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# Concise and Efficient Synthesis of [6]-Paradol

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**ABSTRACT:** An efficient synthesis of [6]-paradol (**1**) has been performed in four steps with a 72.0% overall yield. The present method highlights commercially available materials, convenient isolation with multiple crystallization without involving column chromatography, and a high-purity product (more than 99.2%), and it is amenable to large-scale synthesis.

**KEYWORDS:** *synthesis, [6]-paradol, vanillin, Wittig−Horner reaction, Grignard reaction*



## INTRODUCTION

[6]-Paradol, one of the bioactive components isolated from ginger, has been widely used for food and medicines. Among many ginger ingredients, [6]-paradol exhibits lower pungent flavor, higher water solubility, and various biological activities including anti-inflammation, antioxidation, and antibacteria.[1] It can markedly reduce neuroinflammatory responses by reducing the secretion of iNOS and TNF-$\alpha$,[2] while also protecting the primary hippocampal cells from beta-amyloid (A$\beta$) oligomers and A$\beta$ plaque.[3] In addition to neuroprotective effects, several *in vivo* and *in vitro* studies have also demonstrated that [6]-paradol has a strong effect on diabetes prevention via promotion of glucose utilization[4] and displays significant cytotoxicity against many human tumor cell lines.[5]

Because of its wide range of biological activities, several synthetic protocols for [6]-paradol (**1**) have been reported previously. As shown in Scheme 1, Shih et al. devised a concise route from vanillin (**2**) using a three-step method with a 13.3% overall yield.[6] Galre et al. also used **2** as a starting material to produce **1** using a seven-step method with a moderate overall yield (19.1%).[7] Both of these methods resulted in a relatively low yield of **1**. In addition, Choi et al. reported a more concise protocol to obtain **1** with a satisfactory overall yield (48−58%) via Claisen−Schmidt condensation and palladium hydrogen reduction reaction.[7] Although this route was easy to operate, each step of the protocol required column chromatography for purification; thus, it was not suitable for industrial-scale production. Hori et al. also described synthetic routes using a hydrogen borrowing C−C bond formation reaction for synthesizing phytochemicals and successfully obtained **1** by Pd, Ir catalysis with an overall yield of 65%.[8] This route had a satisfactory overall yield, but the intermediate compound **12** was not commercially available, and the catalyst Ir/chitin was very expensive. In addition, every intermediate in this route needed to be purified by column chromatography, which significantly elevates the cost of production. Overall, all the above routes were not suitable for mass production.

To achieve a novel and more efficient method for large-scale synthesis, a four-step synthetic route was developed in this study. Through multiple recrystallizations, [6]-paradol was obtained with high purity (more than 99.2%) and high yield (72.0% overall yield). In order to protect this valuable synthetic method, we have applied for a patent in China and obtained patent protection (CN110937985).

## RESULTS AND DISCUSSION

The retrosynthetic analysis for **1** is shown in Scheme 2. We anticipated that a reduction reaction and Grignard reaction could translate **16** into target compound **1**. The Wittig−Horner reaction between **19** and **15** could yield compound **16**. Furthermore, compound **15** could be obtained by heating vanillin (**2**) with benzyl bromide, and Weinreb amideb (**19**) could be synthesized from **18** via two conventional reactions.

As shown in Scheme 3, the synthesis commenced with commercially available vanillin (**2**). Using the reported protocol (BnBr, $K_2CO_3$, MeOH, reflux, 2 h),[9] we obtained **15** successfully. Then, the Wittig−Horner reaction of **15** with compound **19**, which was prepared according to the reported method,[10] gave **16** in satisfactory yield (91.5%). Subsequently, **16** underwent a Grignard reaction with heptylmagnesium bromide to afford **17** in good yield (81.2%). To obtain the target compound **1**, we initially attempted to treat **17** with $H_2$ in the presence of Pd/C according to Choi's procedure (5% Pd/C, room temperature, MeOH, 3 h).[7] Unfortunately, a mixture of desired product **1** and byproduct **1a** was produced.

To avoid the formation of **1a**, which may be closely related to the amount of Pd/C in the catalytic hydrogenation reaction,[6] different reaction conditions were screened (Table 1), and dichloromethane was used as the solvent to lower the activity of the catalyst. The yield of **17**, **1**, and **1a** (Figure 1) showed that the amount of Pd/C and various temperatures did not have any influence on the production of **1a**. Furthermore, a

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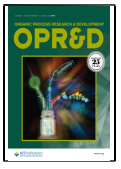





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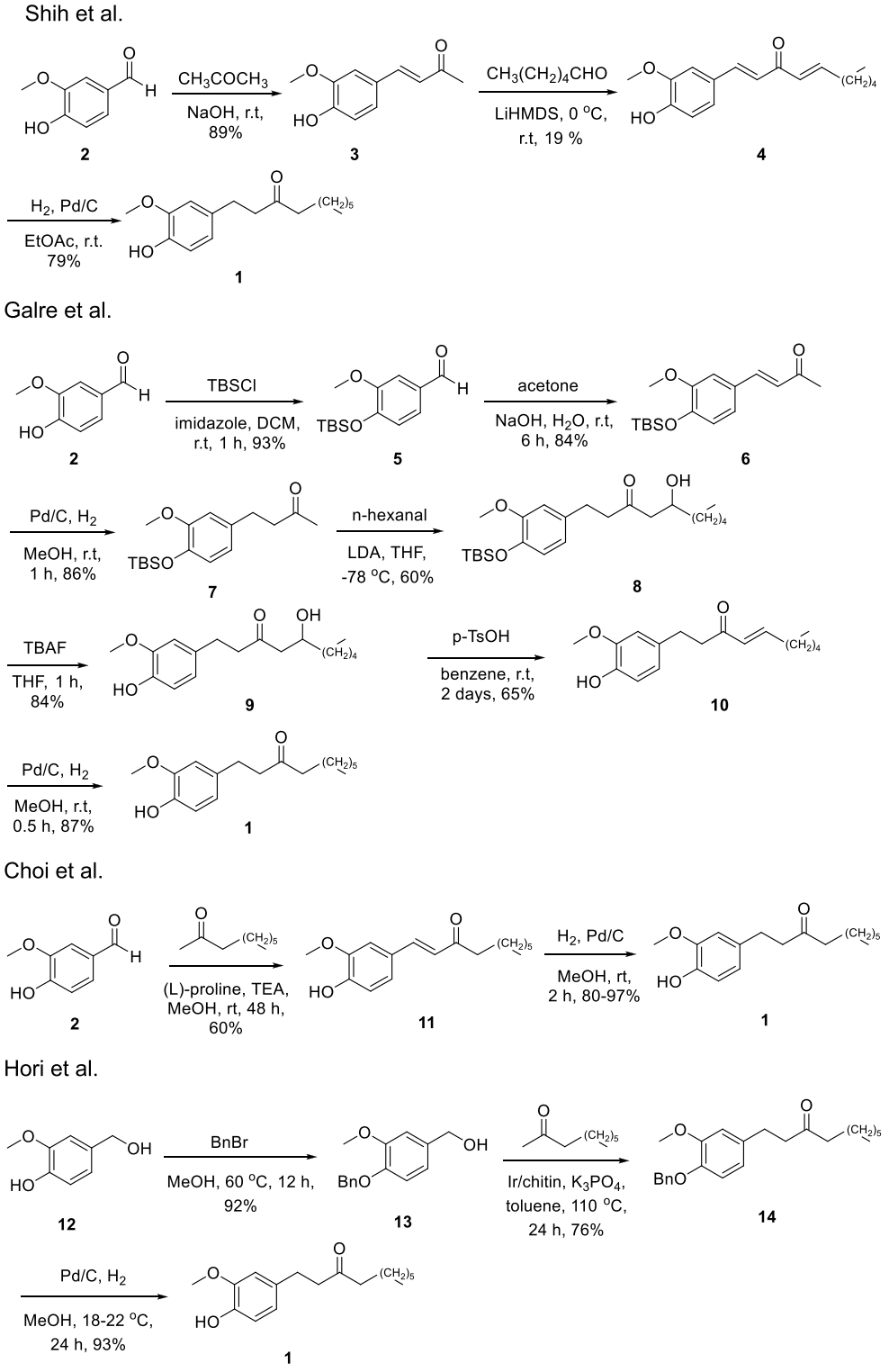
**Scheme 1. Previous Preparations of [6]-Paradol (1)**




prolonged reaction time revealed a smaller amount of desired product **1** along with a larger amount of byproduct **1a**, which may be attributed to the poor selectivity between ketone carbonyl and ethylenic bonds under the action of hydrogen.

Unsatisfied with the above result along with difficultly removing byproduct **1a** by recrystallization, another synthetic strategy was designed (shown in Scheme 4). Given that the carbonyl group on the amide structure is more difficult to reduce by hydrogen compared with ketones, we turned our attention to synthesize **20** using **16** via a reduction reaction in the presence of Pd/C. After overnight reaction at room temperature in $CH_2Cl_2$, a high-purity **20** was successfully obtained with excellent yield (98%).

To optimize the reaction condition of catalytic hydrogenation of compound **17** over palladium on charcoal, different solvents were investigated (Table 2). It is found that the



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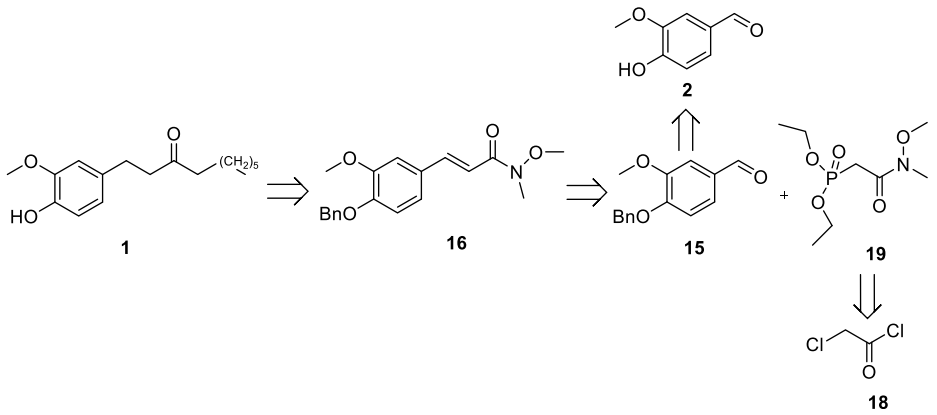
**Scheme 2. Retrosynthetic Analysis of [6]-Paradol (1)**




**Scheme 3. Synthesis of Product 1 and Byproduct 1a**

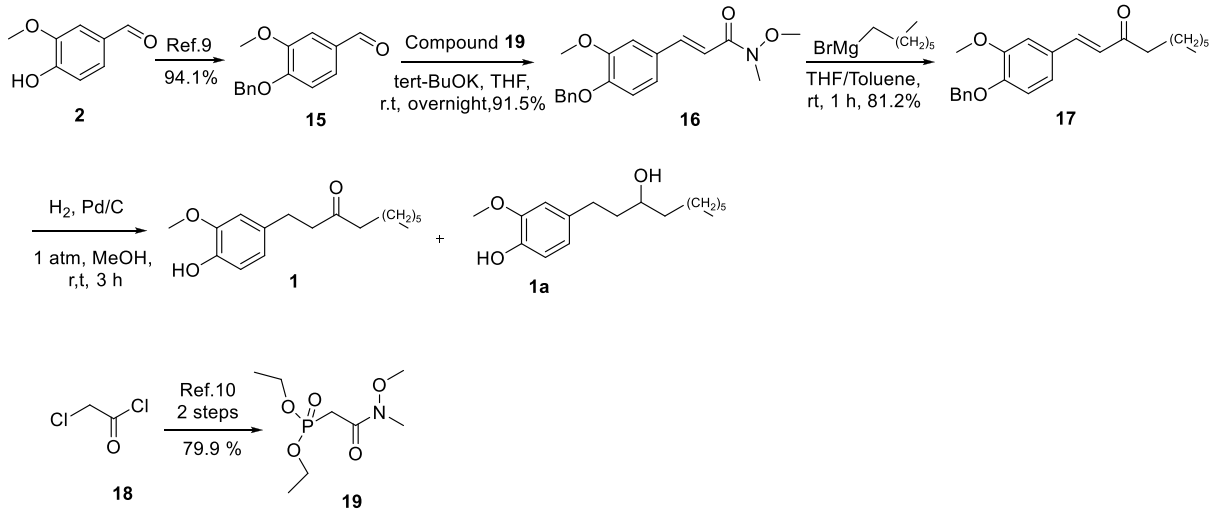



**Table 1. Product Yield under Various Reaction Conditions**

| entry[a] | Pd/C (N) | temp. (°C) | time (h) | yield[b] (17/1/1a) |
|---|---|---|---|---|
| 1 | 0.005 | 25 | 3 | -/56/42 |
| 2 | 0.010 | 25 | 3 | -/52/41 |
| 3 | 0.005 | 0 | 3 | -/55/43 |
| 4 | 0.005 | 50 | 3 | -/46/40 |
| 5 | 0.005 | 25 | 1 | 24/33/11 |
| 6 | 0.005 | 25 | 2 | 13/44/32 |
| 7 | 0.005 | 25 | 5 | -/37/54 |

[a]Compound **17** (500 mg, 2.7 mmol), $CH_2Cl_2$ (10 mL). [b]Conversion and ratio of **17**/**1**/**1a** were determined by HPLC, and the structure was confirmed by $^1$H NMR.

reaction could proceed smoothly in methanol, dichloromethane, THF, ethanol, and ethyl acetate. Importantly, the reaction rate was faster with methanol and ethanol.

With compound **20** in hand, we treated it with heptylmagnesium bromide for 4 h to afford crude [6]-paradol (**1**) in moderate yield (81%). After recrystallization with petroleum ether and cyclohexane (~1:1), high-purity **1** was obtained as a white waxy solid.

## CONCLUSION

In conclusion, we have demonstrated a concise and efficient synthesis for the preparation of high-purity [6]-paradol (**1**) (more than 99.2%) in four steps with an overall yield of 72.0%. The isolation of each product was carried out by recrystallization. Key steps of the strategy included the Wittig−Horner reaction, the Grignard reaction, and a reduction reaction. The proposed synthetic route was straightforward, effective and meaningful for commercial large-scale production.

## EXPERIMENTAL SECTION

Unless otherwise stated, all the chemicals and reagents were obtained commercially and used without further purification. All NMR experiments were carried out on a Mercury 400 or

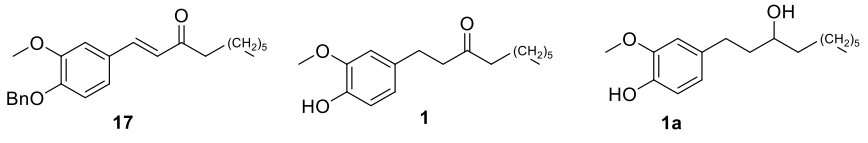



**Figure 1.** Structure of compounds **17**, **1**, and **1a**.



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**Scheme 4. Synthesis of Product 1**

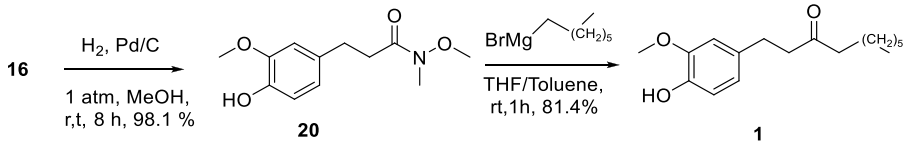


**Table 2. Product Yield under Various Reaction Solvents**

| entry[a] | solvent (N) | time (h) | yield[b] (compound **20**) |
|---|---|---|---|
| **1** | $CH_2Cl_2$ | 3 h | 46% |
| **2** | $CH_2Cl_2$ | 6 h | 61% |
| **3** | MeOH | 3 h | 78% |
| **4** | MeOH | 6 h | 98% |
| **5** | EtOH | 3 h | 72% |
| **6** | EtOH | 6 h | 94% |
| **7** | EtOAc | 3 h | 32% |
| **8** | EtOAc | 6 h | 67% |
| **9** | THF | 3 h | 51% |
| **10** | THF | 6 h | 74% |

[a]Compound **16** (0.5 g, 3.0 mmol), solvent (10 mL). [b]Conversion and ratio of compound **20** was determined by HPLC, and the structure was confirmed by $^1$H NMR.

Bruker AV500 spectrometer using $CDCl_3$ or DMSO-*d6* as the solvent with tetramethylsilane as the internal standard. Coupling constants were given in Hz, and chemical shifts were expressed as $\delta$ values in ppm. The following multiplicity abbreviations were used: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (br) broad, (dd) double doublet, (dt) double triplet. High-resolution mass spectra (HRMS) were obtained with Thermo Exactive Orbitrap plus spectrometer. Thin-layer chromatography was performed using commercially available HSGF 254 precoated plates.

**Diethyl (2-(Methoxy(methyl)amino)-2-oxoethyl)-phosphonate (19).** According to the reported method,[10] to a solution of $K_2CO_3$ (731.4 g, 5.3 mol, 1.2 equiv) in water (5 L), *N*-methyoxymethyl amine hydrochloride aqueous solution (ca. 5.3 M $H_2O$ solution, 1 L, 5.3 mol, 1.2 equiv) was added slowly under 0 °C and stirred for 1 h. Then, a solution of chloroacetyl chloride in $CH_2Cl_2$ (ca. 2.2 M $H_2O$ solution, 2 L, 4.4 mol, 1.0 equiv) was added dropwise to the above reaction solution. After vigorous stirring for 1 h under 0 °C, the mixture was allowed to warm to room temperature and continue to stir for 12 h. The resulting solution was poured into water, and the aqueous phase was extracted with DCM. The organic layers were washed with water and brine and dried over anhydrous $Na_2SO_4$. The dried solution was filtered, and the filtrate was concentrated *in vacuo* to give a colorless oil (565.7 g, yield 92.9%), which was used directly for the next reaction.

Warming triethyl phosphite (684.1 g, 4.12 mol, 1.0 equiv) to 100 °C, then the above colorless oil (565.7 g, 4.12 mol, 1.0 equiv) was added dropwise and kept stirring for 12 h. After that, excess triethyl phosphite was removed by vacuum distillation to give **19** as a yellow oil (940 g), yield 95.4%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.21 (m, 4H, $CH_2$ × 2 of $CH_3CH_2O$), 3.78 (s, 3H, $NCH_3$), 3.21 (s, 3H, $OCH_3$), 3.19 (t, $J$ = 21.9, 2H, $CH_2P$ = O), 1.33 (t, $J$ = 7.2 Hz, 6H, $CH_3$ × 2 of $CH_3CH_2O$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.13 (C═O), 62.52, 61.42, 32.08, 30.69, 16.32, 16.29; HRMS (ESI): calcd for $C_8H_{18}NO_5P$ $[M + H]^+$, 240.0923; found, 240.0992.

**(*E*)-3-(4-(Benzyloxy)-3-methoxyphenyl)-*N*-methoxy-*N*-methyl Acrylamide (16).** To a solution of **19** (930 g, 3.8 mol, 1.2 equiv) in dry THF (4 L), tert-BuOK (437 g, 3.8 mol, 1.2 equiv) was added in batches and stirred for 1 h. Then, a solution of **15** in THF (ca. 3 M THF, 1.1 L, 3.24 mol, 1.0 equiv) was added dropwise to the above mixture at 0 °C. Subsequently, the reaction mixture was allowed to stir overnight at room temperature. The resulting solution was poured into water, and the aqueous phase was extracted with EtOAc. The organic layers were washed with water and brine and dried over anhydrous $Na_2SO_4$. The dried solution was filtered, and the filtrate was concentrated *in vacuo* to give crude **16** as a yellow solid, which was purified by recrystallization (EtOAc/petroleum ether, ∼1:3, 0 °C) to give **16** (white solid, 970 g), yield 91.5%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.66 (d, $J$ = 15.7 Hz, 1H, Ar−H), 7.26−7.44 (m, 5H, Ar−H), 7.08−7.10 (m, 2H, Ar−H), 6.86−6.90 (m, 2H, CH = CH), 5.19 (s, 2H, $CH_2$), 3.93 (s, 3H, $NCH_3$), 3.76 (s, 3H, $OCH_3$), 3.31 (s, 3H, $OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.22, 149.94, 149.76, 143.38, 136.70, 128.60, 127.96, 127.21, 121.89, 113.76, 113.71, 111.05, 71.59, 61.30, 55.95, 32.55; HRMS (ESI): calcd for $C_{19}H_{22}NO_4$ $[M + H]^+$, 328.1471; found, 328.1541.

**(*E*)-1-(4-(Benzyloxy)-3-methoxyphenyl)dec-1-en-3-one (17).** To a solution of magnesium (185 g, 7.69 mol, 3.0 equiv) and $I_2$ (40 g) in dry THF/toluene (∼1:1.5, 5 L), 1-bromoheptane (1.4 kg, 7.69 mol, 3.0 equiv) was added dropwise at 90 °C under Ar atmosphere. After the mixture was stirred for 3 h, it was cooled to 0 °C, and a solution of **16** (840 g, 2.56 mol, 1.0 equiv) was added dropwise. Subsequently, the reaction mixture was heated to room temperature and allowed to stir for 1 h. The reaction mixture was then poured into water, and the aqueous phase was extracted with EtOAc. The organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. The dried solution was filtered, and the filtrate was concentrated *in vacuo* to afford **17** (761 g, 81.2%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.31−7.50 (m, 6H, Ar−H), 7.07 (t, $J$ = 8.4 Hz, 2H, Ar−H), 6.87 (d, $J$ = 8.3 Hz, 1H, Ar−H), 6.61 (d, $J$ = 16.4 Hz, 1H, CH = CH), 5.19 (s, 2H, $CH_2$), 3.92 (s, 3H, $OCH_3$), 2.64 (t, $J$ = 7.4 Hz, 2H, $CH_2$), 1.67 (t, $J$ = 6.7 Hz, 2H, $CH_2$), 1.26−1.32 (m, 8H, $CH_2$ × 4), 0.83−0.88 (m, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.57 (C = O),150.45, 149.91, 142.31, 136.59, 128.61, 128.01, 128.00, 127.21, 124.55, 122.65, 113.62, 110.50, 70.93, 63.05, 31.93, 29.70, 29.66, 29.36, 22.68, 14.07; HRMS (ESI): calcd for $C_{24}H_{31}O_3[M + H]^+$, 367.2195; found, 367.2228.

**3-(4-Hydroxy-3-methoxyphenyl)-*N*-methoxy-*N*-methylpropanamide (20).** A mixture of **16** (900 g, 2.74 mol) and 10% palladium on carbon (50 g) in MeOH (5 L) was stirred under 1 atm of $H_2$ at room temperature for 8 h. Subsequently, the catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to give **20** (644 g) as a grayish-white oil, yield 98.4%, which was used in the next step without further purification. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.83 (d, $J$ = 7.9 Hz, 1H, Ar−H), 6.69−6.72 (m, 2H, Ar−H), 5.73 (br, 1H, OH), 3.86 (s, 3H, $NCH_3$), 3.60 (s, 3H, $OCH_3$), 3.18 (s, 3H, $OCH_3$), 2.89 (t, $J$ = 7.4 Hz, 2H, $CH_2$), 2.71 (t, $J$ = 7.4 Hz, 2H, $CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 207.53 (C═O),


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146.55, 144.05, 133.30, 120.93, 114.45, 111.33, 110.00, 61.32, 55.92, 34.19, 30.51; HRMS (ESI): calcd for $C_{12}H_{18}NO_4$ [M + H]+, 240.1158; found, 240.1217.

**[6]-Paradol (1).** 1-Bromoheptane (1.0 kg, 5.83 mol, 3.0 equiv) was added dropwise to a stirred solution of magnesium (134 g, 5.83 mol, 3.0 equiv) and $I_2$ (20 g) in dry THF/toluene (~1:1.5, 5 L) at 90 °C under Ar atmosphere. The reaction mixture was allowed to stir for 3 h before being cooled to 0 °C, and a solution of **20** in THF (ca. 1.9 M THF solution,1 L, 1.88 mol, 1.0 equiv) was added dropwise. Then, the reaction mixture was allowed to stir for 1 h at room temperature. After completion of the reaction (monitored by TLC), the mixture was slowly poured into 5% HCl solution, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. The dried solution was filtered, and the filtrate was concentrated *in vacuo* to give crude compound **1** as a yellow oil, which was purified by recrystallization (Hexane/petroleum ether, ~1:1, 0 °C) to give **1** (white waxy solid, 970 g), yield 81.4%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.81 (d, $J$ = 8.0 Hz, 1H, Ar−H), 6.64−6.68 (m, 2H, Ar−H), 5.54 (br, 1H, OH), 3.86 (s, 3H, $OCH_3$), 2.82 (t, $J$ = 7.4 Hz, 2H, $CH_2$), 2.68 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 2.36 (t, $J$ = 7.4 Hz, 2H, $CH_2$), 1.50−1.58 (m, 2H, $CH_2$), 1.24−1.28 (m, 8H, $CH_2$ × 4), 0.87 (t, $J$ = 6.7 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 210.75 (C = O), 146.51, 143.99, 133.15, 120.83, 114.42, 111.15, 55.92, 44.68, 43.21, 31.74, 29.62, 29.25, 29.13, 23.88, 22.67, 14.14; HRMS (ESI): calcd for $C_{17}H_{27}O_3$ [M + H]+, 279.1182; found, 279.1921.

Compound **1a** as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.72 (d, $J$ = 7.92 Hz, 1H, Ar−H) 6.55−6.59 (m, 2H, Ar−H), 3.70 (s, 3H, $OCH_3$), 3.48−3.55 (m, 1H, CH), 2.43−2.67 (m, 2H, $CH_2$), 1.58−1.67 (m, 2H, $CH_2$), 1.31−1.38 (m, 2H, $CH_2$), 1.09−1.24 (m, 10H, $CH_2$ × 5), 0.78 (t, $J$ = 6.18 Hz, 3H, $CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 146.44, 143.58, 133.99, 120.71, 114.36, 111.11, 71.24, 55.65, 39.13, 37.39, 31.66, 31.56, 29.51, 29.12, 25.48, 22.48, 13.90; HRMS (ESI): calcd for $C_{17}H_{29}O_3$ [M + H]+, 281.4080; found, 281.4076.

## ■ ASSOCIATED CONTENT

### Supporting Information

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NMR spectra of compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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