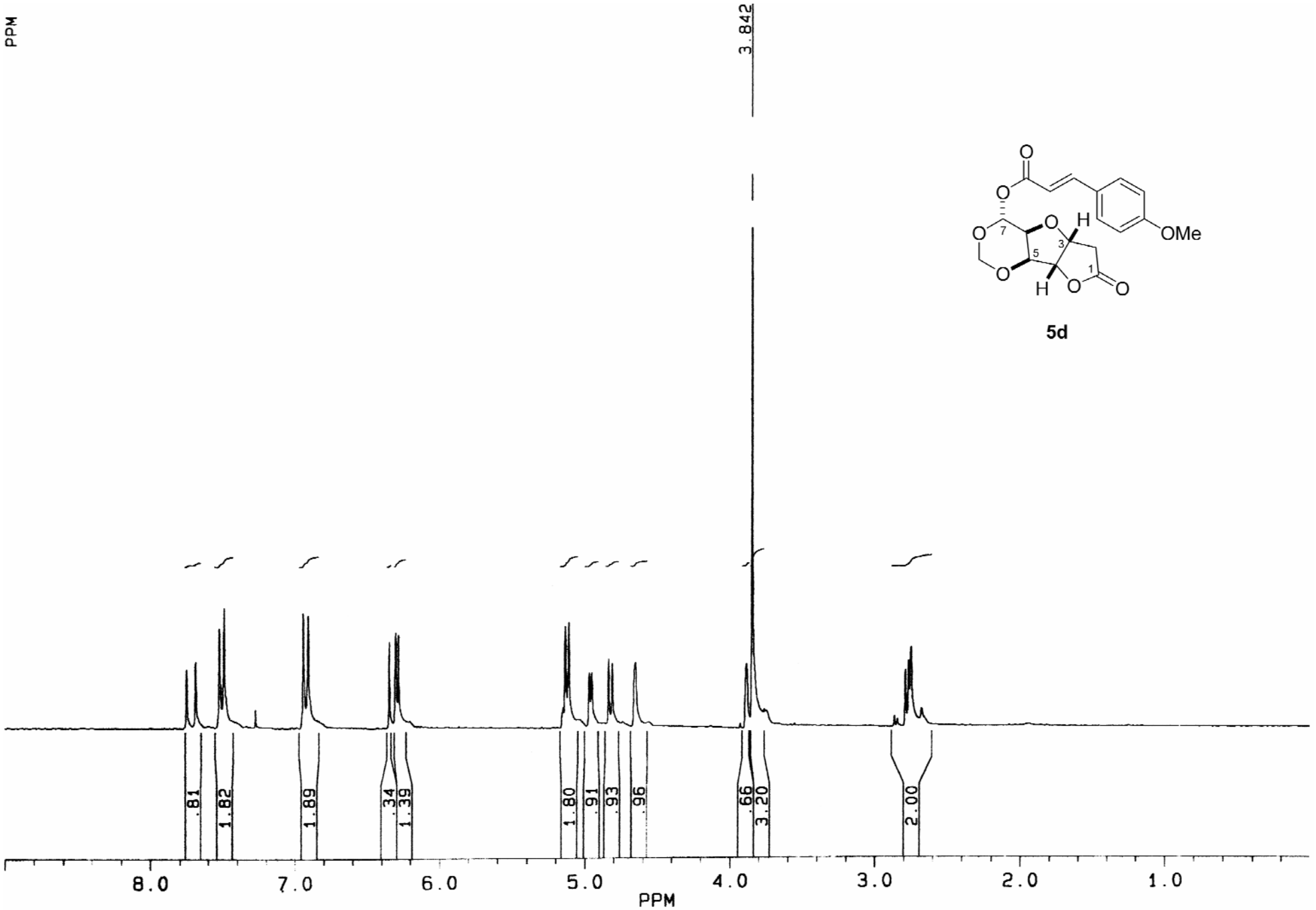
5c

^{13}C NMR Spectrum of Compound 5c (62.9 MHz, $CDCl_3$)



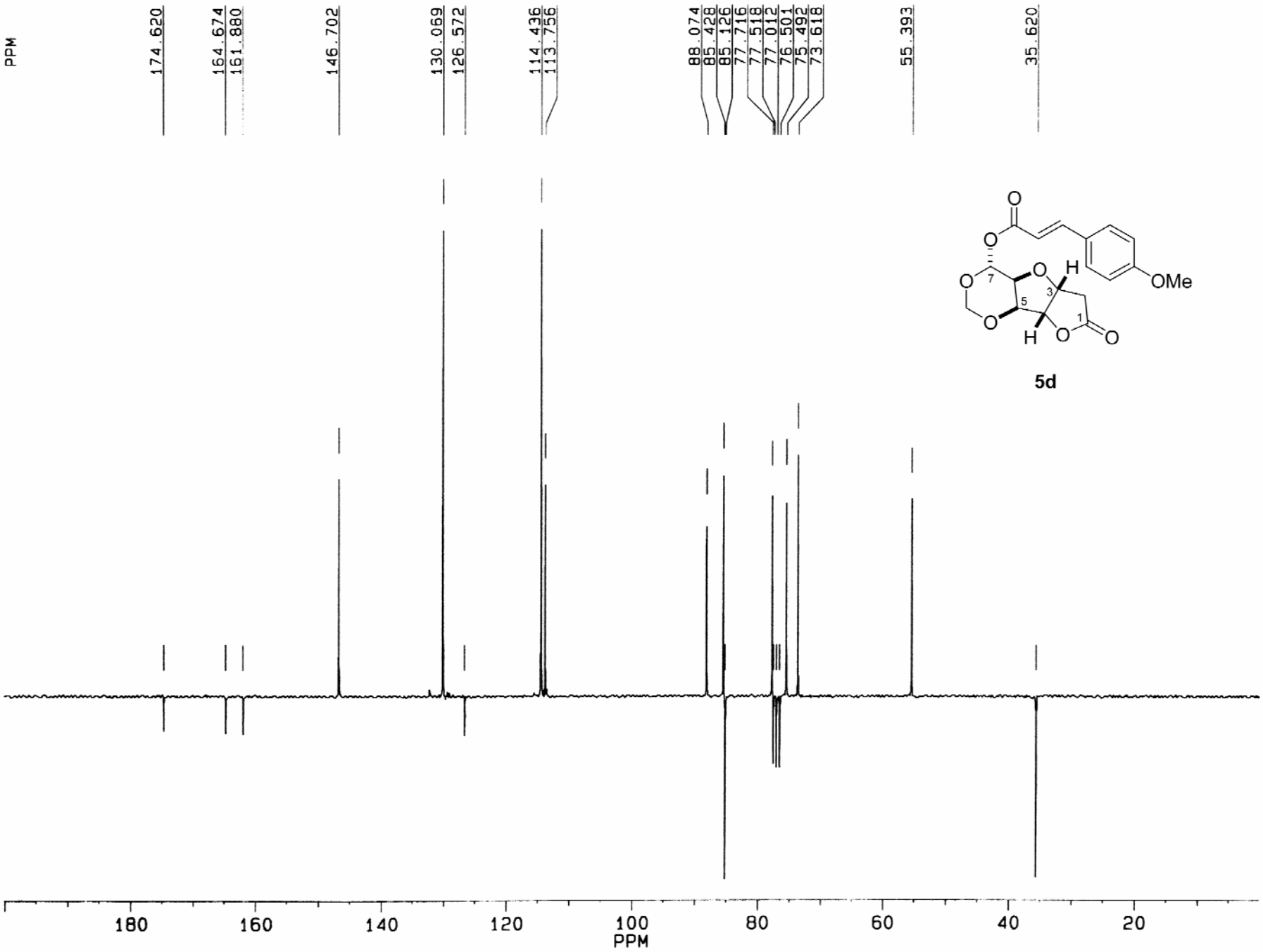
5c

^{1}H NMR Spectrum of Compound 5d (250 MHz, $CDCl_3$)

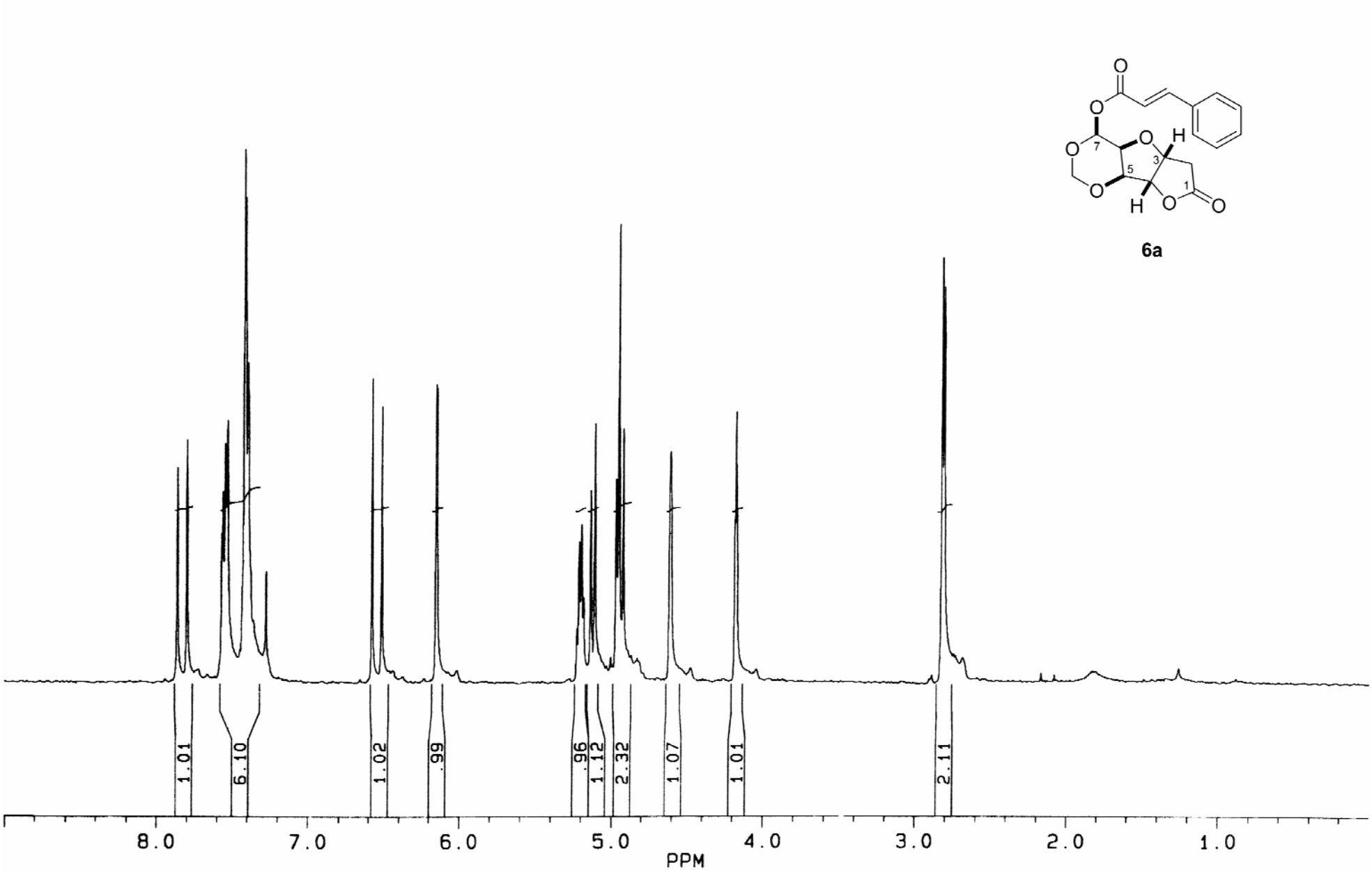


5d

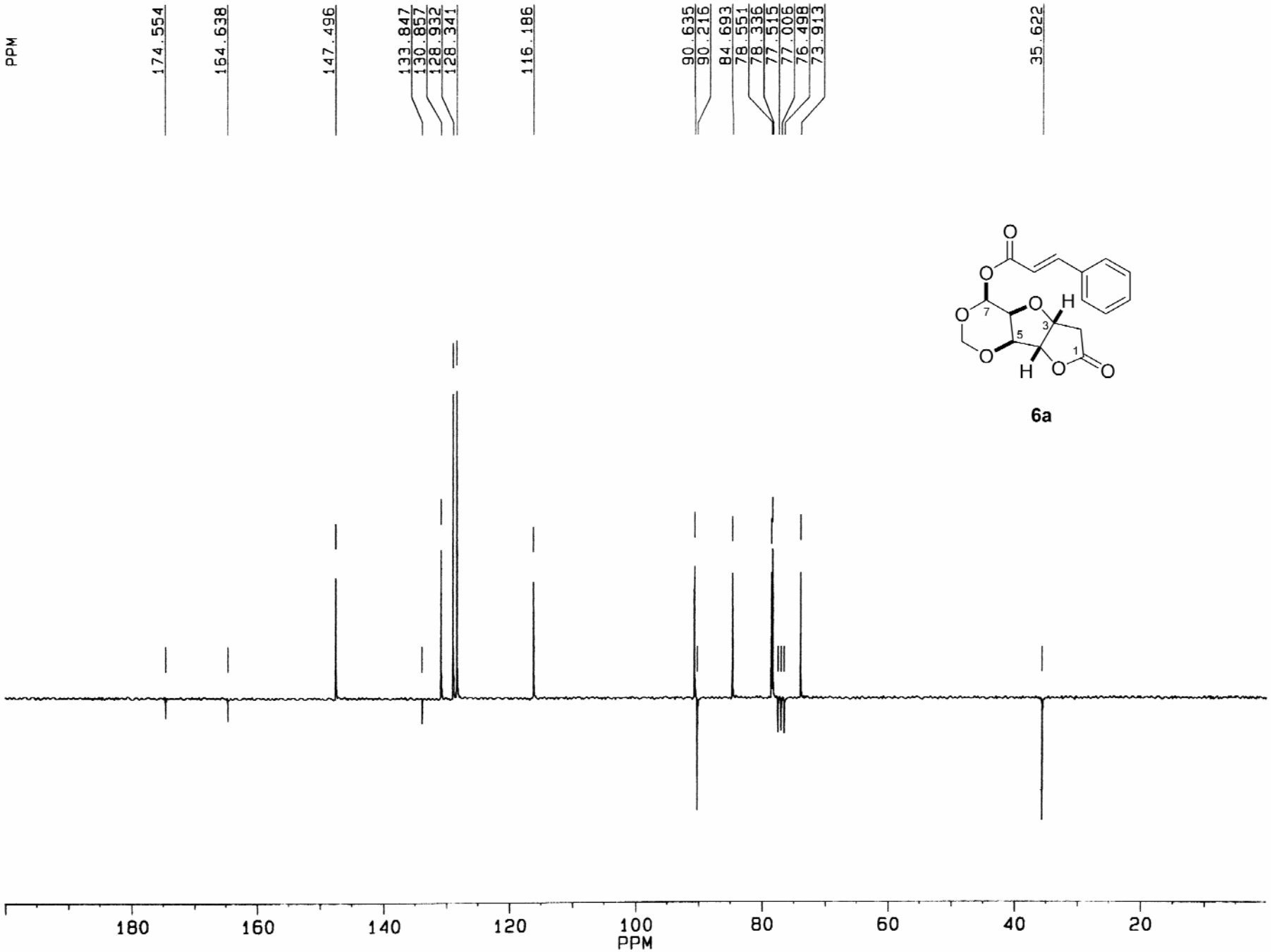
^{13}C NMR Spectrum of Compound 5d (62.9 MHz, $CDCl_3$)



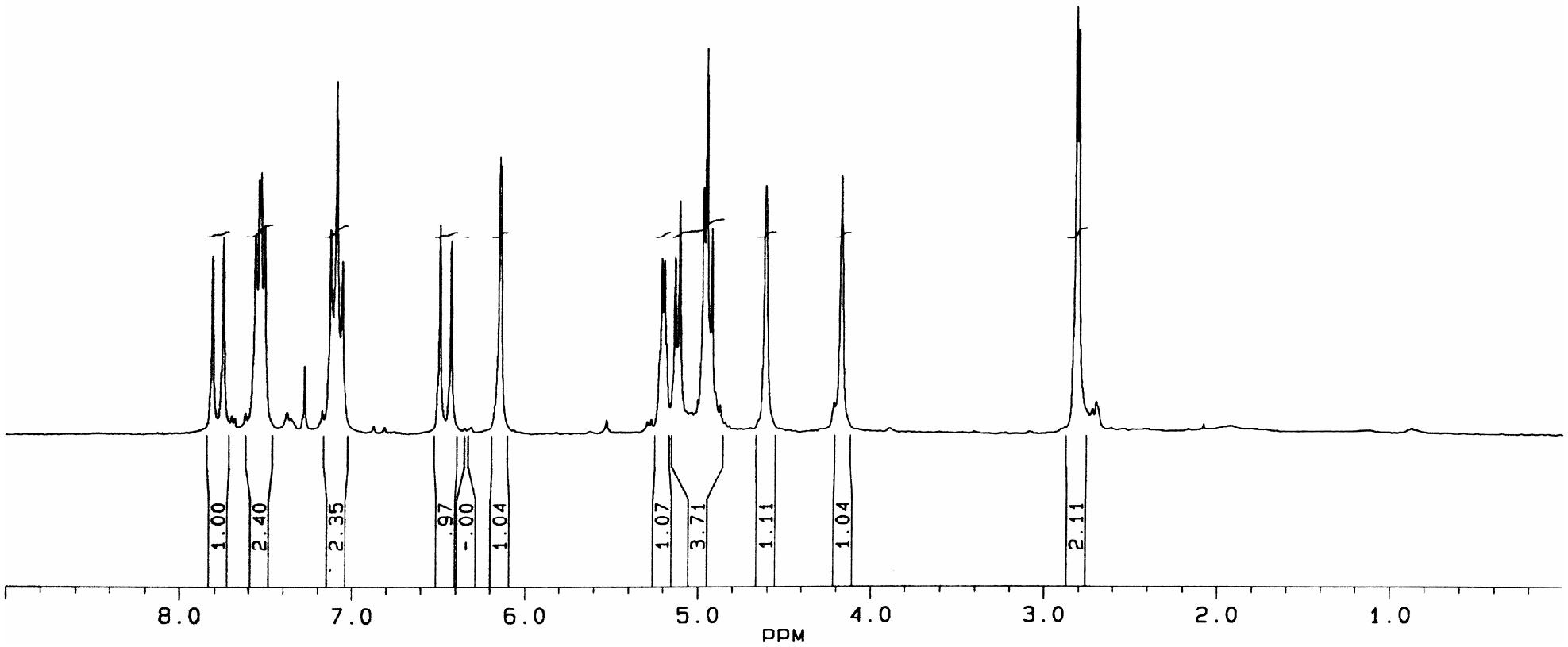
^{1}H NMR Spectrum of Compound 6a (250 MHz, $CDCl_3$)

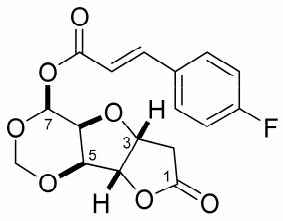


^{13}C NMR Spectrum of Compound 6a (62.9 MHz, $CDCl_3$)



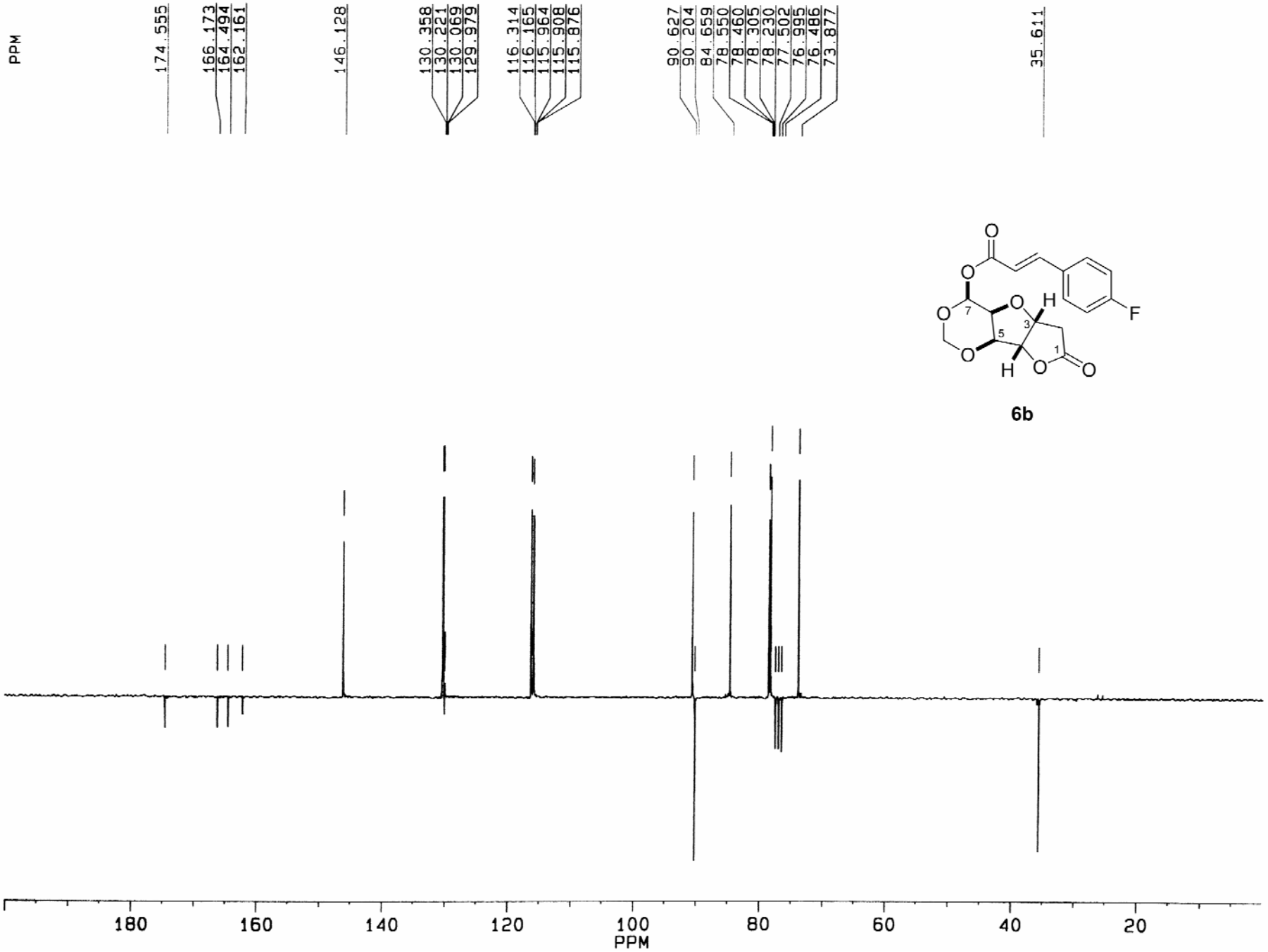
^{1}H NMR Spectrum of Compound 6b (250 MHz, $CDCl_3$)



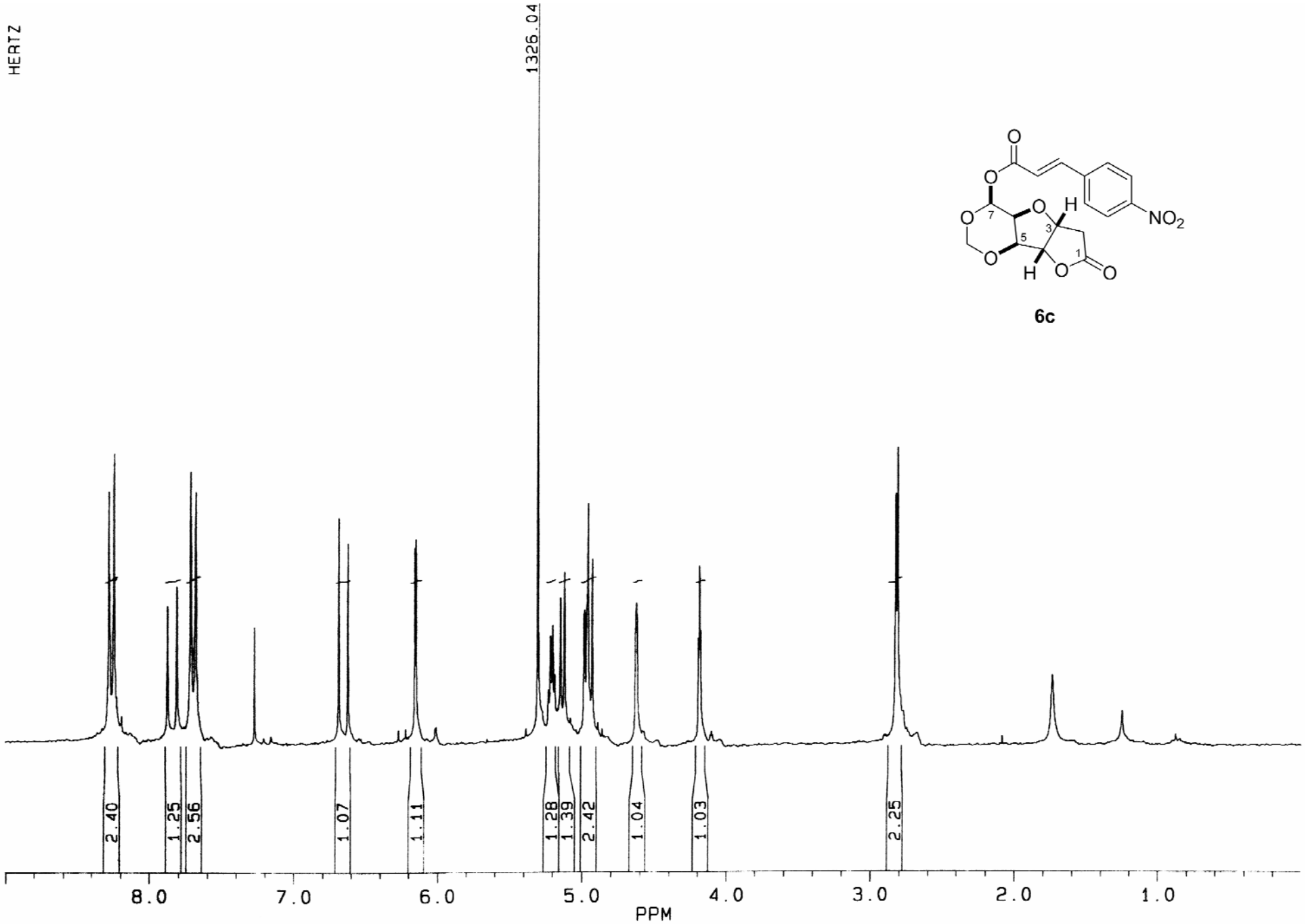


6b

^{13}C NMR Spectrum of Compound 6b (62.9 MHz, $CDCl_3$)

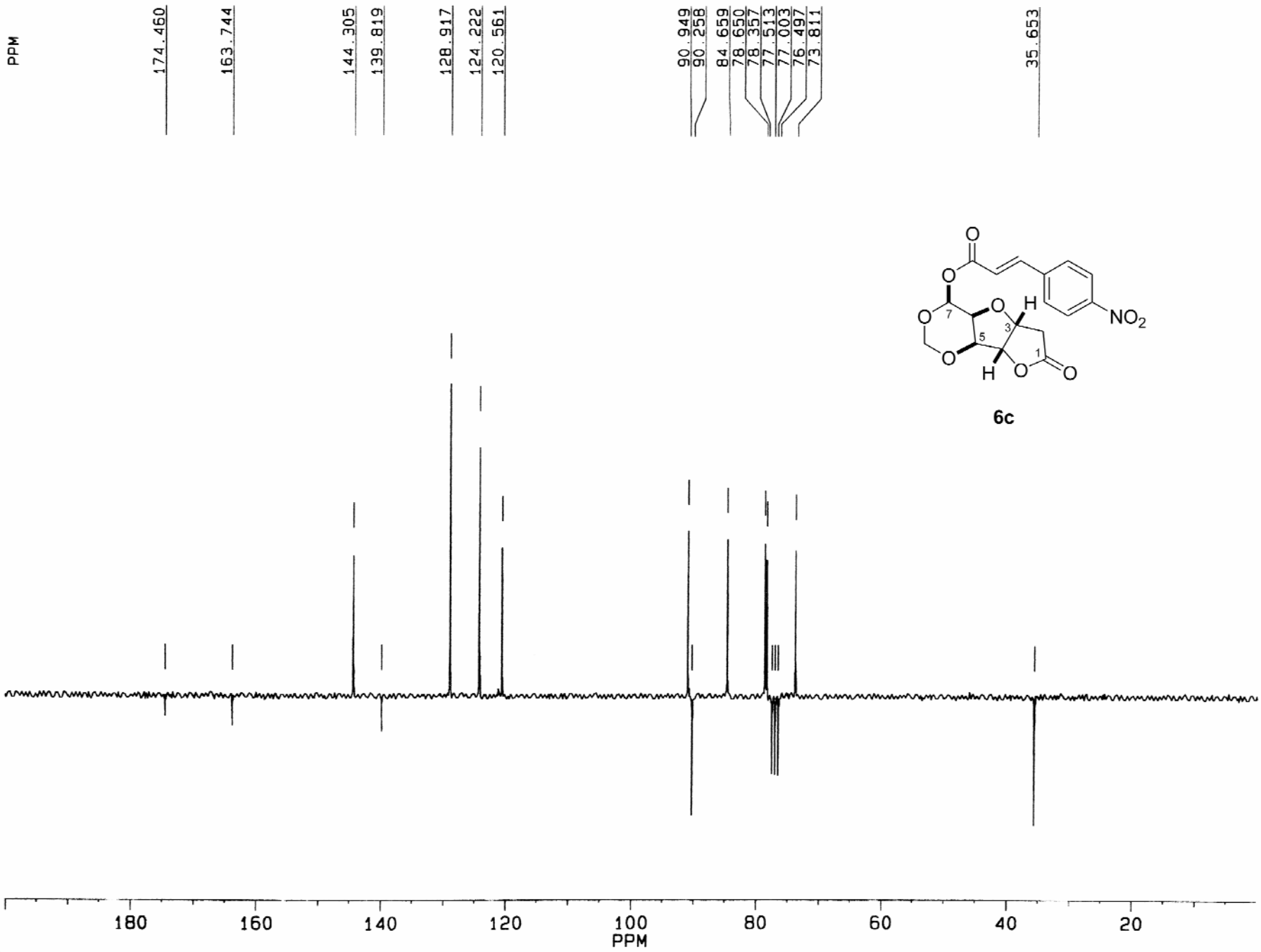


^{1}H NMR Spectrum of Compound 6c (250 MHz, $CDCl_3$)

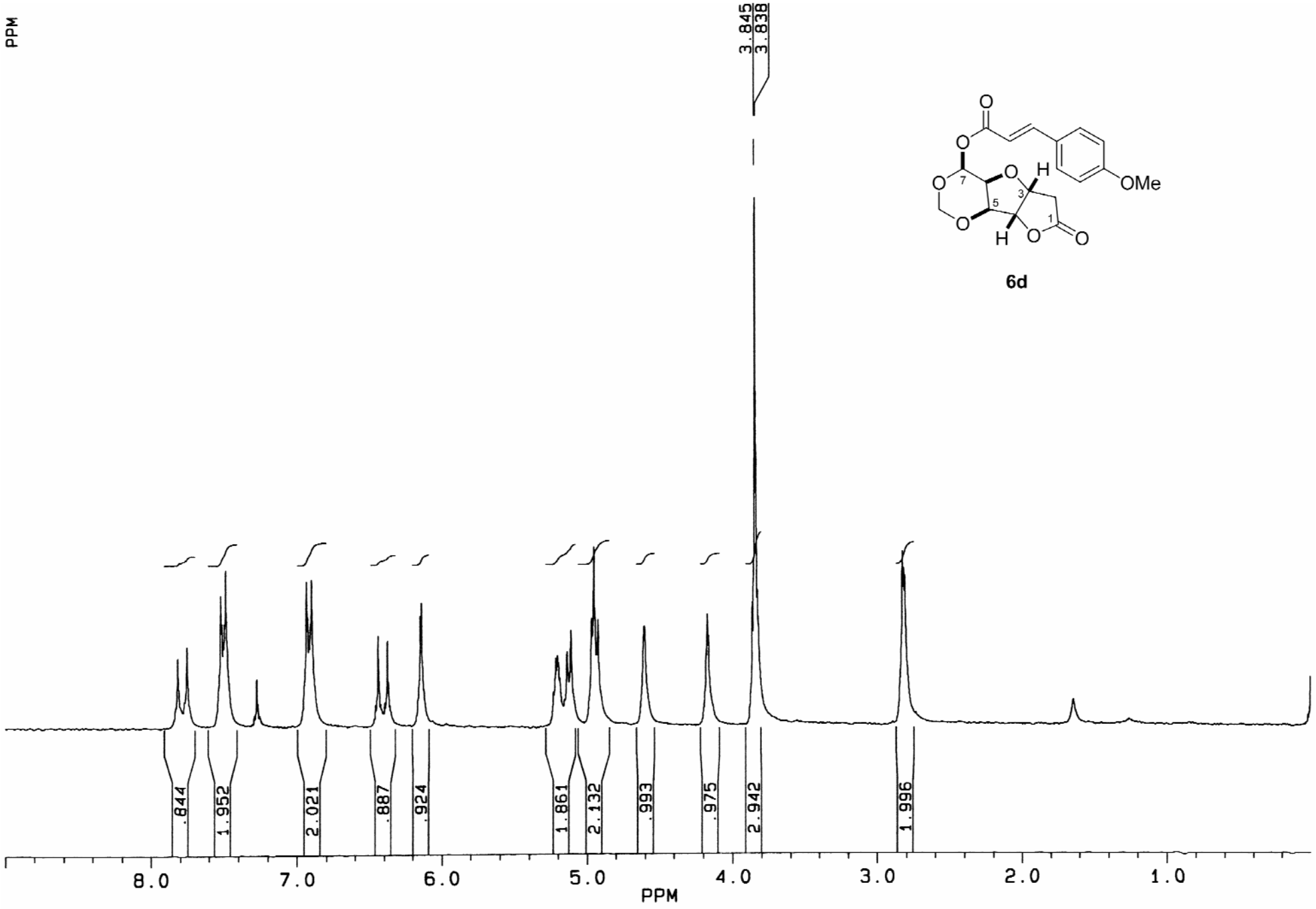


6c

^{13}C NMR Spectrum of Compound 6c (62.9 MHz, $CDCl_3$)



^{1}H NMR Spectrum of Compound 6d (250 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound 6d (62.9 MHz, $CDCl_3$)