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Short Note

(*E*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-5,6,6-trimethylhept-4-en-3-one

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Abstract: The title compound (**1**) was obtained within a project to synthesize analogs of the antiepileptic drug stiripentol. Compound **1** was synthesized by aldol addition of the lithium enolate of 4-(benzo[*d*][1,3]dioxol-5-yl)butan-2-one (**2**) to 3,3-dimethylbutan-2-one (**3**), followed by the dehydration of the resulting β-hydroxy-ketone under acid processing. The structure of **1** was established by 1D and 2D NMR spectroscopy and high-resolution mass spectrometry.

Keywords: stiripentol analogs; aldol addition; lithium enolate; acid dehydration

1. Introduction

Stiripentol (STP) is an aromatic allylic alcohol (4,4-dimethyl-1-[3,4-[methylenedioxy]-phenyl]-1-penten-3-ol) with a 1,3-benzodioxole ring moiety (Figure 1) that has demonstrated effectiveness against Dravet's syndrome (DS) [1,2]. This disease is a form of epileptic encephalopathy characterized by drug-resistant seizures and other clinical dysfunctions [2,3]. STP was authorized by the European Medicines Agency (EMA) in 2007 as an orphan drug for the treatment of DS and was subsequently approved in Japan and Canada in 2012 and in the USA in 2018 [4]. One of the mechanisms of action of STP is the inhibition of the enzyme lactate dehydrogenase (LDH), highly activated during seizures [5], which links STP with primary hyperoxaluria (PH) [6].

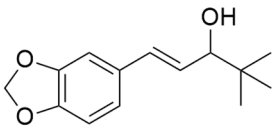

Figure 1. Structure of stiripentol (STP).

Primary hyperoxalurias (PHs) are a group of rare genetic disorders that affect hepatic glyoxylate metabolism, leading to excessive oxalate production in the liver. [7,8]. Traditionally, existing therapies have been primarily supportive, using strategies such as hyperhydration or crystallization inhibitors, until a novel bio-drug (lumasiran) was recently approved as the first medicine to reduce oxalate liver production in patients with type 1 PH [9].

However, the pharmacological strategy of using small organic molecules as inhibitors of the enzymes responsible for oxalate overproduction, including LDH, is currently in its early stages of development for treating PHs [10–13]. At present, only two organic molecules are in clinical studies [6], with only STP having entered Phase 3 clinical trials in August 2024 [14].

In this context, compound **1** was synthesized as part of a study that aims to explore whether compounds with structures related to STP might also inhibit LDH activity and even improve STP's efficacy.

The synthesis of the α,β-unsaturated ketone precursor of STP has been reported in the literature by a Claisen–Schmidt condensation [15]. However, the experimental

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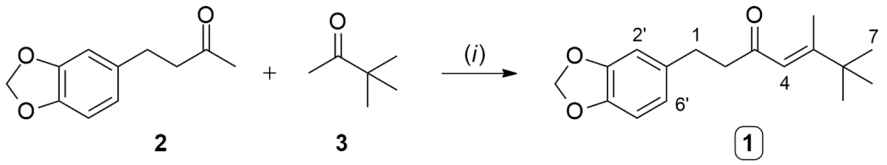
conditions followed in that case (KOH, MeOH-H_2O) were not suitable for the synthesis of the title compound **1** due to the presence of acidic protons in both starting materials (**2** and **3**; Scheme 1), which led to the formation of mixtures. The low electrophilicity of ketones (compared with aldehydes), their tendency to undergo retroaldol reactions, and the formation of unwanted self- or cross-aldol products are behind the difficulties in preparing β,β-disubstituted α,β-unsaturated ketones such as the title enone **1**. In this context, Sugiura et al. reported a $TiCl_4$-promoted aldol reaction between ketones followed by the elimination of the titanoxy group from the Ti-aldolates to properly afford β,β-disubstituted α,β-unsaturated ketones in a one-pot procedure [16]. This protocol improved previous multi-step methods to synthesize such compounds [17–20]. However, we attempted the synthesis of compound **1** by lithium enolate chemistry following standard methodologies [21] for comparison purposes with the above strategies.



Scheme 1. Synthesis of compound **1**. Reagents and conditions: (*i*) (a) LDA, THF, −80 °C; (b) *p*-TsOH, DCM, r.t.

2. Results and Discussion

To synthesize compound **1** regioselectively, the preformed enolate methodology was chosen. Preformed enolates can be obtained regioselectively from non-symmetrical ketones by employing either kinetic or thermodynamic control [22]. Thus, the preparation of the kinetic enolate (lithium enolate) of compound **2** was necessary to synthesize the desired compound **1** (Scheme 1).

The synthesis of the kinetic enolate requires the use of a strong base [22]. Accordingly, a solution of lithium diisopropylamide (LDA) was prepared in situ from diisopropylamine and *n*-butyllithium, which deprotonate the most acidic and accessible protons of ketone **2** (methyl protons). Compound **1** was then synthesized through the reaction of the lithium enolate of piperonyl acetone (**2**) with pinacolone (**3**) following a standard protocol [21] (Scheme 1), yielding the α,β-unsaturated ketone **1** after the dehydration of the resulting β-hydroxycarbonylic crude using *p*-toluenesulfonic acid.

Ketone **1** was formed in low yield (12%) primarily due to the inherent challenges of aldol reactions between ketones. Additionally, the steric hindrance generated by the bulky *tert*-butyl group in pinacolone (**3**) further impeded the attack of the enolate derived from **2**, thereby reducing the overall formation of compound **1**.

Using NMR spectroscopy, the structure of compound **1** was confirmed. In the ^{1}H NMR spectrum (see Figure S1 in Supplementary Materials), a multiplet signal at 6.07–6.08 ppm corresponds to the only olefinic proton present in the molecule. Additionally, two singlet signals are observed at 1.09 pm and 5.90 ppm, corresponding to the protons of the *tert*-butyl group (Me-6a, Me-6b, H-7) and the methylene of the methylenedioxyphenyl group (O-C$\underline{H_2}$-O), respectively, as well as a doublet at 2.12 ppm for the methyl attached to carbon 5. To complete the proton assignment of the aliphatic chain, two multiplet signals are observed between 2.71 and 2.86 ppm, corresponding to the remaining methylene protons (H-1, H-2). Finally, the aromatic protons can be observed displaying a characteristic ABX-type spin system. This consists of three signals, each integrating for one proton: a doublet of doublets at 6.64 ppm (H-6′) and two doublets at 6.69 ppm (H-2′) and 6.71 ppm (H-5′).

The signals corresponding to all hydrogenated carbons in the molecule were assigned using the ^{13}C NMR spectrum (see Figure S2 in Supplementary Materials) and with the aid of the HSQC bidimensional spectrum (see Figure S3 in Supplementary Materials). The quaternary carbons were identified with the aid of the HMBC bidimensional spectrum (see

Figure S4 in Supplementary Materials), where key correlations enabled their unambiguous assignment (Figure 2).

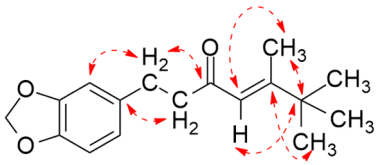


Figure 2. Key correlations in the HMBC spectrum.

3. Materials and Methods

3.1. General Experimental Methods

All solvents and reagents used in the synthesis were purchased and used as received, except tetrahydrofuran (THF), which was previously dried, using standard methodologies [23]. Diisopropylamine (DIPA) and *n*-butyllithium (*n*-BuLi) were purchased from Sigma-Aldrich (Merck KGaA, Darmstadt, Germany), compound **2** was purchased from Sensient Fragrances (Sensient Technologies, Milwaukee, WI, USA), compound **3** was purchased from Fluka (Merck KGaA, Darmstadt, Germany), and *p*-toluenesulfonic acid (*p*-TsOH) was purchased from Panreac (Panreac Química, Barcelona, Spain). All solvents (*n*-hexane (Hex), diethyl ether (Et_2O), dichloromethane (DCM), and THF) were purchased from VWR (Avantor, Radnor, PA, USA).

Reactions were monitored by analytical thin-layer chromatography (TLC) on silica gel 60 F_{254} precoated aluminum sheets (0.25 mm, Merck Chemicals, Darmsdadt, Germany), and spots were visualized using UV light (λ = 254 nm). The purification of the synthesized α,β-unsaturated ketone **1** was carried out by column chromatography (CC) using Silica gel 60 (particle size 0.040–0.063 mm) (Merck Chemicals, Darmsdadt, Germany).

^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance 400 spectrometer (Bruker Daltonik GmbH, Bremen, Germany) operating at 400 and 100 MHz for ^{1}H and ^{13}C, respectively. Deuterated chloroform ($CDCl_3$) was used as a solvent. Chemical shifts (in ppm) were referenced to solvent peaks as an internal reference. The coupling constants (*J*) are expressed in hertz (Hz). The coupling system is described using the following abbreviations: *s*, singlet; *d*, doublet; *m*, multiplet; *dd*, doublet of doublets. The total assignment of ^{1}H and ^{13}C signals was made using 2D NMR spectra, such as COSY, HSQC, and HMBC.

Gas chromatography–mass spectra (GC–MS) was conducted on a Thermo Trace GC 1610 gas chromatograph coupled to a Thermo Orbitrap Exploris GC 240 mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). The GC was equipped with a TG-5SILMS capillary column (30 m × 0.25 mm × 0.25 µm); carrier gas He, flow rate 1.2 mL/min; temperature programmed from 50 °C to 110 °C at 10 °C/min, then from 110 °C to 225 °C at 12 °C/min, then from 225 °C to 250 °C at 15 °C/min, and remaining at 250 °C for 17.25 min; injector temperature 300 °C. The sample was injected using the split mode (ratio 1:100). High-resolution mass spectra (HRMS) were registered on the previously described equipment using an ionizing voltage of 70 eV (EI).

*3.2. Synthesis of Compound **1***

In a dry round-bottom flask, DIPA (0.5 mL, 3.45 mmol) and dry THF (6 mL) were placed. The solution was cooled to 0 °C, and *n*-BuLi (1.5 mL of 2.5 M hexane solution, 3.63 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min. The resulting LDA solution thus prepared was cooled to −83 °C using an EtOAc:solid CO_2 bath. Then, a solution of 4-(3′,4′-methylenedioxyphenyl)butan-2-one (**2**, 600 mg, 3.12 mmol) in dry THF (1 mL) was added dropwise. Ten minutes after the end of the addition of compound **2**, 3,3-dimethylbutan-2-one (**3**, 0.3 mL, 2.69 mmol) was added. The reaction mixture was allowed to stir by keeping the flask in the bath without adding more solid CO_2 to it (TLC monitored using Hex:Et_2O 4:6). When the reaction was finished (1.5 h), water (3 mL) was

added dropwise very slowly. Then, Et_2O (30 mL) was added, and the organic phase was washed with brine (20 mL). The aqueous layer was subsequently extracted twice with Et_2O (2 × 30 mL). The combined organic phases were dried over anh. Na_2SO_4, and the solvent was removed under reduced pressure. The resulting complex mixture was immediately dissolved in DCM (20 mL), followed by the addition of *p*-TsOH (600 mg, 3.09 mmol). The solution was stirred at room temperature while monitoring the reaction progress by TLC (Hex:Et_2O 4:6). Once the reaction was finished (2 h), a solution of 10% $NaHCO_3$ (*w/v*) (30 mL) was added, and the mixture was extracted with DCM (2 × 30 mL). Finally, the organic phase was washed with brine (2 × 30 mL), dried over anh. Na_2SO_4, and the solvent was removed in vacuo. The resulting product was purified by column chromatography (CC).

The purification step was performed by CC using mixtures of Hex:Et_2O. With the 95:5 mixture of solvents, pure compound **1** was obtained as a yellowish oil (91 mg, 12% yield).

•(*E*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-5,6,6-trimethylhept-4-en-3-one (**1**) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.71 (*d*, $J_{5',6'}$ = 8.0 Hz, 1H, H-5′), 6.69 (*d*, $J_{2',6'}$ = 1.8 Hz, 1H, H-2′), 6.64 (*dd*, $J_{6',5'}$ = 8.0 Hz, $J_{6',2'}$ = 1.8 Hz, 1H, H-6′), 6.07–6.08 (*m*, 1H, H-4), 5.90 (*s*, 2H, O-C$\underline{H}_2$-O), 2.81–2.86 (*m*, 2H, H-1), 2.71–2.76 (*m*, 2H, H-2), 2.12 (*d*, $J_{5a,4}$ = 1.2 Hz, 3H, H-5a), 1.09 (*s*, 9H, H-6a, H-6b, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.0 (C-3), 166.2 (C-5), 147.7 (C-3′), 145.8 (C-4′), 135.4 (C-1′), 121.2 (C-6′), 120.1 (C-4), 109.0 (C-2′), 108.3 (C-5′), 100.9 (O-$\underline{C}H_2$-O), 46.6 (C-2), 38.0 (C-6), 30.1 (C-1), 28.7 (C-6a, C-6b, C-7), 16.0 (C-5a). HRMS (EI) (M^+) calc. for $C_{17}H_{22}O_3$ 274.15689, found 274.15665; *m/z* (%): 274.15665 (M^+, 4), 217.08604 ($M^+ - C_4H_9$, 95), 135.04413 (100), 125.09617 (54), 119.04922 (13), 97.10122 (18), 77.03863 (16), 55.05427 (29).

4. Conclusions

The novel compound (*E*)-1-(benzo[*d*][1,3]dioxol-5-yl)-5,6,6-trimethylhept-4-en-3-one (**1**) was synthesized through cross-aldol condensation based on lithium enolate chemistry. However, the low electrophilicity of ketones, combined with the steric hindrance caused by the bulky *tert*-butyl group in pinacolone (**3**), significantly prevented the attack of the enolate derived from **2**, thereby reducing the overall formation of compound **1**. Nevertheless, pure compound **1** was isolated as a yellowish oily mass and properly characterized. In addition, it could be of interest to compare in the future the results reported here with those arising from the application of the methodology ($TiCl_4$-promoted aldol reaction) described by Sugiura et al. [16].

Supplementary Materials: The following supporting information can be downloaded: Figures S1–S5: NMR spectra; Figure S6: High-resolution mass spectrum.

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Data Availability Statement: Data are contained within the article and Supplementary Materials.

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

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