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*Original Article*

# IN SEARCH FOR A CONVENIENT, SCALABLE SYNTHESIS OF 5-(3,4-DIHYDROXYPHENYL)-γ-VALEROLACTONE (DHPV): A CLOSER INSPECTION OF A CONDENSATION/ELIMINATION/HYDROGENATION ROUTE

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**ABSTRACT**

5-(3,4-Dihydroxyphenyl)-γ-valerolactone (DHPV) is a natural product, which is produced in the human gut by a microbial metabolism of (epi)catechins. Despite this postbiotic metabolite is known for its significant pharmacological potential, there are no reports on its convenient synthesis in multigram quantities. With an aim of finding a convenient source of DHPV for preclinical studies, we have undertaken an effort to verify the potential of a literature method based on a condensation/elimination/hydrogenation sequence. We have reproduced the protocol for both reaction steps and identified bottlenecks that may be addressed to further improve the proposed pathway. These findings constitute a solid background for finding a suitable way to obtain DHPV for its further pharmacological evaluation.

**KEYWORDS:** 5-(3,4-dihydroxyphenyl)-γ-valerolactone synthesis; DHPV synthesis; postbiotic metabolites; proanthocyanidine metabolites; (epi)catechin metabolites.

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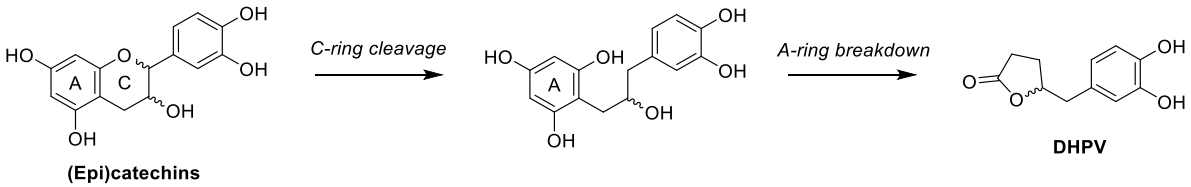
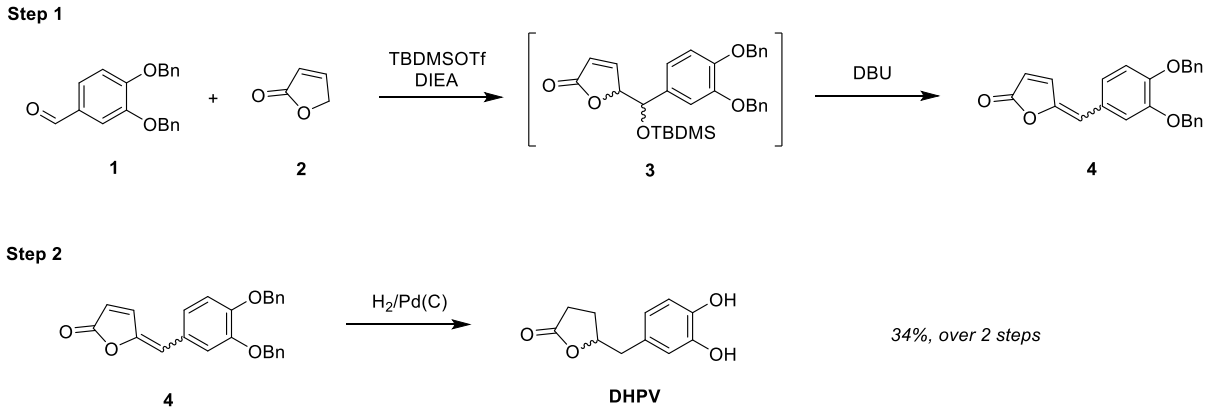
## 1. Introduction

Proanthocyanidines are a group of polyphenols that are ubiquitously found in foods like fruit, vegetables, coffee, tea, red wine and cocoa products. They are only poorly absorbed from the gut and become broken down to smaller compounds by the microbiota present in the colon (Scheme 1). (+/-)-5-(3,4-Dihydroxyphenyl)-γ-valerolactone (DHPV) is the main metabolite of common proanthocyanidines – (epi)catechins [1-3]. Contrary to the precursor compounds, DHPV is absorbed into the bloodstream and has been shown to display interesting *in vitro* properties [4], such as: cardioprotective [5], anticancer [6], anti-inflammatory [7] and anti-platelet [8], which makes it a potentially useful




**Scheme 1.** Microbial metabolism of (epi)catechins leading to DHPV.




**Scheme 2.** Synthesis of (+/-)-5-(3,4-dihydroxyphenyl)-γ-valerolactone (DHPV) by Chang and co-workers [12].

natural product for prevention and treatment of human diseases. DHPV can only be obtained in small quantities from the natural sources. On the other hand, it has a relatively simple chemical structure, therefore chemical synthesis appears to be a plausible method for producing this compound in large quantities. One of our projects required multigram quantities of DHPV for advanced preclinical studies.

Surprisingly, a literature survey showed that despite the potential medical applications of the compound, there are only few methods published in the scientific literature that relate to its chemical synthesis [4,9-12]. Moreover, none of these reports disclosed a process of obtaining the compound at a scale larger than ~1 g. Nevertheless, we were primarily interested in employing the literature methods to obtain large quantities of the compound rather than in developing new synthetic pathways *de novo*. Most of the published protocols appeared rather tedious, consisting in several synthetic steps and provided either modest yields of the product or required expensive and hazardous reagents. We turned our attention to one method described by Chang and co-workers (Scheme 2) [12]. It consisted of two reaction steps. In the first step, the reaction of 3,4-dibenzyloxybenzaldehyde **1** with furan-2(5*H*)-one **2** in the presence of tert-butyldimethylsilyl triflate (TBDMSOTf) gave the key silyloxy **3**. A subsequent addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) triggered an elimination reaction, leading to a one-pot formation of a conjugated diene **4**. In the second step of the synthesis, **4** was subjected to a simultaneous catalytic debenzylation/ double bond hydrogenation to give the target DHPV. From all the reported methods of DHPV synthesis, this pathway appeared most suitable for our goals because of its operational simplicity and a relatively low cost of reagents and solvents. Therefore, in this work, we attempt to verify the robustness of the method and assess its potential scalability to obtain DHPV in multigram quantity.

## 2. Materials and methods

### 2.1. General remarks

Reagents were purchased from commercial suppliers without additional purification. Anhydrous solvents for the first synthesis step were purchased from commercial sources, and the reaction was conducted under argon. HPLC-grade methanol was used for catalytic hydrogenation step. Solvents for flash column chromatography (FC) were distilled before use. The compound purification was performed by FC on Merck silica gel 60 (particle size 0.040–0.063 mm, 230-400 mesh ASTM). Analytical thin layer chromatography was performed using Merck TLC Silica gel 60 glass plates. Nuclear magnetic resonance (NMR) spectroscopy data were collected using Varian 500 MHz VNMRS or Agilent 400-MR DD2 400 MHz spectrometers and analyzed using MNova. Liquid chromatography-mass spectrometry (LC-MS) analyses were performed on an Agilent 1220 Infinity II Gradient LC system coupled with an Agilent LC-MSD single-quadrupole detector, column: Poroshell 120, EC-C18 (3.0 × 50 mm, 2.7 µm particle size), mobile phase: MeCN/water, detection: UV monitoring at 220 and 254 nm wavelengths.

### 2.2. General procedure for the synthesis of 5-(3,4-bis(benzyloxy)benzylidene)furan-2(5H)-one (4)

Reaction solvent (10 mL per 1 mmol of the limiting substrates) was stirred in a round bottom flask. Furan-2(*5H*)-one (1.0 eq.) and TBDMSOTf or trimethylsilyl chloride (TMSCl) (1.1 eq.) were added, followed by 3,4-dibenzyloxybenzaldehyde (1.0 eq.). Next, *N*,*N*-diisopropyl-*N*-ethylamine (DIPEA) (3.0 eq.) was added slowly. The mixture was stirred for one hour. DBU (2.0 eq.) was added dropwise, after which stirring was continued for one hour. In some instances, the reaction conditions varied slightly, for specific details please refer to Table 1 in the Results section. The reaction mixture was concentrated using a rotary evaporator. The resulting oil was subjected to FC on $SiO_2$, eluent: cyclohexane to cyclohexane/ethyl acetate 1:1 (v/v). The fractions containing purified product (TLC) were pooled, transferred to a flask, concentrated using a rotary evaporator and dried under high vacuum.

### 2.3. General procedure for the catalytic hydrogenation of 4

A stirred mixture of diene **4** (1.0 eq.) in HPLC-grade acetonitrile (3.5 mL per 1 mmol of substrate) was degassed by a steady passage of argon for 15 min. Next, 10% Pd on carbon (0.01 eq. Pd) was added and hydrogen gas was bubbled through for 30 min. The reaction mixture was stirred at room temperature for 18 h under a positive pressure of hydrogen (maintained by a balloon filled with hydrogen gas), when the LC–MS analysis indicated complete conversion of the substrate. Argon was bubbled through the reaction mixture. The catalyst was removed by filtration on celite pad, which was then washed with acetonitrile. The filtrate was concentrated using a rotary evaporator and the crude product (DHPV) was purified by FC on $SiO_2$, eluent: cyclohexane/ethyl acetate 6:1 to 1:1 (v/v).

### 2.4. Compound characterization

**(5*E*)-(3,4-bis(benzyloxy)benzylidene)furan-2(5*H*)-one (4):** brown oil; LC-MS (ESI+): m/z 385 [M+H]+; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.54 - 7.22 (m, 13H, Ar-H), 6.91 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.13 (dd, *J* = 5.3, 0.9 Hz, 1H, Ar-H), 5.89 (s, 1H, CH), 5.22 (s, 2H, $CH_2$-Ar), 5.20 (s, 2H, $CH_2$-Ar). (Appendix, Figure A2).

**5-(3,4-Dihydroxyphenyl)-γ-valerolactone (DHPV):** white solid; m.p. 126—130 ℃ (lit. m.p. 128—130 ℃ [13]) LC-MS (ESI+): m/z 209 $[M+H]^+$; $^1$H NMR (500 MHz, $CD_3OD$) δ 6.72 - 6.70 (m, 2H, Ar-H), 6.57 (dd, *J* = 8.0, 2.1 Hz, 1H, Ar-H), 4.74 - 4.69 (tt, *J* = 7,2, 6.1 Hz, 1H), 2.88 (dd, *J* = 14.0, 6.2 Hz, 1H), 2.79 (dd, *J* = 14.0, 6.2 Hz, 1H) overlapped with residual $CH_3OH$, 2.52 - 2.44 (m, 1H), 2.33 (ddd, *J* = 17.7, 9.5, 4.8, 1H), 2.23 (dddd, *J* = 12.8, 9.8, 6.8, 4.8 Hz, 1H), 1.99 - 1.91 (m, 1H). (Appendix, Figure A7).

### 3. Results

We first examined the one-pot condensation/elimination step of the literature pathway. The results are summarized in Table 1. The original experimental protocol by Chang and co-workers [12] for this reaction utilized 1.157 mmol of reagents **1** and **2**, providing 0.167 g of the diene **4** (38% yield, Table 1, Entry 1). Initially, we performed the reaction on a roughly twice larger scale (2.38 mmol of the building blocks). In general, we used the same conditions as those described in the literature, but we opted to verify whether tetrahydrofuran (THF) and dichloromethane (DCM) can be used interchangeably as solvents. The reason for this was the ambiguity of the literature source, in which THF is mentioned in the scheme caption whereas DCM is described as the solvent in the experimental section. Further, the original experimental protocol did not specify the amount of TBDMSOTf employed in the condensation. Since the reaction leading to the silyloxy **3** is most likely not a catalytic process but a three-component condensation/elimination, we assumed that at least an equimolar amount of TBDMSOTf must be used for full conversion of the starting materials. Using THF as a solvent resulted in the formation of a complex post-reaction mixture, as judged by the TLC analysis (Table 1, Entry 2). Hence, isolation of **4** was not attempted as it would be inseparable from the byproducts. First attempt to use DCM led to the formation of target diene **4** (Table 1, Entry 3). However, even though the product was purified by FC, substantial amounts of impurities were detected by the $^1$H NMR analysis of the product (Appendix, Fig. 1A). Repeating the experiment in exactly same conditions provided analytically pure **4** (Table 1, Entry 4). However, we found the chromatographic purification tedious. Further, separation of the *E*- isomer of **4** from its *Z*- counterpart and from the unreacted 3,4-dibenzyloxybenzaldehyde **1** was impractical, thus it needed to be discarded in the purification process. Although this attempt gave only 14% of the pure *E*-isomer **4** ($^1$H NMR, Appendix, Fig. A2), we decided to further scale up the process, using 6.28 mmol of the limiting reagents (Table 1, Entry 5). This gave **4** in 33% yield, which was similar to the one reported in the literature. Although the $^1$H NMR analysis indicated the presence of some impurities after FC purification (Appendix, Fig. A3), we considered this result promiscuous and proceeded with a further scale-up to 31.41 mmol (Table 1, Entry 6). This gave **4** in a 55% yield. Again, minor impurities were detected by $^1$H NMR (Appendix, Fig. A4).

All these attempts utilized a slight excess of the relatively expensive TBDMSOTf to generate the silyloxy **3**. Therefore, we posed a question if TMSCl can be used as a cheaper alternative, as this would lead to the formation of a similar silyloxy intermediate. However, an initial experiment run on a 3.14 mmol scale gave only 8% of **4** (Table 1, Entry 7), which was of low purity (Appendix, Fig. 5). Prolonging the elimination reaction time to 3 days did not provide better results and **4** was formed with a similar yield (13%, Table 1, Entry 8) and purity ($^1$H NMR, Appendix, Fig. A6).

The results show that in our hands **4** can be obtained on a few-gram scale, in yields comparable to those described by Chang and co-workers. However, the significant loss of yield is to be expected upon extensive repurification of the reaction product. Hence, we next verified, if we can obtain satisfactory yields of the second reaction leading to the target DHPV. Therefore, we subjected the partially contaminated samples of diene **4** to the Pd – catalyzed removal of benzyl protecting groups from the phenolic hydroxyls, with the parallel reduction of two double bonds. Following the literature protocol, a 2.08 mmol sample of **4** (obtained using conditions from Table 1, Entry 5) was hydrogenated to give **DHPV** in a 59% yield [12]. In another attempt, using a larger amount (17.29 mmol) of diene **4** from experiment (obtained using conditions from Table 1, Entry 6), the reaction yield dropped further, to 40%, after purification.

**Table 1.** Investigation of the condensation/elimination step[a].

| Entry | Scale [mmol] | Solvent | Activator | Yield [g] |
|---|---|---|---|---|
| **1** | 1.157 | THF or DCM | TBDMSOTf | 0.167 (38%)[b] |
| **2** | 2.38 | THF | TBDMSOTf | - |
| **3** | 2.38 | DCM | TBDMSOTf | 0.417 (45%) |
| **4** | 2.38 | DCM | TBDMSOTf | 0.133 (14%)[c] |
| **5** | 6.28 | DCM | TBDMSOTf | 0.800 (33%) |
| **6** | 31.41 | DCM | TBDMSOTf | 6.640 (55%) |
| **7** | 3.14 | DCM | TMSCl | 0.098 (8%) |
| **8**[d] | 3.14 | DCM | TMSCl | 0.152 (13%) |

[a]Unless otherwise stated, each reaction was performed using 1.0 eq. of building blocks 1 and 2, 1.1 eq. of TBDMSOTf and 3.0 eq. of DIPEA, for 1 h. Subsequently it was run for additional 1 h after treatment with 2.0 eq. of DBU; [b]General reaction conditions and yield taken from the literature [12]; [c]Yield of the analytically pure product; [d]The reaction was run for additional 3 days after treatment with 2.0 eq. of DBU.

## 4. Discussion

Reproducibility of experimental protocols and scalability are important features of a synthetic pathway that influence its application to obtain a target compound in a large scale. In this work we have assessed if the method described by Chang and co-workers has the potential to provide a postbiotic metabolite DHPV in amounts required for the advanced preclinical development of the compound. First, we have clarified minor, formal shortcomings of the experimental protocol for the condensation/elimination step, i.e. the ambiguous solvent description and unknown amount of TBDMSOTf used in the reaction. Next, we made an attempt to gradually scale-up the process (up to 31.41 mmol). In general, we were able to reproduce the literature results. However, it must be noted that a significant drop of chemical yield may be experienced during the repurification of the compound by FC on silica, among others because of the very similar retention of unreacted aldehyde **1** and the respective *E*- and *Z*- isomers of the target diene **4**. Finally, although the presence of impurities does not inhibit the final catalytic hydrogenation reaction leading to DHPV, the chemical yield of the target compound drops considerably upon use of the partially purified substrate. In conclusion, the investigated literature pathway may be suitable for further scale up, however, optimization of the purification process of **4** and testing the alternative conditions of the subsequent catalytic hydrogenation reaction may be required for better effectiveness and fully reproducible results.

**Author Contributions:** Conceptualization, J.G., S.G., J.K, J.P. and M.D.; methodology, M.N., M.S., M.W. and M.D.; validation, M.N, M.S., K.K. and M.D.; investigation, M.S., K.K., M.N., M.W.; resources, J.P. and M.D.; data curation, M.S., M.N. and M.D.; writing—original draft preparation, M.S., K.K. and M.D.; writing—review and editing, M.S,. K.K., M.N., M.W. and M.D.; visualization, K.K and M.D.; supervision, M.D.; project administration, J.P. and M.D.; funding acquisition, J.G., S.G., J.K., J.P. and M.D. All authors have read and agreed to the published version of the manuscript.

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**Conficts of interest:** The authors declare no conflicts of interest.

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## Appendix

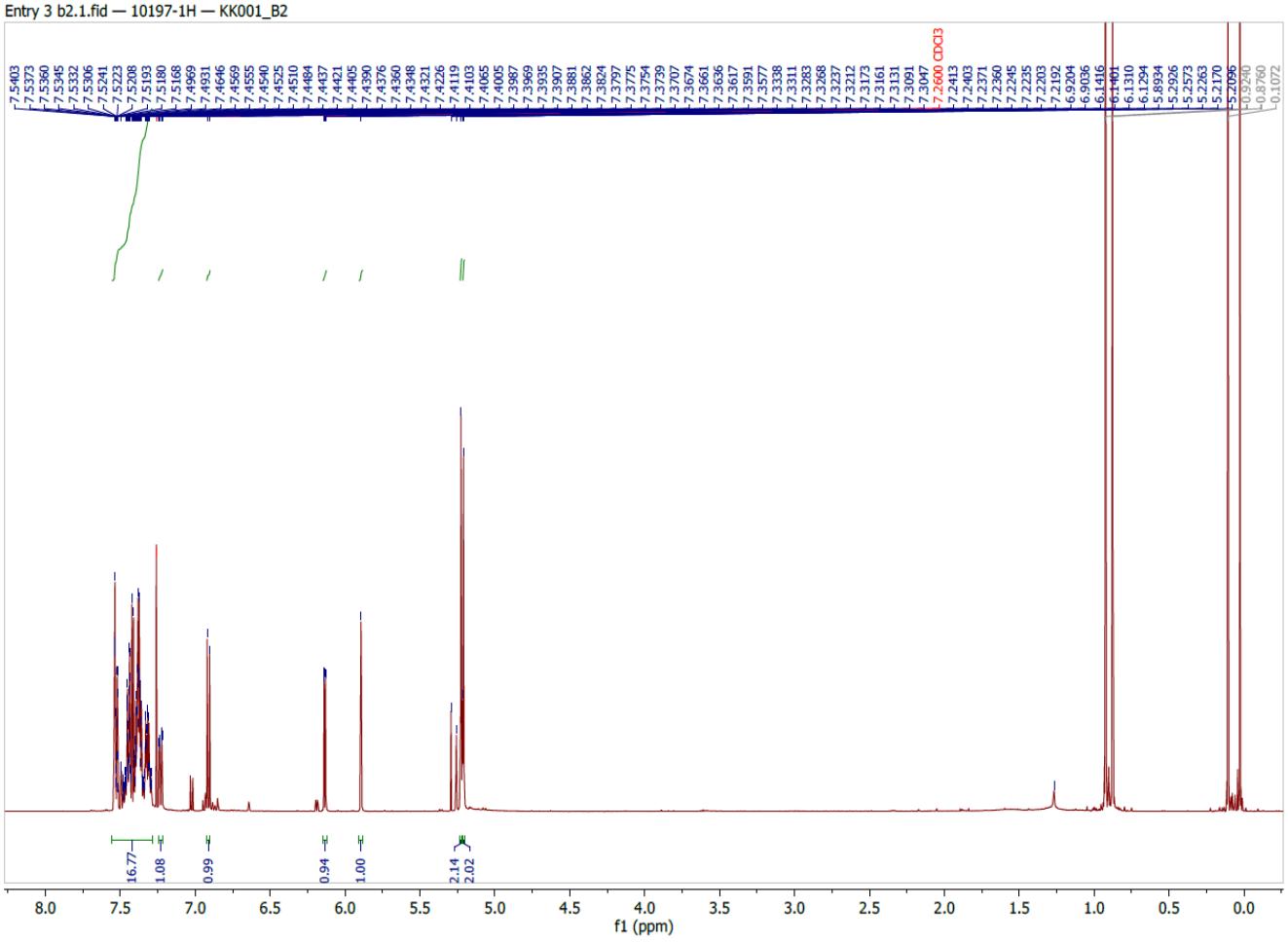


**Fig. A1.** $^{1}$H NMR spectrum (500 MHz, $CDCl_3$) of **4** obtained using conditions described in Table 1, Entry 3

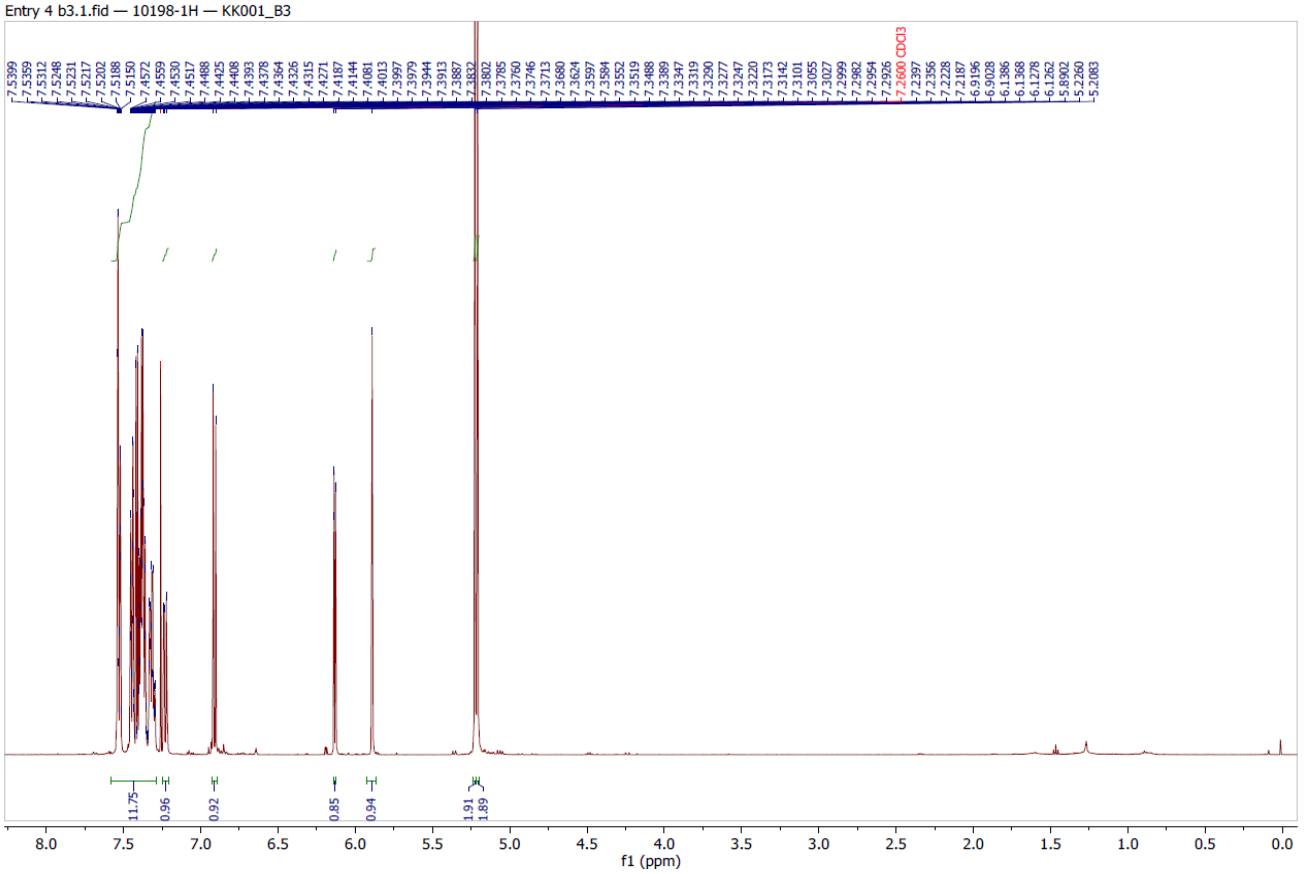


**Fig. A2.** $^{1}$H NMR spectrum (500 MHz, $CDCl_3$) of **4** obtained using conditions described in Table 1, Entry 4

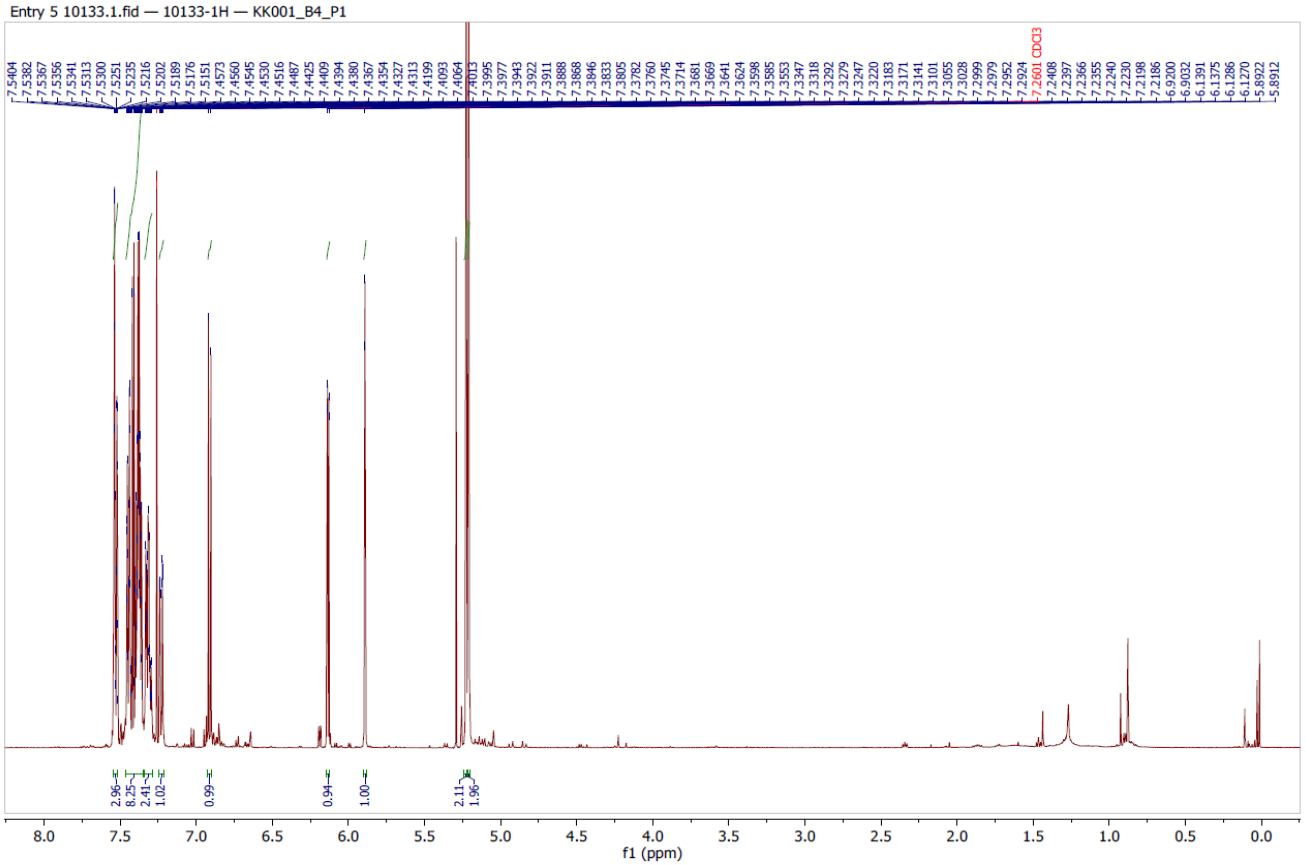


**Fig. A3.** $^{1}$H NMR spectrum (500 MHz, $CDCl_3$) of **4** obtained using conditions described in Table 1, Entry 5

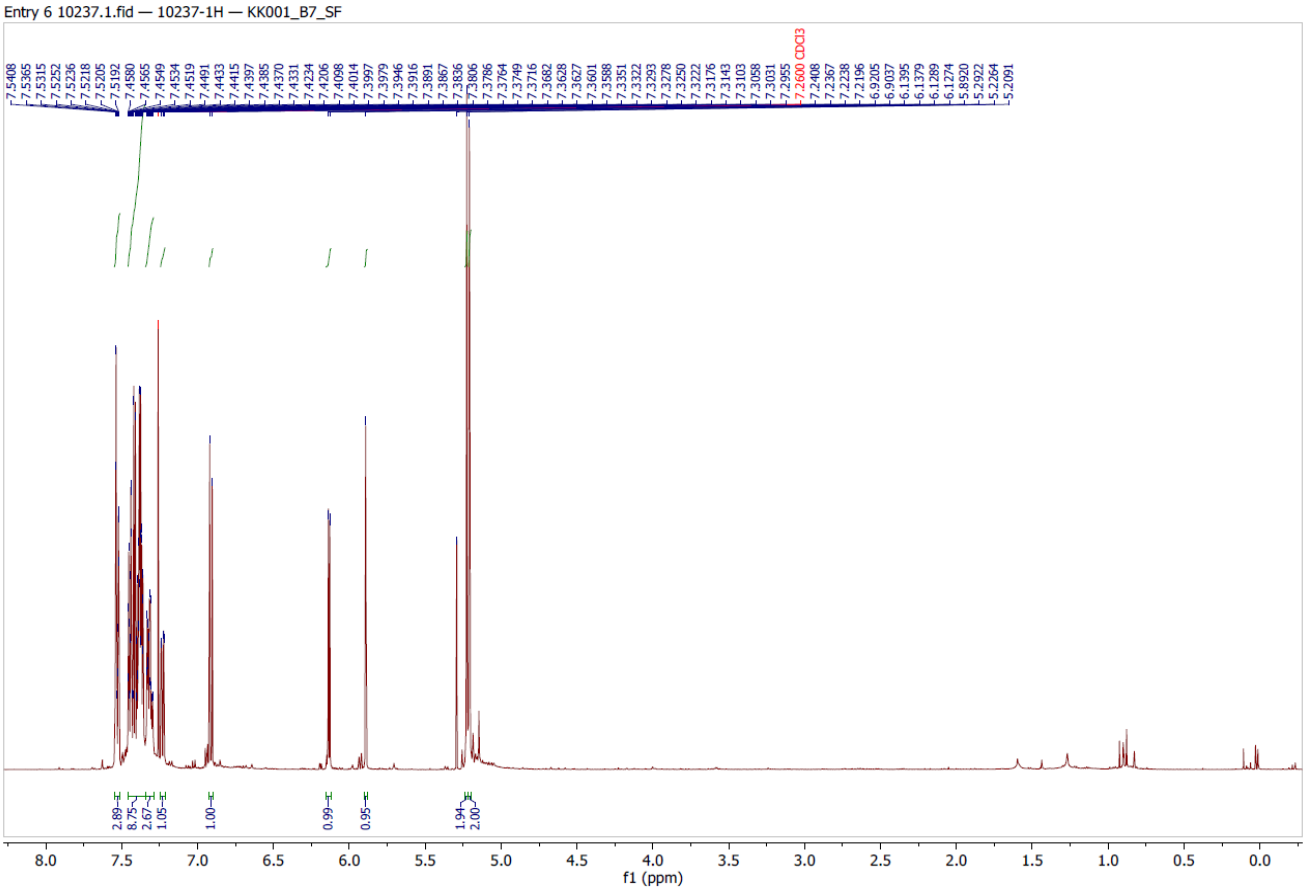


**Fig. A4.** $^{1}$H NMR spectrum (500 MHz, $CDCl_3$) of **4** obtained using conditions described in Table 1, Entry 6

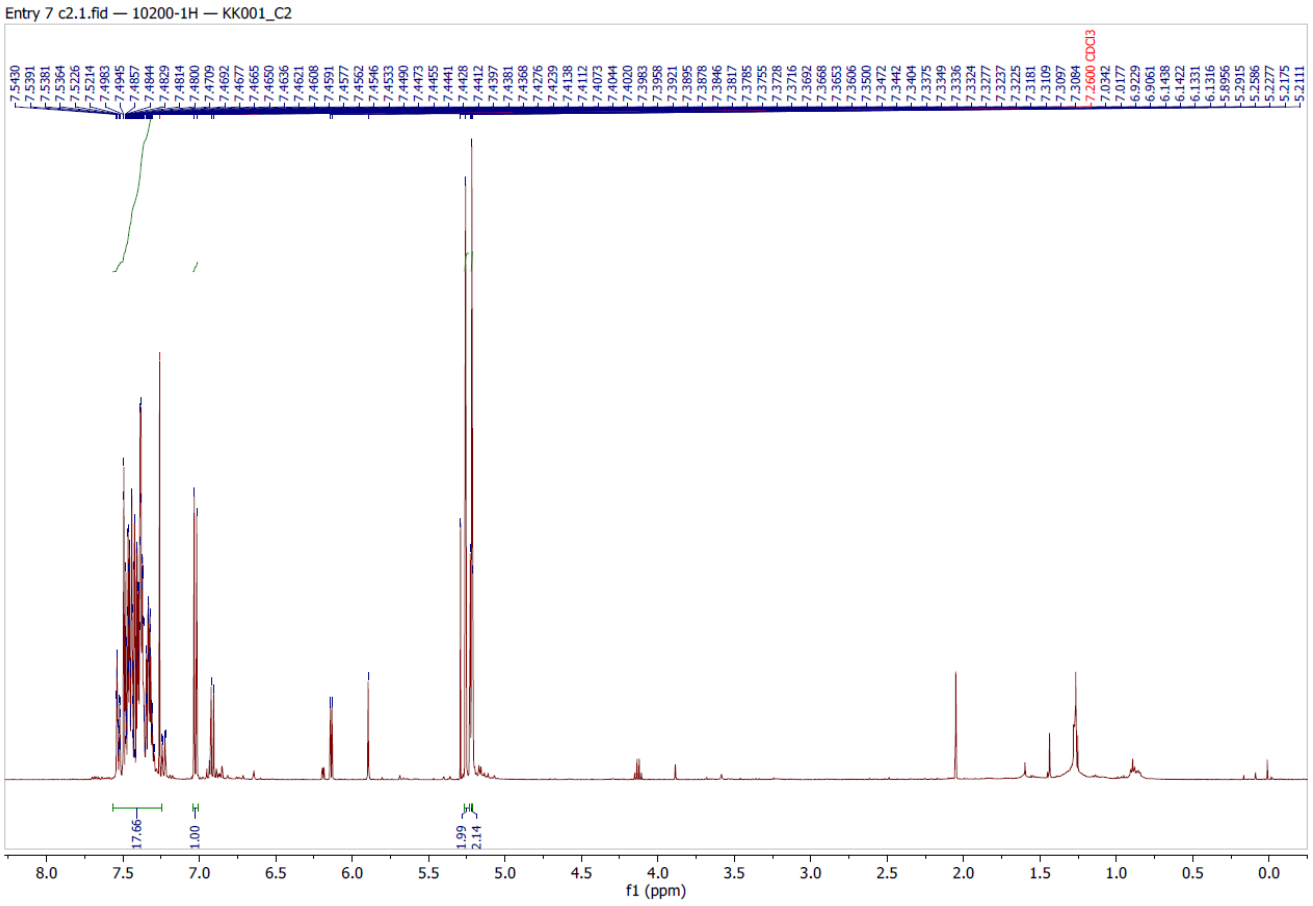


**Fig. A5.** $^{1}$H NMR spectrum (500 MHz, $CDCl_3$) of **4** obtained using conditions described in Table 1, Entry 7

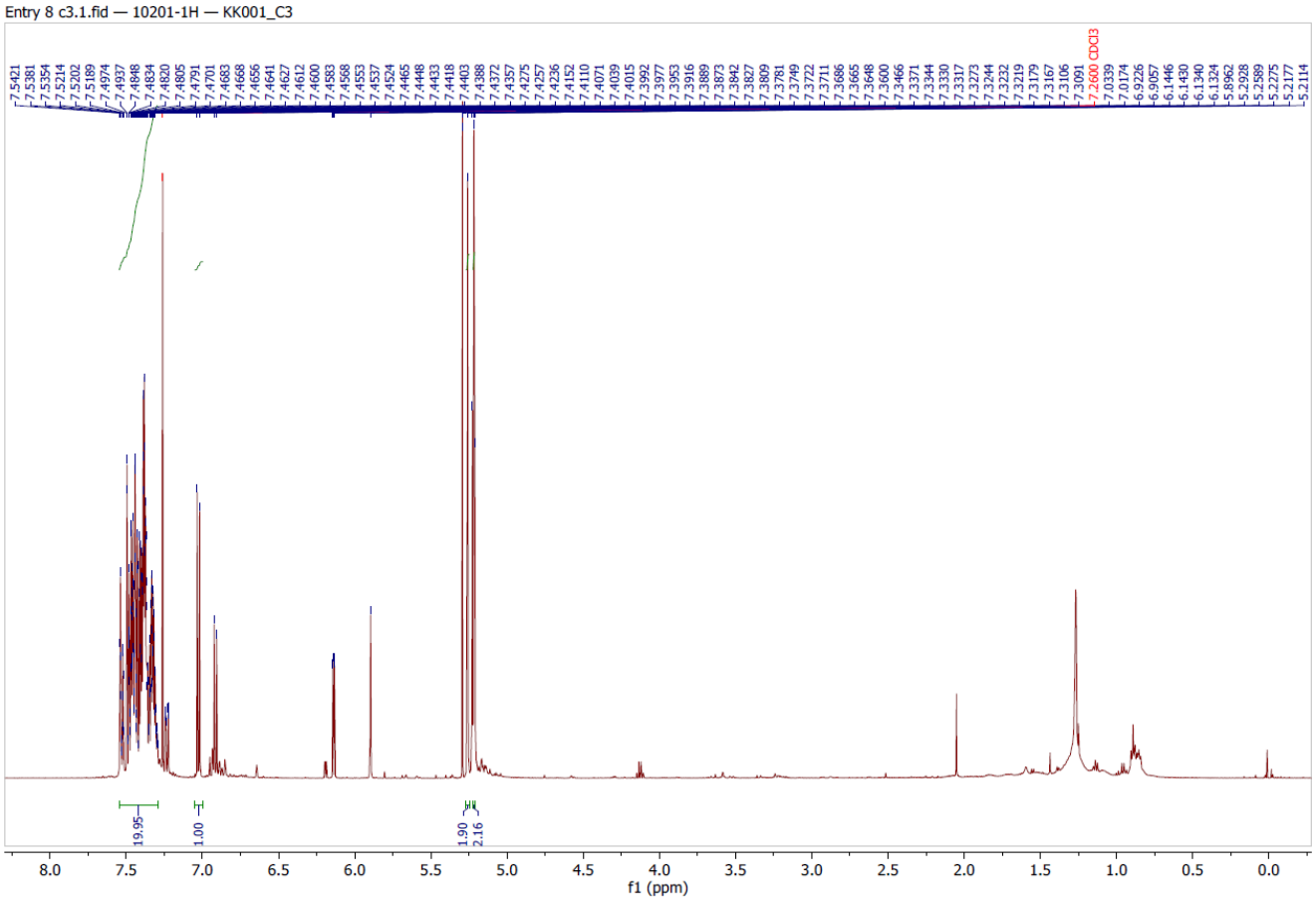


**Fig. A6.** $^{1}$H NMR spectrum (500 MHz, $CDCl_3$) of **4** obtained using conditions described in Table 1, Entry 8

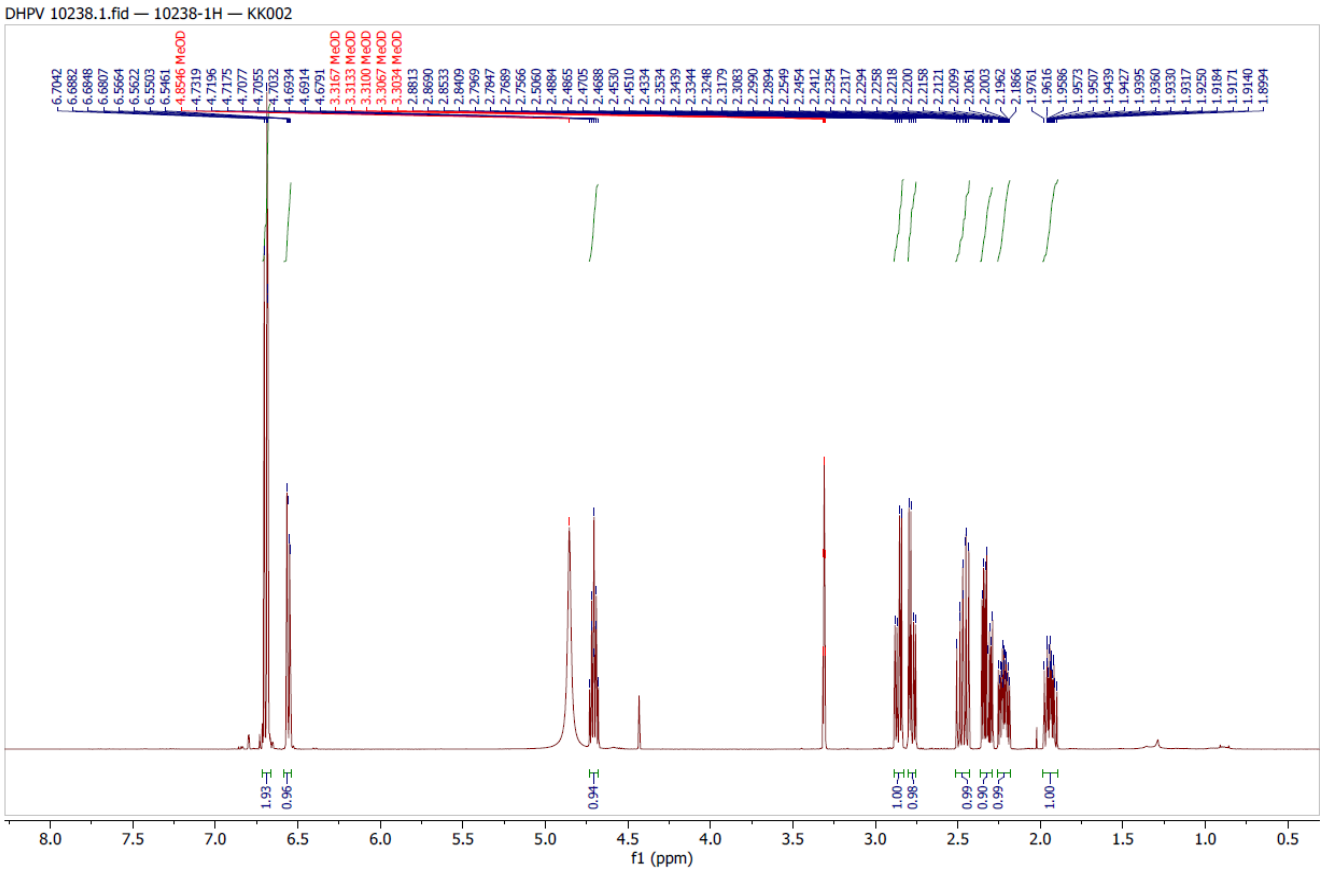


**Fig. A7.** $^{1}$H NMR spectrum (500 MHz, $CD_3OD$) of DHPV

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