molbank

MDPI

Short Note

4,7-Dimethoxy-6-propyl-2*H*-1,3-benzodioxole-5-carbaldehyde

Dmitry V. Tsyganov and Victor V. Semenov *

N. D. Zelinsky Institute of Organic Chemistry Russian Academy of Sciences, 47 Leninsky Prospect, 119991 Moscow, Russia; tsyg@ioc.ac.ru

* Correspondence: vs@ioc.ac.ru; Tel.: +7-499-1356343

Abstract: A simple intermediate for the synthesis of methoxy-analogues of coenzymes Q with substituents having various chain lengths based on natural polyalkoxyallylbenzene apiol has been developed.

Keywords: quinone; coenzyme; apiol; cancer; antitumor; formylation

1. Introduction

1,4-Quinones and hydroquinones with various functional substituents alongside the isoprenoid and long chains is an important cancer-related class of coenzymes Qn. Simple coenzyme Q_0 was found to possess antitumor properties, in particular, it inhibits the metastasis of breast [1], skin (melanoma) [2], and ovarian [3] cancer in mice. The majority of the syntheses of Qn coenzymes are based on the incorporation of hydrocarbon chains into an already prepared quinone, coenzyme Q_0, by oxidative radical reactions, which have a number of drawbacks [4].

2. Results and Discussion

We found an easy method for synthesizing the intermediates of Q_0 and its analogues with methoxy, methylenedioxy, methyl and alkyl substituents in the ring based on allylpolymethoxybenzenes (like apiol **1**) that are easily isolated in large quantities from CO_2 extracts of parsley and dill seeds [5]. Previously, it was shown that apiol aldehyde **2** is oxidized by the Baeyer–Villiger reaction to the corresponding phenol **3** and then to quinone **4** [6] (Scheme 1). Recently, it was shown that apiole **1**, dihydroapiol **5**, and a number of other derivatives [7,8] inhibited colon cancer cells COLO 205.

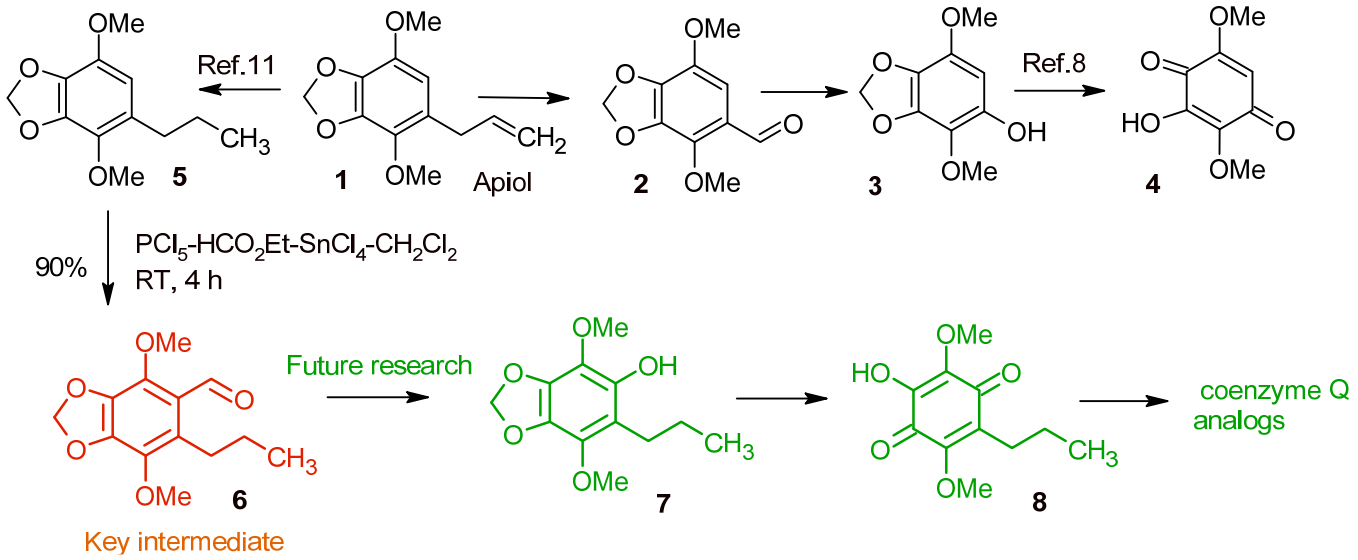
The oxidative rearrangement of apiol aldehyde derivatives (like **6**) with various substituents in the ortho position would make coenzyme Q analogs available, where a methoxy group is present instead of a methyl group. In this work, we developed a procedure for obtaining one of the key intermediates **6** for the future synthesis of a series of coenzyme Q analogues through intermediate phenol **7** and quinone **8** from apiol **1**, which we isolated from parsley essential oil, in the amount of several kg. Aldehyde **6** was obtained by the formylation of dihydroapiol **5**, according to a previously developed procedure, in the presence of $SnCl_4$ [8] with a yield of 90% (Scheme 1). The hydrogenation of apiol **1** to dihydroapiol **5** was carried out on highly porous ceramic block Pd-catalyst according to our procedure [9]. The target **6** was obtained during 1 h at 0 °C in high yield with the help of simple separation and crystallization from EtOH. Mass spectrum **6** confirmed the molecular weight and the presence of the fragment (MW–HCO = 233). The IR spectrum showed a clear band of the carbonyl group (1609, 1674 cm^{-1}). The ^1H; and ^{13}C; spectra of compound **6** contained the aldehyde group (10.25 and 189.8 ppm, respectively), as well as all the corresponding signals of the methoxy, methylenedioxy, and propyl groups (See experiment and Supplementary Materials).

check for updates

Citation: Tsyganov, D.V.; Semenov, V.V. 4,7-Dimethoxy-6-propyl-2*H*-1,3-benzodioxole-5-carbaldehyde. *Molbank* **2023**, *2023*, M1676. https://doi.org/10.3390/M1676

Academic Editors: Antonio Salomone and Serena Perrone

Received: 23 May 2023
Revised: 19 June 2023
Accepted: 21 June 2023
Published: 27 June 2023



Scheme 1. Aldehyde **6** was obtained by the formylation of dihydroapiol **5**.

As a result of this work, the simple synthesis of an important intermediate for the preparation of coenzyme methoxy analogues based on the available Apiol was developed.

3. Materials and Methods

Melting points were measured using a Boetius melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-500 instrument (working frequencies of 500.13 MHz (^{1}H) and of 125.76 MHz (^{13}C), respectively). Chemical shift values were reported in parts per million (ppm) and referenced to the appropriate NMR solvent peaks (see Supplementary Materials). Spin–spin coupling constants (*J*) were reported in hertz (Hz). Mass spectra (*m*/*z*) were recorded on a Finnigan MAT/INCOS 50 mass spectrometer at 70 eV using direct-probe injection. Elemental analysis was performed on the automated Perkin-Elmer 2400 CHN microanalyzer. All solvents and reagents were purified according to standard procedures.

Synthesis of 4,7-Dimethoxy-6-propyl-2H-1,3-benzodioxole-5-carbaldehyde ***6***

1. Preparation of the formylation mixture: Ethyl formate as a single portion (11.0 g, 148 mmol) was added to a suspension of PCl_5 (26.7 g, 128 mmol) in dry CH_2Cl_2 (40 mL) and refluxed for 4 h ($CaCl_2$ tube). A solution of dichloromethyl methyl ether (128 mmol) was obtained.
2. A solution of 4,7-dimethoxy-5-propyl-1,3-benzodioxole **5** [9] (2.1 g, 9.3 mmol) in formylation mixture (12.8 mmol) and dry CH_2Cl_2 (15 mL) was added dropwise to a solution of $SnCl_4$ (7.0 g, 27 mmol) in dry CH_2Cl_2 (15 mL) at −10 °C. The reaction mixture was kept for 1 h at 0 °C and poured into water (100 mL). The organic layer was separated, washed with water (3 × 50 mL), and dried over $MgSO_4$. After removal of the solvent, the product was recrystallized from EtOH. White powder; 2.1 g (90%); mp 69–71 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, Me, *J* 7.3 Hz), 1.34–1.42 (m, 2H, CH_2), 2.815 (t, 2H, $ArCH_2$, *J* 7.7 Hz), 3.83 (s, 3H, OMe), 3.95 (s, 3H, OMe), 6.16 (s, 2H, OCH_2 O), 10.25 (s, ^{1}H, CHO). ^{13}C NMR (DMSO-d_6) δ: 14.12, 23.85, 27.01, 60.08, 60.68, 102.60, 120.04, 132.35, 136.33, 136.90, 142.59, 143.93, 189.79. EIMS *m*/*z*: 252 ($[M]^+$, 90%), 251 (38), 237 (30), 235 (18), 223 (100), 209 (57), 208 (31), 207 (17), 193 (18), 179 (18), 151 (12), 121 (11), 92 (19), 91 (28), 79 (34), 77 (50), 69 (22), 67 (25), 66 (29), 65 (35), 64 (22), 63 (29), 53 (43), 51 (39), 41 (26). IR (KBr) ν_{max}: 1609, 1674 (CO), calculated for $C_{13}H_{16}O_5$ C, 61.90; H, 6.39; found C, 61.96; H, 6.42.

Supplementary Materials: The following supporting information can be downloaded online, Copies of ^{13}C, ^{1}H-NMR and mass-spectra for the compound **6**.

Author Contributions: Conceptualization, V.V.S.; methodology, V.V.S.; validation, D.V.T.; formal analysis, D.V.T.; investigation, D.V.T.; resources, V.V.S.; data curation, D.V.T.; writing—original draft preparation, V.V.S.; writing—review and editing, V.V.S.; visualization, D.V.T.; supervision, V.V.S.; project administration, V.V.S.; funding acquisition, V.V.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compound **1** and **6** are available from the authors.

References

1. Yang, H.-L.; Thiyagarajan, V.; Shen, P.-C.; Mathew, D.C.; Lin, K.-Y.; Liao, Y.-W.; Hseu, Y.-C. Anti-EMT Properties of CoQ_0 Attributed to PI3K/AKT/NFKB/MMP-9 Signaling Pathway Through ROS-mediated Apoptosis. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 186. [CrossRef] [PubMed]
2. Hseu, Y.-C.; Thiyagarajan, V.; Tsou, H.-T.; Lin, K.-Y.; Chen, H.-J.; Lin, C.-M.; Liao, J.-W.; Yang, H.-L. In Vitro and in Vivo Anti-tumor Activity of CoQ_0 Against Melanoma Cells: Inhibition of Metastasis and Induction of Cell-cycle Arrest and Apoptosis Through Modulation of Wnt/β-catenin Signaling Pathways. *Oncotarget* **2016**, *7*, 22409–22426. [CrossRef] [PubMed]
3. Hseu, Y.-C.; Tsai, T.-J.; Korivi, M.; Liu, J.-Y.; Chen, H.-J.; Lin, C.-M.; Yang, H.-L. Antitumor Properties of Coenzyme Q_0 Against Human Ovarian Carcinoma Cells via Induction of ROS-mediated Apoptosis and Cytoprotective Autophagy. *Sci. Rep.* **2017**, *7*, 8062. [CrossRef] [PubMed]
4. Yafei, J.; Wanmei, X.; Wenhu, J.; Yue, W. Practical Synthesis of 2,3,4,5-Tetramethoxytoluene. *Synth. Commun.* **2006**, *36*, 1961–1965. [CrossRef]
5. Semenov, V.V.; Rusak, V.A.; Chartov, E.M.; Zaretsky, M.I.; Konyushkin, L.D.; Firgang, S.I.; Chizhov, A.O.; Elkin, V.V.; Latin, N.N.; Bonashek, V.M.; et al. Polyalkoxybenzenes from Plant Raw Materials 1. Isolation of Polyalkoxybenzenes from CO_2 Extracts of *Umbelliferae* Plant Seeds. *Russ. Chem. Bull. Int. Ed.* **2007**, *56*, 2448–2455. [CrossRef]
6. Tsyganov, D.V.; Chernysheva, N.B.; Salamandra, L.K.; Konyushkin, L.D.; Atamanenko, O.P.; Semenova, M.N.; Semenov, V.V. Synthesis of Polyalkoxy-3-(4-Methoxyphenyl)Coumarins with Antimitotic Activity from Plant Allylpolyalkoxybenzenes. *Mendeleev Commun.* **2013**, *23*, 147–149. [CrossRef]
7. Lien, H.; Kuo, P.; Huang, C.; Kao, J.; Lin, H.; Yang, D.; Lai, Y. Study of the Anti-Proliferative Activity of 5-Substituted 4,7-Dimethoxy-1,3-Benzodioxole Derivatives of SY-1 from *Antrodia camphorata* on Human COLO 205 Colon Cancer Cells. *Evid.-Based Complement. Altern.* **2009**, *2011*, 450529. [CrossRef]
8. Shi, L.-S.; Chao, C.-H.; Shen, D.-Y.; Chan, H.-H.; Chen, C.-H.; Liao, Y.-R.; Wu, S.-J.; Leu, Y.-L.; Shen, Y.-C.; Kuo, Y.-H.; et al. Biologically Active Constituents from the Fruiting Body of *Taiwanofungus camphorates*. *Bioorg. Med. Chem.* **2011**, *19*, 677–683. [CrossRef] [PubMed]
9. Varakutin, A.E.; Muravsky, E.A.; Shinkarev, I.Y.; Khrustalev, V.N.; Semenov, V.V. Hydrogenation of Plant Polyalkoxybenzene Derivatives: Convenient Access to Coenzyme Q_0 Analogues. *Mendeleev Commun.* **2020**, *30*, 599–601. [CrossRef]