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Two efficient methods for the total synthesis of the natural diarylheptanoid 7-(4-hydroxyphenyl)-1-phenylheptan-3-one

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Abstract: Diarylheptanoids are compounds with an ArC_7Ar structure, where two aromatic rings are connected by a seven-carbon chain. To date, over 500 structurally diverse diarylheptanoids have been isolated from nature. These compounds are generally minor secondary metabolites found in plants. Natural diarylheptanoids possess a wide range of biological activities, making their short and efficient total synthesis important for enabling further research on these substances. In this study, two efficient synthesis methods developed for the compound 7-(4-hydroxyphenyl)-1-phenylheptan-3-one, which is isolated as a minor component from *Alpinia officinarum*, are presented.

Keywords: Linear diarylheptanoid; 7-(4-hydroxyphenyl)-1-phenylheptan-3-one, total synthesis; *Alpinia officenarum*; natural product.

1. Introduction

Diarylheptanoids are a special class of natural products with an ArC_7Ar structure, where two aromatic rings are connected by a seven-carbon chain. To date, over 500 diarylheptanoid compounds have been isolated from nature, and various review articles on these compounds have been published over the past 30 years.[1-7] Diarylheptanoids are generally obtained from the roots, rhizomes, and seeds of different species belonging to plant families such as Aceraceae, Actinidiaceae, Betulaceae, Burseraceae, Casuarinaceae, Juglandaceae, Leguminosae, Myricaceae, and Zingiberaceae.[7] Depending on the structure of the C_7 alkane chain, diarylheptanoids can be found in linear or cyclic forms. Thus, diarylheptanoids are generally divided into four categories: i) linear diarylheptanoids, ii) macrocyclic biaryl heptanoids, iii) macrocyclic diaryl ether heptanoids, iv) heptane chain-cyclized diarylheptanoids.[8] Natural linear diarylheptanoids have both phenolic and non-phenolic examples, some of which are shown in Figure 1.

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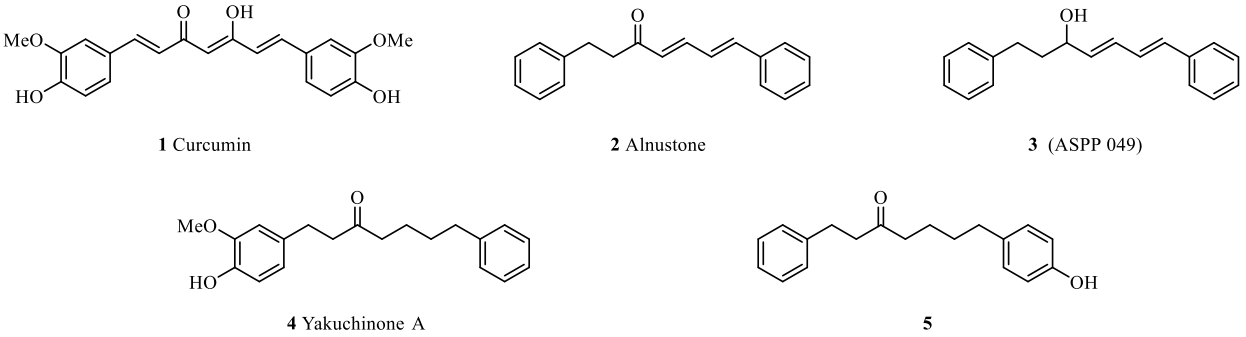


Figure 1. Examples of phenolic and non-phenolic linear diarylheptanoids

The first and most widely known example of natural linear diarylheptanoids is Curcumin (**1**). Curcumin (**1**) is a molecule with C_2 symmetry in its heptane chain and contains a 2,4-diketone with two α, β-unsaturated alkene structure. This compound was first isolated from *Curcuma longa* by Vogel and Pelletier in 1815.[9] Found in the rhizomes of *C. longa* (turmeric) in amounts of 3-5% by weight, curcumin is one of the most well-known and studied natural products. As a result, thousands of studies on curcumin have been conducted, revealing numerous biological activities, and research is still ongoing. On this context, Curcumin is known to have biological activities such as anticancer, antibacterial, antiviral, antifungal, antiinflammatory, antioxidant, antifertility, anticoagulant, antiangiogenic, antimutagenic, antiproliferative, antioxidative stress, anti-HIV and anti-AIDS, anti-Alzheimer, and antidiabetic etc.[10]

A non-phenolic diarylheptanoid called alnustone (**2**) was extracted from *Alnus pendula* in 1971.[11] It has been reported that alnustone is a broad-spectrum bioactive compound. Its antihepatotoxic, antiinflammatory, antibacterial, antiemetic, and estrogenic properties have led to reports of its anticancer efficacy.[12, 13] Studies by Wang et al. demonstrated that alnustone (**2**) may significantly reduce the growth of various cancer cells, especially hepatocellular carcinoma (HCC) cells.[14]

(4*E*,6*E*)-1,7-Difenilhepta-4,6-dien-3-ol (**3**) (ASPP 049), a natural diarylheptanoid, has been reported as antiinflamatuar,[15] antiemetic,[16] phytoestrogen[17] activities. Recently Bhukhai et al. reported that the diarylheptanoid **3** enhances the effects of Epo and displays estrogenic activity via ERα-mediated activation of STAT5, MAPK/ERK, and PI3K/AKT signaling pathways. Therefore, it could be used as an innovative therapeutic strategy in combination with physiological concentrations or lower Epo for the treatment of patients with anemia.[18]

Yakuchinone A (**4**) was first isolated from *Alpinia oxyphyilus* fruits by Itokawa et al. in 1981.[19] It has been reported to have antioxidative , antiadipocyte differentiation, antitumor and anthelmintic activities.[20]

Compound **5**, a natural diarylheptanoid, is a molecule structurally similar to yakuchinone A (**4**) and can therefore be assumed to be its demethoxylated structural isomer. The compound was isolated from *Alpiniae officinarum* as a minor constituent in 2004 (4.1 mg/16 kg).[21] The plant has been used as a traditional Chinese medicine such as stomach ache, treating colds, invigorating the circulatory system etc. The only semi-synthesis of compound **5** was made in 1985 via catalytic hydrogenation of (*E*)-7-(4-hydroxyphenyl)-1-phenylhept-4-en-3-one isolated from *Alpiniae officinarum*.[22]

In this study, we present the first total synthesis of 7-(4-hydroxyphenyl)-1-phenylheptan-3-one (**5**) reported in the literature and introduce two synthetic methodologies for this purpose. The methodologies we used involve a synthetic curcuminoid **8** and a synthetic alnustone derivative **11**. Therefore, the synthetic approach not only achieves the target compound but also contributes to the diarylheptanoid library through compounds synthesized in the intermediate steps.

2. Experimental

2.1. Chemical Material and Apparatus

Reactions were monitored by Thin Layer Chromatography (TLC) and NMR spectroscopy. The ^{1}H NMR and ^{13}C NMR spectra were recorded with 400 (100) MHz Bruker (Bruker Corp., Billerica, MA, USA) and Varian (Varian Medical Systems, Palo Alto, CA, USA) instruments. Exchangeable hydrogens or carbons were indicated with the same letters. Melting points were measured using a Gallenkamp melting point device.

2.2. Chemistry

*2.2.1. Synthesis of (1E,4E,6E)-7-(4-methoxyphenyl)-1-phenylhepta-1,4,6-trien-3-one (**8**)*

4-Phenylbut-3-en-2-one (**6**) (0.50 g, 3.42 mmol) was dissolved in 1.25 mL of H_2O and 1.50 mL of EtOH. To this solution, *p*-methoxycinnamaldehyde (**7**) (0.56 g, 3.42 mmol) dissolved in 1.25 mL of H_2O and 1.50 mL of EtOH were added. Then, 0.023 mL of 10% NaOH solution was added to the reaction mixture, and the reaction was stirred at 25 °C for 48 hours. After the reaction was monitored by TLC and deemed complete, 20 mL of H_2O was added to quench the reaction. The organic phase was separated by extraction with EtOAc (3 × 75 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure using an evaporator. The crude product was purified by recrystallization from EtOAc-hexane to give (1*E*,4*E*,6*E*)-7-(4-methoxyphenyl)-1-phenylhepta-1,4,6-trien-3-one (**8**) as a solid yellow compound (0.94 g, 95%). M.p. 114-115 °C. R_f: 0.71 (1:4 EtOAc/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68 (d, 1H, H-1, *J* = 15.4 Hz), 7.61 (m, 2H, H-2' and H-6', *J* = 7.5 Hz), 7.53 (dd, 1H, H-5, *J* = 14.7 Hz, *J* = 10.8 Hz), 7.45 (dm, 2H, H-2" and H-6" *J* = 8.8 Hz), 7.43-7.38 (m, 3H, H-3', H-4' and H-5'), 7.02 (d, 1H, H-4, *J* = 15.7 Hz), 6.98 (d, 1H, H-7, *J* = 15.4 Hz), 6.90 (dm, 2H, H-3"and H-5", *J* = 8.8 Hz), 6.84 (dd, 1H, H-6, *J* = 15.4 Hz, *J* = 10.8 Hz) 6.59 (d, 1H, H-4, *J* = 15.4 Hz), 3.84 (s, 3H, OCH_3) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$ = 77.0): δ 188.9 (C-3), 160.5 (C-4"), 144.0 (C-1), 142.6 (C-5), 141.5 (C-7), 134.9 (C-1'), 130.3 (C-4'), 129.0 (C-1"), 128.9 (C-2"/6"), 128.8 (C-2'/6'^{a}), 128.3 (C-3'/5'^{a}), 127.8 (C-6), 125.5 (C-4), 124.8 (C-2), 114.3 (C-3"/5"), 55.3 ($COCH_3$).

*2.2.2. Synthesis of (4E,6E)-7-(4-methoxyphenyl)-1-phenylhepta-4,6-dien-3-one (**11**)*

4-Phenylbutan-2-one (1.0 g, 6.75 mmol) (**10**) was dissolved in 10 mL of THF and the mixture was cooled to 0 °C (solution A). In a separate flask, AcOH (0.04 g, 7.42 mmol) and pyrrolidine (0.050 g, 7.42 mmol) were dissolved in 5 mL of THF at 0 °C (solution B). Under a nitrogen atmosphere, Solution B was added dropwise to solution A. The reaction mixture was stirred at this temperature for 30 minutes. Then, a solution of p-methoxycinnamaldehyde (**7**) (1.09 g, 6.75 mmol) in 10 mL of THF was added dropwise to the reaction mixture. The resulting mixture was stirred at room temperature for 48 hours. The solvent was removed under reduced pressure using an evaporator. To the residue, 10 mL of H_2O and 1 M HCl solution were added to adjust the pH to 4. The organic phase was extracted with 3 × 50 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using 10% EtOAc-hexane to yield (4*E*,6*E*)-7-(4-methoxyphenyl)-1-phenylhepta-4,6-dien-3-one (**11**) as a yellow solid (1.50 g, 80%). R_f: 0.62 (1:4 EtOAc/hexane). M.p. 108-110 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41 (dm, 2H, H-2", H-6", *J* = 8.8 Hz), 7.31 (dd, 1H, H-5, *J* = 15.4 Hz, *J* = 10.8 Hz), 7.32-7.18 (m, 5H, Ph), 6.89 (d, 2H, H-3" and H-5", *J* = 8.8 Hz), 6.87 (d, 1H, H-7, *J* = 15.4 Hz), 6.75 (dd,1H, H-6, *J* = 15.4 Hz , *J* = 10.8 Hz), 6.24 (d, 1H, H-4, *J* = 15.2 Hz), 3.81 (s, 3H, OCH_3,), 3.00-2.88 (A_2B_2, 4H, 2 x H-1 and 2 x H-2) ppm; ^{13}C-NMR (100 MHz): δ 199.6 (C-3), 160.8 (C-4"), 143.5 (C-1'), 141.6 (C-5), 141.5 (C-1"), 129.1 (C-3'/5'^{a}), 129.0 (C-2"/6"^{a}), 128.7 (C-4'), 128.6 (C-2'/6'^{a}), 126.3 (C-6), 124.8 (C-4), 114.5 (C-3"/C-5"), 55.5 (OCH_3), 42.5 (C-2), 30.5 (C-1).

*2.2.3. Synthesis of 7-(4-methoxyphenyl)-1-phenylheptan-3-one (**9**):*

*2.2.3.1. Preparation of Compound **9** from Compound **8***

0.02 g of Pd/C was placed into a two-necked flask, and 100 mL of MeOH cooled to 0 °C was added. Curcuminoid **8** (2.00 g, 6.89 mmol) dissolved in 20 mL of MeOH was then added to the mixture. The reaction apparatus was connected to a 3 L hydrogen balloon. While stirring the reaction mixture at room temperature, a small amount of H_2 gas was passed through the balloon, and the mixture was subjected to vacuum. This process was repeated two more times to remove oxygen from the reaction environment. The reaction mixture was then stirred under a hydrogen atmosphere at room temperature for 6 hours. After monitoring the reaction by TLC, the reaction was stopped, and the solid parts were filtered off and discarded. The solvent was removed under reduced pressure using an evaporator. The product was purified by column chromatography using 10% EtOAc-hexane to yield 7-(4-methoxyphenyl)-1-phenylheptan-3-one (**9**) as a colorless oil (1.63 g, 80%). R_f: 0.52 (1:9 EtOAc-hexane).

*2.2.3.2. Preparation of Compound **9** from Compound **11***

The procedure described above for catalytic hydrogenation of 7-(4-methoxyphenyl)-1-phenylhepta-1,4,6-trien-3-one (**8**) was applied to 7-(4-methoxyphenyl)-1-phenlyheptan-4,6-dien-3-one (**11**) to give 7-(4-methoxyphenyl)-1-phenylheptan-3-one (**9**) as a colerless oil in a yield of 80%.

*Compound **9***: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.25 (m, 2H, H-2', H-6'), 7.29-7.16 (m, 3H, H-3', H-4' and H-5'), 7.08 (dm, 2H, H-2"and H-6" *J* = 8.8 Hz), 6.83 (dm, 2H, H-3" and H-5", *J* = 8.5 Hz), 3.79 (s, 3H, OCH_3), 2.89 (t, H_2C-1 , *J* = 7.6 Hz), 2.71 (t, 2H, H_2C-2 , *J* = 8.0 Hz), 2.55 (t, 2H, H_2C-7, *J* = 7.3 Hz), 2.40 (t, 2H, H_2C-4 , *J* = 7.0 Hz), 1.65-1.50 (m, 4H, H_2C-5, H_2C-6) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$ = 77.0): δ 210.4 (C-3), 157.9 (C-4"), 141.4 (C-1'), 134.3 (C-1"), 129.5 (C-2"/6"[a]), 128.8 (C-2'/6'[a]), 128.6 (C-3'/5'[a]), 126.4 (C-4'), 113.9 (C-3"/5"), 55.5 (OCH_3), 44.5 (C-2), 43.1 (C-4), 35.0 (C-7), 31.5 (C-5), 30.0 (C-1), 23.6 (C-6).

*2.2.4. Synthesis of 7-(4-hydroxyphenyl)-1-phenylheptan-3-one (**5**)*

7-(4-Methoxyphenyl)-1-phenylheptan-3-one (**9**) (0.50 g, 69 mmol) was dissolved in 20 mL of dry CH_2Cl_2 at 0 °C under a nitrogen atmosphere. Under the same reaction conditions, a solution of BBr_3 (0.42 g, 0.16 mL, 1.69 mmol) in 10 mL of dry CH_2Cl_2 was added dropwise with stirring. The reaction mixture was stirred at room temperature for 6 hours, and the completion of the reaction was monitored by TLC. The mixture was cooled to 0 °C, and 10 mL of methanol was added and stirred for 1 hour. The solvent was then removed under reduced pressure using an evaporator. After adding 10 mL of H_2O, the organic phase was extracted with 3 × 50 mL of EtOAc. The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure using an evaporator, yielding 7-(4-hydroxyphenyl)-1-phenylheptan-3-one (**5**) as a colerless oil (0.45 g, 90%). R_f: 0.43 (1:4 EtOAc-hexane. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.27 (m, 2H, H-3', H-5'), 7.22-7.17 (m, 3H, H-2', H-4' and H-6'), 7.01 (dm, 2H, H-2" and H-6", *J* = 8.8 Hz), 6.79 (dm, 2H, H-3" and H-5", *J* = 8.8 Hz), 2.91 (t, 2H, H_2C-1 *J* = 7.7 Hz), 2.75 (t, 2H, H_2C-2, *J* = 7.7 Hz), 2.53 (t, 2H, H_2C-7, *J* = 7.2 Hz), 2.42 (t, 2H, H_2C-4, *J* = 7.0 Hz), 1.63-1.53 (m, 4H, H_2C-5 and H_2C-6 ppm; ^{13}C-NMR (100 MHz, $CDCl_3$ = 77.0): δ 211.5 (C-3), 153.9 (C-4"), 140.9 (C-1'), 133.9 (C-1"), 129.3 (C-2"/6"), 128.5 (C-2'/6'[a]), 128.3 (C-3'/5'[a]), 126.1 (C-4'), 115.2 (C-3"/5"), 44.1 (C-2), 42.9 (C-4), 34.7 (C-7), 31.1 (C-5), 29.7 (C-1), 23.3 (C-6).

The ^{1}H NMR and ^{13}C NMR data were in good agreement the data reported for the isolated compound in the literature.[21]

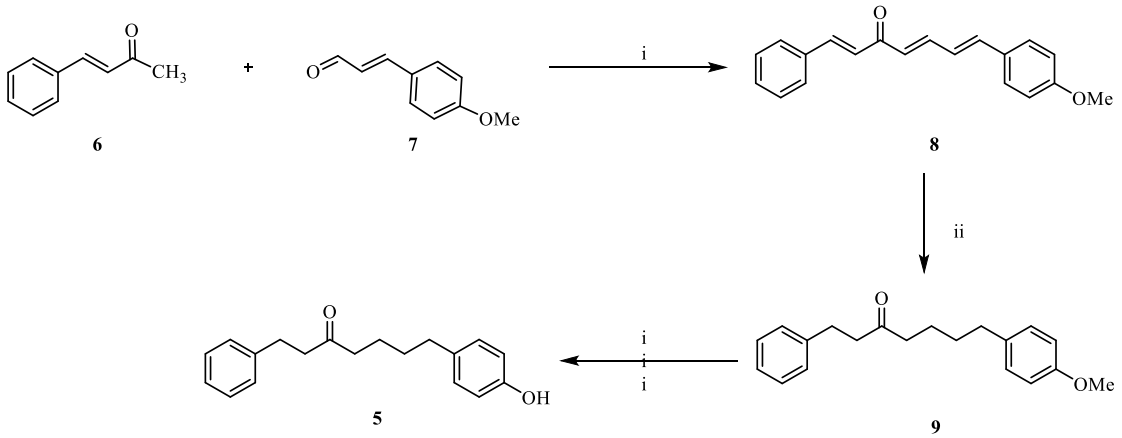
2.3.5. Synthesis of (4E,6E)-7-(4-methoxyphenyl)-1-phenylhepta-4,6-dien-3-ol (***12***)

(4*E*,6*E*)-7-(4-Methoxyphenyl)-1-phenylhepta-4,6-dien-3-one (**11**) (0.50 g, 1.7 mmol) was dissolved in 10 mL of EtOH. To this mixture, $CeCl_3 \cdot 7H_2O$ (0.28 g, 0.7 mmol) was added and stirred for 30 min. Then, $NaBH_4$ (0.077 g, 2.05 mmol) was added to the reaction mixture and stirred for 1 hour by monitoring by TLC. After the reaction was completed, 10 mL of H_2O was added to the reaction mixture. The organic phase was extracted with 2 × 30 mL of EtOAc and dried over Na_2SO_4. After the removal of the solvent under reduced pressure using an evaporator, (4*E*,6*E*)-7-(4-methoxyphenyl)-1-phenylhepta-4,6-dien-3-ol (**12**) was obtained as a yellow solid. (0.453 g, 90%). R_f: 0.48 (1:4 EtOAc-hexane). M.p. 71-72 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.10 (m, 7H, Ph), 6.86 (d, 2H, H-3''/H-5'', *J* = 8.7 Hz), 6.65 (dd, 1H, H-6, *J* = 15.6, *J* = 10.3 Hz), 6.51 (d, 1H, H-7, *J* = 15.6 Hz), 6.36 (dd, H-5, *J* = 15.1 Hz, *J* = 10.4 Hz), 5.80 (dd, 1H, H-4, *J* = 15.1, *J*= 6.8 Hz), 4.22 (q, 1H, H-3, *J* = 6.6 Hz), 2.80-2.67 (m, 2H, H_2C(1), 2.00-1.85 (m, 2H, H_2C(2) ppm; 1.85-1.70 (bs, OH) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$ = 77.0):, δ 159.5 (C-4''), 142.1 (C-1'), 135.3 (C-4), 132.7 (C-7), 131.6 (C-5), 130.1 (C-1''), 128.7 (C-2'/6'[a]), 128.6 (C-3'/5'[a]), 127.9 (C-2''/ C-6''[a]), 126.4 (C-4'[b]), 126.1 (C-6[b]), 114.3 (C-3''/ C-5''), 72.3 (C-3), 55.5 (OCH_3), 39.0 (C-1), 31.9 (C-2).

The ^{1}H NMR and ^{13}C NMR data were in good agreement the data reported by Han et al. for the compound **12**.[23]

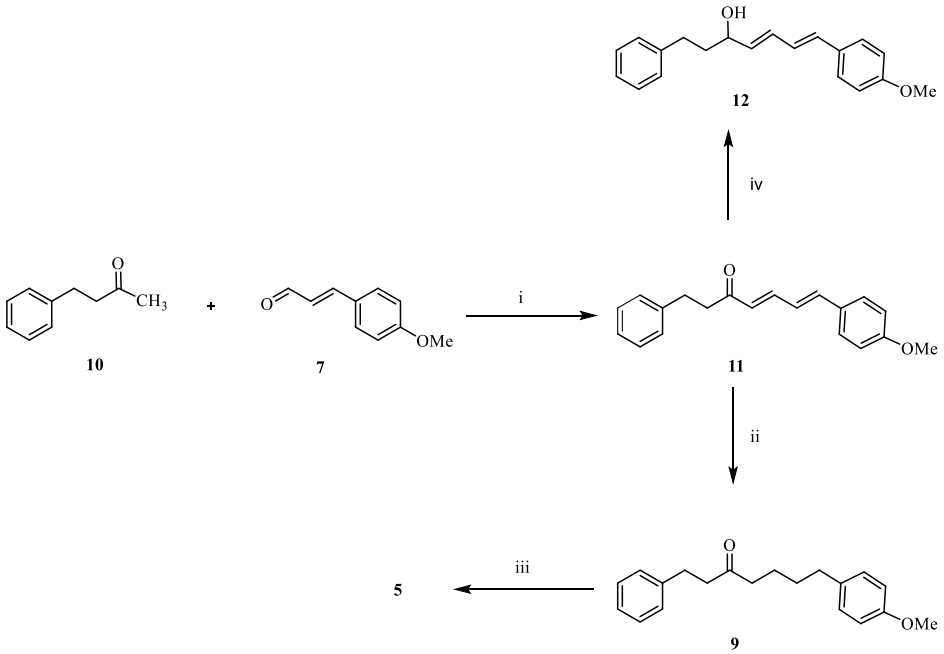
3. Results and Discussion

In this study, a simple and efficient synthesis of the natural product diarylheptanoid, 7-(4-hydroxyphenyl)-1-phenylheptan-3-one (**5**), was achieved using two different methods. For this purpose, 4-phenylbut-3-en-2-one (**6**) and *p*-methoxycinnamaldehyde (**7**) were treated with concentrated NaOH in EtOH-H_2O, undergoing a Claisen-Schmidt condensation. As a result of this aldol condensation reaction, (1*E*,4*E*,6*E*)-7-(4-methoxyphenyl)-1-phenylhepta-1,4,6-trien-3-one (**8**) was synthesized with a 95% yield. Subsequently, the C=C bonds of compound **8** were reduced using H_2 gas in the presence of a Pd/C catalyst, yielding 7-(4-methoxyphenyl)-1-phenylheptan-3-one (**9**) with an 80% yield. In the final step, the aryl methyl ether bond of compound **9** was cleaved with BBr_3, producing the natural product **5** with a 90% yield (Scheme 1). Thus, the natural product **5** was obtained in three steps starting from 4-phenylbut-3-en-2-one (**6**) with an overall yield of 68% using this method.



Scheme 1. Synthesis of natural product **5** starting from **6**. i) NaOH, EtOH-H_2O, 25 °C, 48 h, %95; ii) H_2, Pd/C (cat), MeOH, rt, 6 h, %80; iii) BBr_3, CH_2Cl_2, N_2 atm, 0 °C →25 °C, 6 h, %90

In the second method, 4-phenylbutan-2-one (**10**) was subjected to condensation with p-methoxycinnamaldehyde (**7**) in dry THF in the presence of pyrrolidine and AcOH, resulting in the formation of diarylheptanoid **11** with an 80% yield. 4-Phenylbutan-2-one (**10**) is an asymmetric n-alkyl methyl ketone. In such ketones, nucleophilic enamine species are formed on the methyl carbon.[24] Consequently, the nucleophilic attack of compound **10** on cinnamaldehyde **7** occurred on the methyl group, leading to the formation of compound **11** as the sole product. The C=C double bonds of diarylheptanoid **11** were then reduced using H_2 gas in the presence of a Pd/C catalyst, yielding heptanone **9** with an 80% yield. The demethylation of compound **9** with BBr_3 produced the natural product **5** with a 90% yield (Scheme 2). Thus, in the second method, the natural product **5** was obtained in three steps starting from 4-phenylbutan-2-one (**10**) with an overall yield of 57%.



Scheme 2. Synthesis of natural product **5** diarylheptanoid **12** starting from **10**. i) Pyrrolidine, AcOH, THF, N_2 atm, 0 °C →25 °C, 48 h, 80%; ii) H_2, Pd/C (cat), MeOH, rt, 6 h, 80%; iii) BBr_3, CH_2Cl_2, N_2 atm, 6 h, 90%; iv) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, rt, 1 h, 90%

4. Conclusion

In conclusion, two methods were developed for the synthesis of the natural diarylheptanoid compound **5** from different starting materials. Additionally, the synthesis of five linear diarylheptanoids was efficiently achieved: compound **8**, curcuminoid; compound **11**, an alnustone-derived diarylheptanoid; compound **12**, an ASPP 049-derived diarylheptanoid; and compound **9**, a synthetic diarylheptanoid.

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Supporting Information

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