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Synthesis of Two Alnustone-Like Natural Diarylheptanoids via 4 + 3 Strategy

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Abstract: The first total synthesis of (4E,6E)-1,7-bis(3,4-dihydroxyphenyl)-hepta-4,6-dien-3-one and an alternative synthesis of (4E,6E)-1,7-bis(4-hydroxyphenyl)-hepta-4,6-dien-3-one, two natural diarylheptanoids, mainly based on Claisen–Schmidt condensation were described. The crucial steps of the syntheses were the condensation of OH-protected 4-aryl-2-butanones with OH-protected 3-aryl-acrylaldehydes by the in situ enamination and then deprotection of OH groups to give the corresponding natural diarylheptanoids.

Keywords: 1,7-Bis(3,4-dihydroxyphenyl)-hepta-4,6-dien-3-one, 1,7-bis(4-hydroxyphenyl)-hepta-4,6-dien-3-one, Claisen–Schmidt condensation, diarylheptanoid, in situ enamination, synthesis

INTRODUCTION

Diarylheptanoids, which have two aryl rings attached to C-1 and C-7 of a seven-carbon chain, are a special class of natural products. The first review of natural diarylheptanoids was published by Cleason et al.,[1] and they reported the isolation and characterization of approximately

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Dedicated to Professor Metin Balcı on the occasion of his 60th birthday.
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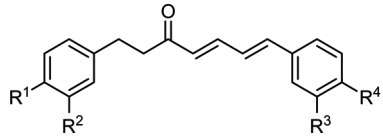


1; $R^1=R^2=R^3=R^4=H$ (Alnustone)
2; $R^1=R^2=R^3=R^4=OH$
3; $R^1=R^4=OH$, $R^2=R^3=H$
4; $R^1=R^4=OH$, $R^2=H$, $R^3=OMe$ (Tsaokoarylone)

Figure 1. Alnustone and alnustone-like natural diarylheptanoids.

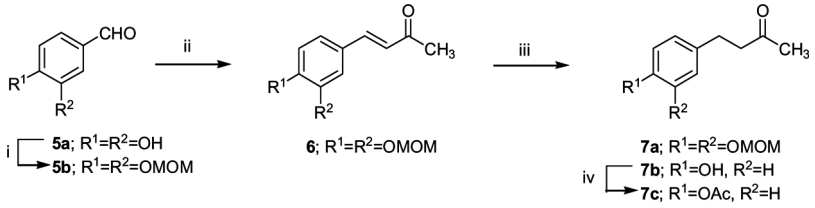
120 naturally occurring diarylheptanoids up to 1993. In a second review,[2] including the literature of 1993–1999, 75 new diarylheptanoids had been reported for the later 7 years. To our knowledge, after this, more than 100 new diarylheptanoids were reported in the literature. Studies have revealed that diarylheptanoids show several biological activities e.g., anti-inflammatory,[3] antispasmodic,[4] antiemetic,[5] antihepatatoxic,[6] antiproliferative,[7] and cancer-preventive[8] properties.

Alnustone (**1**), a nonphenolic natural diarylheptanoid, was reported to have anti-inflammatory,[9] antihepatotoxic,[6] antiemetic,[5] and antibacterial[10] activities. Three phenolic alnustone-like natural diarylheptanoids (**2–4**) have been reported to have some important biological activities: **2** with 5-lipoxygenase inhibiting activity[11] and stronger antioxidant activity[12] than L-ascorbic acid and alpha-tocopherol, **3** with quinone reductase (QR)–inducing activity,[13] and tsaokoarylone (**4**) with cytotoxic activity[14] (Fig. 1).

In our previous study, we reported an alternative, efficient, and short synthesis of alnustone (**1**) by the condensation of 4-phenyl-2-butanone and cinnamaldehyde.[15] Moon et al.[14] have recently synthesized tsaokoarylone (**4**) based on the base-catalyzed condensation of 4-(4-hydroxyphenyl)-2-butanone with 3-methoxy-4-hydroxy-cinnamaldehyde. Xu and Li[16] synthesized **3** by a lithium diisopropylamide (LDA)-promoted condensation of 4-(4-(methoxymethoxy)phenyl)butan-2-one with 4-(methoxymethoxy)-cinnamaldehyde. To the best of our knowledge, there is no synthetic report for the preparation of natural diarylheptanoid **2**. In this study, we describe the first synthesis of **2** and an alternative, easy synthesis of **3** based on in situ enamination.

RESULTS AND DISCUSSION

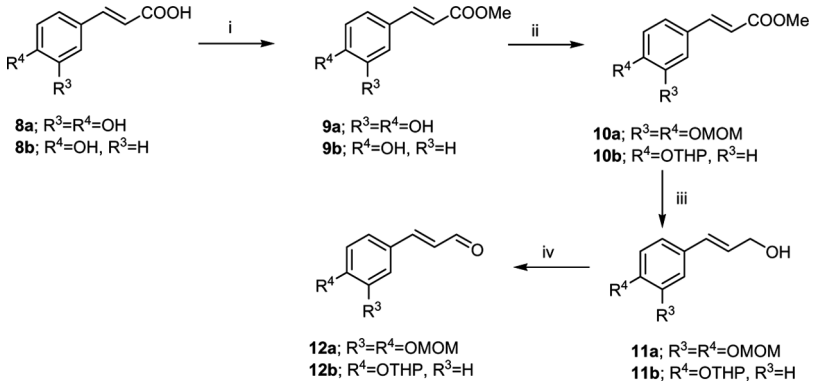
Our synthesis is based on a $4+3$ strategy with the condensation of 4-aryl-2-butanones (which have a four-carbon chain) and cinnamaldehydes (which have a three-carbon chain). The preparation of 4-aryl-2-butanones is shown in Scheme 1. For this, methoxymethyl (MOM)-protected 3,4-dihyroxy-benzaldehyde **5b** was condensed with acetone to give benzalacetone **6**, from which benzylacetone **7a** was prepared by



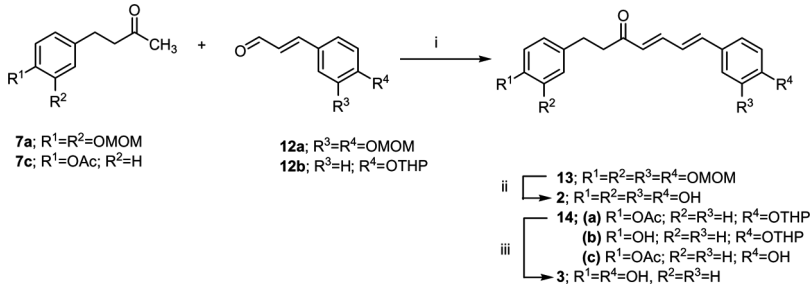
Scheme 1. (i) MOMCl, K_2CO_3, acetone, reflux, 2.5 h, 70%; (ii) acetone, 10% NaOH, rt, 3 h, 91%; (iii) H_2 (gas), Pd-C (cat.), 12 h, 79%; (iv) Ac_2O-pyridine, 0 °C → 25 °C, 20 h, 80%.

Pd-C-catalyzed hydrogenation. On the other hand, commercially available 4-(4-hydroxyphenyl)butan-2-one (**7b**) was converted to the corresponding acetate derivative **7c** by acetylation with Ac_2O-pyridine.

For the preparation of cinnamaldehydes **12a** and **b**, we used commercially available cinnamic acids **8a** and **b** as starting materials. Acid-catalyzed esterification of the acids **8a** and **b** with methanol (MeOH) gave the ester derivatives **9a** and **b**. Protections of OH groups in **9a** and **b** were performed in two different ways. While MOM protection of **9a** gave **10a**, tetrahydropyranyl (THP) protection of **9b** afforded **10b**. The reduction of the cinnamic esters **10a** and **b** with $LiAlH_4$ gave cinnamyl alcohols **11a** and **b**. The oxidation of the cinnamyl alcohols **11a** and **b** with active MnO_2 afforded cinnamaldehydes **12a** and **b** (Scheme 2).



Scheme 2. (i) MeOH, p-TsOH (cat.), reflux, 24 h, **9a**: 84%, **9b**: 92%; (ii) **10a**: MOMCl, acetone, reflux, 1 h, 75%; **10b**: DHP, CF_3COOH (cat.), CH_2Cl_2, 48 h, 90%; (iii) **11a**: $LiAlH_4$, Et_2O, 0°C → 25°C, 4 h, then H_2O, 66%; **11b**: $LiAlH_4$, Et_2O 0 °C → 25 °C, 13 h, then H_2O, 80%. (iv) **12a**: MnO_2, CH_2Cl_2, 10 h, 44%; **12b**: MnO_2, acetone, 10 h, 82%.



Scheme 3. (i) Pyrrolidine, AcOH, Et_2O, 0 °C → 25 °C, 12 h, then 0.1 M HCl, **13**: 73%; (ii) 1M HCl, ether, 50 °C, 1h, 95% (iii) MeOH, p-TsOH (cat.), reflux, 20 h, 59% via **12b**.

The most critical step of the synthesis was the condensation of butanoids **7a** and **c** and cinnamaldehydes **12a** and **b** to give diarylheptanoids. Baranovsky et al.[17] synthesized alnustone-like diarylheptanoids via a 4 + 3 strategy based on LDA-promoted aldol condensations of 4-aryl-2-butanones and 3-aryl-acrylaldehydes. However, this method includes a two-step reaction: (**i**) addition of enolate prepared from 4-aryl-2-butanones to 3-aryl-acrylaldehydes to give beta-hydroxyketones and (ii) acid-catalyzed elimination of water. Itokawa et al.[18] reported a successive method in one step for the condensation of 6-aryl-2-hexanone and benzaldehydes to give 1,7-diaryl-1-hepten-3-ones. This method includes a condensation based on in situ enamination using pyrrolidine and AcOH. In our previous study,[15] we successively used the latter method for the synthesis of alnustone by the condensation of benzylacetone and cinnamaldehyde. Therefore, in the present study, we preferred the same method for the condensation of 4-aryl-2-butanones **7a** and **c** and cinnamaldehydes **12a** and **b**. Our results are shown in Scheme 3.

The condensation of MOM-protected **7a** and **12a** gave diarylheptanoid derivative **13** from which the natural diarylheptanoid **2** was easily obtained by treatment with 1 M HCl. However, the condensation of the acetylated butanoid **7c** and THP-protected cinnamaldehyde **12b** gave a mixture of **14a–c**. Because all groups attached to oxygen atoms may be easily removed, the mixture of **14a–c** was subjected to trans-esterification to give the natural product **3** itself.

CONCLUSION

In this article, we described the first synthesis of natural diarylheptanoid **2** and an alternative, easy synthesis of natural product **3**. We showed

again that in situ enamination can be used for the preparation of alnustone-like diarylheptanoids in the presence of sensitive protective groups such as MOM or THP.

EXPERIMENTAL

General Information

Column chromatography (CC) used silica gel 60 (70–230 mesh). Thin-layer chromatography (TLC) used aluminum-backed silica-gel 60 F_{254} plates (Merck). Solvents were purified and dried by standard procedures before use. Melting points were measured with a Büchi-539 cap. melting-point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra at 400 or 100 MHz, 200 or 50 MHz, were determined on Varian spectrometer (δ in ppm, J in Hz). Carbon and hydrogen assignments were made by comparison of similar structures: Interchangeable protons and carbons were marked with the same letter (i.e.,^{a,b,c}). Electron-impact ionization–mass spectrometry (EI-MS) was measured on a Thermo-Finnigan mass analyzer in m/z (rel. int., %). Elemental analyses were carried out with a Leco CHNS-932 instrument.

3,4-Bis(methoxymethoxy)benzaldehyde (5b)

K_2CO_3 (2.00 g, 14.5 mmol) and methoxymethyl chloride (1.170 g, 1.1 mL, 14.5 mmol) were added to a solution of 3,4-dihydroxybenzaldehyde (**5a**) (0.500 g, 3.6 mmol) in acetone (40 mL). The mixture was refluxed for 2.5 h. The precipitate was filtered and dispatched. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), washed with water (3×10 mL), and dried (Na_2SO_4). The evaporation of the solvent gave **5b** as a brown oil (0.57 g, 70%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.86 (s, 1H, CHO); 7.47 (d, 1H, H-2, $J_{2,6} = 1.5$ Hz); 7.41 (dd, 1H, H-6, $J_{5,6} = 8.2$ Hz, $J_{2,6} = 1.5$ Hz); 7.23 (d, 1H, H-5, $J_{5,6} = 8.2$ Hz); 5.32 (s, 4H, $2 \times OCH_2O$); 3.53 (s, 6H, $2 \times OCH_3$); ^{1}H NMR spectrum is in agreement with data given in the literature.[19]

(E)-4-(3,4-Bis(methoxymethoxy)phenyl)but-3-en-2-one (6)[20]

3,4-Bis(methoxymethoxy)benzaldehyde (**5b**) (0.500 g, 2.21 mmol) was dissolved in acetone (0.165 mL, 0.130 g, 2.24 mmol). To this solution, 25 mL 10% NaOH was added. While the mixture was being magnetically stirred

at rt for 3 h, progress of the reaction was monitored by TLC. The organic phase was extracted with benzene and dried (Na_2SO_4). The evaporation of the solvent under reduced pressure gave **6** as a brown oil (0.540 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 1H, H-4, $J_{3,4} = 16.3$ Hz); 7.37 (bs, 1H, H-2′); 7.16 (m, as quasi bs, 2H, H-5′ and H-6′); 6.66 (d, 1H, H-3, $J_{3,4} = 16.3$ Hz); 5.27 (s, 2H, OCH_2O); 5.25 (s, 2H, OCH_2O); 3.52 (s, 3H, OCH_3); 3.51 (s, 3H, OCH_3); 2.35 (s, 3H, $[C(O)CH_3]$. ^{13}C NMR (100 MHz, $CDCl_3$) 198.5 (C-2); 149.6 (C-4′^{a}); 147.7 (C-3′^{a}); 143.3 (C-4); 129.1 (C-1′); 126.2 (C-6′); 123.9 (C-3); 116.5 (C-5′^{b}); 116.0 (C-2′^{b}); 95.7 ($O\underline{C}H_2O$); 95.3 ($O\underline{C}H_2O$); 56.5 (2C, $2 \times O\underline{C}H_3$); 27.6 (C-1).

4-(3,4-Bis(methoxymethoxy)phenyl)butan-2-one (7a)[20]

Pd–C (50 mg) and benzalacetone **6** (0.500 g, 1.88 mmol) in EtOAc (50 mL) were placed into a 100-mL flask. A balloon filled with H_2 gas (3 L) was fitted to the flask. The mixture was deoxygenated by flushing with H_2 and then hydrogenated at rt for 12 h. The catalyst was removed by filtration.The evaporation of the solvent under reduced pressure gave **7a** as a brown oil (0.400 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, 1H, H-5′, $J_{5',6'} = 8.4$ Hz); 6.94 (d, 1H, H-2′, $J_{2',6'} = 2.2$ Hz); 6.72 (dd, 1H, H-6′, $J_{5',6'} = 8.4$ Hz, $J_{2',6'} = 2.2$ Hz); 5.17 (s, 2H, OCH_2O); 5.15 (s, 2H, OCH_2O); 3.47 (s, 3H, OCH_3); 3.46 (s, 3H, OCH_3); 2.78 (A_2 part of A_2B_2 system, m, 2H, $2 \times$ H-3^a); 2.69 (B_2 part of A_2B_2 system, m, 2H, $2 \times$ H-4^a); 2.09 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1 (C-2); 147.5 (C-3′^{a}); 145.7 (C-4′^{a}); 135.7 (C-1′); 122.3 (C-6′); 117.2 (C-2′^{b}); 117.1 (C-5′^{b}); 95.8 ($O\underline{C}H_2O$); 95.7 ($O\underline{C}H_2O$); 56.4 ($O\underline{C}H_3$); 56.3 ($O\underline{C}H_3$); 45.4 (C-3); 30.2 (C-4); 29.4 (C-1).

4-(4-Acetoxyphenyl)butan-2-one (7c)[21]

4-(4-Hydroxyphenyl) butan-2-one (**7b**) (1.000 g, 6.09 mmol) and Ac_2O (0.920 g, 9.11 mmol) were placed into a 100-mL flask. The solution was cooled to 0°C, and pyridine (1 mL) was added. The mixture was stirred at rt for 20 h. The reaction mixture was cooled to 0°C, and 1 M HCl (20 mL) was added. The organic phase was extracted with CH_2Cl_2 (2×25 mL), washed with saturated $NaHCO_3$ (2×10 mL) and dried (Na_2SO_4). The evaporation of the solvent under reduced pressure gave **7c** as a yellow oil (1.000 g; 80%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22–7.18 (AA′ part of AA′XX′ system, m, 2H, H-2′/6′); 7.03–6.99 (XX′ part of AA′XX′ system, m, 2H,

H-3′/5′); 2.94–2.73 (A_2B_2 system, m, 4H, 2 × H-3 and 2 × H-4); 2.26 (s, 3H, CH_3); 2.15 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.7 (C-2); 169.2 (CO of ester); 148.7 (C-4′); 138.2 (C-1′); 129.0 (C-2′/6′); 121.2 (C-3′/5′); 44.7 (C-3); 31.9 (C-4); 29.7 (C-1); 20.8 ($\underline{C}H_3$ of acetate).

(E)-Methyl 3-(3,4-dihydroxyphenyl)acrylate (9a)

Fifty mg of p-TsOH was added to a solution of caffeic acid (**8a**) (1.88 g, 10.4 mmol) in 50 mL of MeOH. The mixture was refluxed for 24 h. The excess of MeOH was evaporated under reduced pressure. The residue was dissolved in EtOAc (50 mL), washed with saturated Na_2CO_3 (3 × 5 mL), and dried (Na_2SO_4). The evaporation of the solvent gave ester **9a** as a yellow solid (1.700 g, 84%). Mp 156–158°C. Lit.[22] mp 152–153°C; lit.[23] mp 158°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55 (d, 1H, H-3, $J_{2,3} = 15.9$ Hz); 7.04 (d, 1H, H-2′, $J_{2',6'} = 2.2$ Hz) 6.95 (dd, 1H, H-6′, $J_{5',6'} = 8.1$ Hz; $J_{2',6'} = 2.2$ Hz); 6.78 (d, 1H, H-5′, $J_{5',6'} = 8.1$ Hz); 6.26 (d, 1H, H-2, $J_{2,3} = 15.9$ Hz); 4.93 (bs, 2H, 2 ArOH) 3.75 (s, 3H, OCH_3). ^{1}H NMR spectrum is in agreement with data given in the literature.[23]

(E)-Methyl 3-(4-Hydroxyphenyl)acrylate (9b)

The procedure described previously for the synthesis of **9a** was applied to (4-hydroxyphenyl)acrylic acid **8b** in MeOH to give **9b** in a yield of 92%. Colorless solid. Mp 136–137°C. Lit.[24] mp 138–139°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 (d, 1H, H-3, $J_{2,3} = 16.0$ Hz); 7.44–7.40 (AA′ part of AA′XX′ system, quasi d, 2H, H-2′/6′, $J = 8.6$ Hz); 6.90–6.86 (XX′ part of AA′XX′ system, quasi d, 2H, H-3′/5′, $J = 8.6$ Hz); 6.30 (d, 1H, H-2, $J_{2,3} = 16.0$ Hz); 3.82 (s, 3H, OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.1 (C-1); 158.1 (C-4′); 145.1 (C-3); 130.1 (C-2′/6′); 127.1 (C-1′); 116.0 (C-3′/5′); 115.0 (C-2); 51.8 ($O\underline{C}H_3$). ^{1}H NMR and ^{13}C NMR spectra are in agreement with data given in the literature.[24]

(E)-Methyl 3-(3,4-Bis(methoxymethoxy)phenyl)acrylate (10a)

K_2CO_3 (3.56 g, 25.7 mmol) and methoxymethyl chloride (2.070 g, 1.95 mL, 25.7 mmol) were added to a solution of methyl caffeate (**9a**) (1.00 g, 5.15 mmol) in acetone (40 mL). The mixture was refluxed for 1 h. The precipitate was filtered and dispatched. The solvent was removed under reduced pressure. Chromatography of the crude product on a

silica-gel column (30 g) eluting with 3:7 EtOAc/hexane gave **10a** as a yellow oil (1.090 g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 1H, H-3, $J_{2,3} = 16.1$ Hz); 7.35 (d, 1H, H-2′, $J_{2',6'} = 1.5$ Hz); 7.15 (d, 1H, H-5′, $J_{5',6'} = 8.6$ Hz); 7.13 (dd, 1H, H-6′, $J_{5',6'} = 8.6$ Hz, $J_{2',6'} = 1.5$ Hz); 6.32 (d, 1H, H-2, $J_{2,3} = 16.1$ Hz); 5.26 (s, 2H, OCH_2O); 5.24 (s, 2H, OCH_2O); 3.79 (s, 3H, OCH_3 of ester); 3.52 (s, 3H, OCH_3); 3.50 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8 (C-1); 149.4 (C-3′^{a}); 147.6 (C-4′^{a}); 144.6 (C-3); 129.0 (C-1′); 123.6 (C-6′); 116.5 (C-5′^{b}); 116.3 (C-2′^{b}); 115.8 (C-2^b); 95.7 (OCH_2O); 95.3 (OCH_2O); 56.5 (2C, $2 \times OCH_3$); 51.8 (OCH_3 of ester). ^{1}H NMR spectrum is in agreement with data given in the literature.[22]

(E)-Methyl 3-(4-(tetrahydro-2 H-pyran-2-yloxy)phenyl) Acrylate (10b)

3,4-Dihydro-2H-pyran (3.000 g, 35.7 mmol) was added to a solution of acrylic ester **9b** (4.00 g, 22.5 mmol) in CH_2Cl_2 (20 mL). The mixture was cooled to 0°C, and five drops of CF_3COOH were added. The resulting mixture was magnetically stirred at rt for 48 h. The mixture was washed with brine (2×10 mL) and dried ($MgSO_4$). After the evaporation of the solvent, recystallization of the crude product from CH_2Cl_2–hexane gave **10b** as a yellow solid (5.300 g, 90%). Mp 64–65°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, 1H, H-3, $J = 16.0$ Hz); 7.43–7.40 (AA′ part of AA′XX′ system, d, 2H, H-2′/6′, $J = 8.8$ Hz); 7.02–6.99 (XX′ part of AA′XX′ system, d, 2H, H-3′/5′, $J = 8.8$ Hz); 6.28 (d, 1H, H-2, $J_{2,3} = 16.0$ Hz); 5.43 (t, 1H, H-2″, $J = 3.1$ Hz); 3.82 (ddd, A part of AB system, 1H, H-6″, $J = 12.1$ Hz, $J = 9.5$ Hz, $J = 2.9$ Hz); 3.75 (s, 3H, OCH_3); 3.58 (dddd, B part of AB system, 1H, H-6″, $J = 12.1$ Hz, $J = 3.9$ Hz, $J = 3.9$ Hz, $J = 1.1$ Hz); 2.00–1.92 (m, 1H); 1.85–1.81 (m, 2H); 1.79–1.51 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.6 (C-1); 158.9 (C-4′); 144.5 (C-3); 129.5 (C-2′/6′); 127.9 (C-1′); 116.7 (C-3′/5′); 115.6 (C-2); 96.2 (C-2″); 62.0 (C-6″); 51.5 (OCH_3); 30.2 (C-3″); 25.1 (C-5″); 18.6 (C-4″). Anal. calcd for $C_{15}H_{18}O_4$ (262.3); C, 68.68; H, 6.92. Found: C, 68.74; H, 7.07.

(E)-3-(3,4-Bis(methoxymethoxy)phenyl)prop-2-en-1-ol (11a)

A solution of acrylic ester **10a** (0.690 g, 2.45 mmol) in Et_2O (10 mL) was added dropwise to a slurry of $LiAlH_4$ (0.046 g, 1.23 mmol) in dry Et_2O (10 mL) at 0°C. While the mixture was magnetically stirred at rt, progress of the reaction was monitored by TLC. After completion of the reaction (4 h), the mixture was cooled to 0°C, and 2 mL of H_2O were added. The precipitate was filtered and dispatched. EtOAc (30 mL) and H_2O (10 mL)

were added to this mixture. The organic phase was separated and dried ($MgSO_4$). Removal of the solvent gave the cinnamyl alcohol **11a** as a brownish oil (0.412 g, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, 1H, H-2′, $J_{2',6'} = 2.2$ Hz); 7.10 (d, 1H, H-5′, $J_{5',6'} = 8.4$ Hz); 6.97 (dd, 1H, H-6′, $J_{5',6'} = 8.4$ Hz, $J_{2',6'} = 2.2$ Hz); 6.53 (bd, 1H, H-3, $J_{2,3} = 15.9$ Hz); 6.26 (dt, 1H, H-2, $J_{2,3} = 15.9$ Hz, $J_{1,2} = 5.7$ Hz); 5.24 (s, 2H, OCH_2O); 5.23 (s, 2H, OCH_2O); 4.29 (d, 2H, 2 × H-1, $J_{1,2} = 5.7$ Hz); 3.52 (s, 3H, OCH_3); 3.51 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6 (C-3′^{a}); 147.1 (C-4′^{a}); 131.8 (C-1′); 130.6 (C-3); 127.8 (C-2); 121.2 (C-6′); 116.9 (C-2′^{b}); 114.8 (C-5′^{b}); 95.7 ($O\underline{C}H_2O$); 95.6 ($O\underline{C}H_2O$); 63.7 (C-1); 56.4 (2C, 2 × $O\underline{C}H_3$). ^{1}H NMR spectrum is in agreement with data given in the literature.[22]

(E)-3-(4-(tetrahydro-2 H-pyran-2-yloxy)phenyl)prop-2-en-1-ol (11b)[25]

The procedure described previously for the synthesis of **11a** was applied to ester **10b** to give yellow oil **11b** (80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.23 (AA′ part of AA′XX′ system, d, 2H, H-2′ and H-6′, $J = 8.8$ Hz); 6.98–6.94 (XX′ part of AA′XX′ system, d, 2H, H-3′ and H-5′, $J = 8.8$ Hz); 6.49 (A part of AB system, d, 1H, H-3, $J_{2,3} = 15.7$ Hz); 6.18 (B part of AB system, dt, 1H, H-2, $J_{2,3} = 15.7$ Hz, $J_{1,2} = 5.9$ Hz); 5.38 (t, 1H, H-2″, $J = 3.3$ Hz); 4.22 (t, 2H, 2 × H-1, $J_{1,2} = 5.9$ Hz); 3.87 (ddd, A part of AB system, 1H, H-6″, $J =$ 12.6 Hz, $J = 9.9$ Hz, $J = 3.3$ Hz); 3.57 (dt, B part of AB system, 1H, H-6″, $J = 12.6$ Hz, $J = 3.9$ Hz); 2.61 (bs, 1H, OH); 1.99–1.55 (m, 6H, 2 × H-3″, 2 × H-4″, 2 × H-5″). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4 (C-4′); 130.4 (C-2); 130.2 (C-1′); 127.3 (C-2′/6′); 126.6 (C-3); 116.3 (C-3′/5′); 96.1 (C-2″); 63.4 (C-1); 61.8 (C-6″); 30.1 (C-3″); 25.0 (C-5″); 18.6 (C-4″). Anal. calcd. for $C_{14}H_{18}O_3$ (234.29): C, 71.77; H, 7.74. Found: C, 71.84; H, 7.78.

(E)-3-(3,4-Bis(methoxymethoxy)phenyl)acrylaldehyde (12a)[26]

Freshly prepared MnO_2 (0.420 g) was added to a solution of **11a** (0.690 g, 2.74 mmol) in CH_2Cl_2 (40 mL). The mixture was magnetically stirred at rt for 10 h. The mixture was filtered, and the precipitate was dispatched. After the removal of the solvent, the chromatography of the residue on a silica-gel column eluting with 2:1 EtOAc–hexane gave **12a** as a brown oil (0.306 g, 44%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, 1H, H-1; $J_{1,2} = 7.7$ Hz); 7.38 (d, 1H, H-3, $J_{2,3} = 15.8$ Hz); 7.38 (bs, 1H, H-2′); 7.18 (m, 2H, H-5′ and H-6′); 6.60 (dd, 1H, H-2, $J_{2,3} = 15.8$ Hz, $J_{1,2} = 7.7$ Hz); 5.27 (s, 2H,

OCH_2O); 5.24 (s, 2H, OCH_2O); 3.51 (s, 3H, OCH_3); 3.50 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8 (C-1); 152.7 (C-3); 150.2 (C-3′^{a}); 147.7 (C-4′^{a}); 128.7 (C-1′); 127.6 (C-2); 124.2 (C-6′); 116.4 (C-5′^{b}); 116.3 (C-2′^{b}); 95.8 ($O\underline{C}H_2O$); 95.3 ($O\underline{C}H_2O$); 56.6 ($O\underline{C}H_3$); 56.5 ($O\underline{C}H_3$).

(E)-3-(4-(Tetrahydro-2 H-pyran-2yloxy) Phenyl)acryl Aldehyde (12b)

Freshly prepared MnO_2 (3.70 g, 42.5 mmol) was added to a solution of **11b** (1.000 g, 4.27 mmol) in dry acetone (30 mL). The mixture was magnetically stirred at rt for 10 h. The mixture was filtered, and the precipitate was dispatched. The evaporation of the solvent gave **12b** as yellow solid (0.810 g, 82%). Mp 96–98°C (CH_2Cl_2–hexane). Lit.[25] mp 65–67°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, 1H, H-1, $J_{1,2} = 7.7$ Hz); 7.50 (AA′ part of AA′XX′ system, d, 2H, H-2′/6′, $J = 8.8$ Hz); 7.41 (d, 1H, H-3, $J_{2,3} = 15.7$ Hz); 7.08 (XX′ part of AA′XX′ system, d, 2H, H-3′/5′, $J = 8.8$ Hz); 6.60 (dd, 1H, H-2, $J_{2,3} = 15.7$ Hz, $J_{1,2} = 7.7$ Hz); 5.48 (t, 1H, H-2″, $J = 3.1$ Hz); 3.84 (A part of AB system, ddd, 1H, H-6″, $J = 11.9$ Hz, $J = 11.3$ Hz, $J = 3.0$ Hz); 3.61 (B part of AB system, dddd, 1H, H-6″, $J = 11.9$ Hz, $J = 3.6$ Hz, $J = 3.6$ Hz, $J = 1.1$ Hz); 2.02–1.58 (m, 6H, 2 × H-3″, ″, 2 × H-4″, 2 × H-5″). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7 (C-1); 159.6 (C-4′); 152.7 (C-3); 130.3 (C-2′/6′); 127.3 (C-1′); 126.6 (C-2); 116.8 (C-3′/5′); 96.0 (C-2″); 62.0 (C-6″); 30.0 (C-3″); 25.0 (C-5″); 18.4 (C-4″). Anal. calcd. for $C_{14}H_{16}O_3$ (232.28): C, 72.39; H, 6.94. Found: C, 72.35; H, 7.02.

(4E,6E)-1,7-Bis(3,4-bis(methoxymethoxy)phenyl)hepta-4,6-dien-3-one (13)

A solution of **7a** (0.110 g, 0.41 mmol) in dry ether (10 mL) was cooled to 0°C. While the solution was being magnetically stirred at the same temperature, a solution of pyrrolidine (0.015 g, 0.22 mmol) in ether (1 mL) and then AcOH (0.015 g, 0.25 mmol) in dry ether (1 mL) were added. The mixture was stirred at the same temperature for 30 min. A solution of acrylaldehyde **12a** (0.080 g, 0.32 mmol) in ether (5 mL) was added dropwise to the mixture, and the resulting mixture was stirred at rt for 12 h. Five mL of 0.1 M HCl were added to the mixture. The organic phase was extracted with Et_2O (2 × 10 mL) and dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue on a silica-gel column (20 g) eluting with 7:3 hexane–EtOAc gave **13** as a yellow oil (0.116 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, 1H, H-5, $J_{4,5} = 15.4$ Hz, $J_{5,6} = 10.6$ Hz), 7.29 (d, 1H, H-2″, $J_{2'',6''} = 2.2$ Hz); 7.12 (A part of AB system, d, 1H, H-5″, $J_{5'',6''} = 8.8$ Hz); 7.05 (B part of AB system, d, 1H,

H-6″, $J_{5'',6''} = 8.8$ Hz); 7.04 (A part of AB system, d, 1H, H-5′, $J_{5',6'} = 8.4$ Hz); 7.01 (d, 1H, H-2′, $J_{2',6'} = 2.2$ Hz); 6.85 (A part of AB system, d, 1H, H-7, $J_{6,7} = 15.4$ Hz); 6.79 (B part of AB system, dd, 1H, H-6′, $J_{5',6'} = 8.4$ Hz, $J_{2',6'} = 2.2$ Hz); 6.74 (B part of AB system, dd, 1H, H-6, $J_{6,7} = 15.4$ Hz, $J_{5,6} = 10.6$ Hz); 6.26 (d, 1H, H-4, $J_{4,5} = 15.4$ Hz); 5.25 (s, 2H, OCH_2O); 5.24 (s, 2H, OCH_2O); 5.21 (s, 2H, OCH_2O); 5.19 (s, 2H, OCH_2O); 3.53 (s, 3H, OCH_3); 3.51 (s, 3H, OCH_3); 3.50 (s, 3H, OCH_3); 3.50 (s, 3H, OCH_3); 2.90–2.85 (A_2B_2 system, m, 4H, 2 × H-1 and 2 × H-2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6 (C-3); 148.5 (C-4″); 147.7 (C-3″); 147.5 (C-3′); 145.8 (C-4′); 143.2 (C-5); 141.3 (C-7); 136.1 (C-1′); 130.9 (C-1″); 129.0 (C-4); 125.7 (C-6); 122.6 (C-6″^{a}); 122.4 (C-6′^{a}); 117.2 (2C, C-5″^{b} and C-2′^{b}); 116.6 (C-5′^{b}); 115.0 (C-2″^{b}); 96.3 ($O\underline{C}H_2O$); 95.8 ($O\underline{C}H_2O$); 95.7 ($O\underline{C}H_2O$); 95.7 ($O\underline{C}H_2O$); 56.5 (2C, 2 × $O\underline{C}H_3$); 56.4 ($O\underline{C}H_3$); 56.3 ($O\underline{C}H_3$); 42.7 (C-2); 30.0 (C-1).

(4E,6E)-1,7-Bis(3,4-dihydroxyphenyl)hepta-4,6-dien-3-one (2)

To a solution of **13** (0.116 g, 0.23 mmol) in ether (5 mL), 1 M HCl (2 mL) was added. The mixture was stirred at 50°C for 1 h. Ten mL of ether were added. The organic phase was separated, washed with water (2 × 2 mL), and dried (Na_2SO_4). Removal of the solvent and filtration of the residue on a short silica-gel column (2 g) gave **2** as yellow oil (0.071 g, 95%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.36 (dd, 1H, H-5, $J_{4,5} = 15.4$ Hz, $J_{5,6} = 10.8$ Hz), 6.98 (d, 1H, H-2″, $J_{2'',6''} = 2.0$ Hz), 6.89 (A part of AB system, d, 1H, H-7, $J_{6,7} = 15.7$ Hz); 6.87 (A part of AB system, dd, 1H, H-6″, $J_{5'',6''} = 8.3$ Hz, $J_{2'',6''} = 2.0$ Hz); 6.76 (B part of AB system, dd, 1H, H-6, $J_{6,7} = 15.7$ Hz, $J_{5,6} = 10.8$ Hz); 6.74 (B part of AB system, d, 1H, H-5″, $J_{5'',6''} = 8.3$ Hz); 6.66 (A part of AB system, d, 1H, H-5′, $J_{5',6'} = 8.1$ Hz); 6.64 (d, 1H, H-2′, $J_{2',6'} = 2.0$ Hz); 6.52 (B part of AB system, dd, 1H, H-6′, $J_{5',6'} = 8.1$ Hz, $J_{2',6'} = 2.0$ Hz); 6.22 (d, 1H, H-4, $J_{4,5} = 15.4$ Hz), 2.89–2.73 (A_2B_2 system, m, 4H, 2 × H-1 and 2 × H-2). ^{13}C NMR (100 MHz, CD_3OD) δ 201.8 (C-3); 147.3 (C-4″); 145.5 (C-3″); 145.0 (C-3′); 143.3 (C-4′); 143.3 (C-5) 142.8 (C-7); 132.9 (C-1′); 128.6 (C-1″); 127.6 (C-4); 123.8 (C-6); 120.7 (C-6″); 119.4 (C-6′); 115.3 (C-5″); 115.3 (C-2′); 115.2 (C-5′); 113.4 (C-2″); 42.0 (C-2); 30.0 (C-1). ^{1}H NMR and ^{13}C NMR spectra are in agreement with data given in the literature.[12]

(4E,6E)-1,7-Bis(4-hydroxyphenyl)hepta-4,6-dien-3-one (3)

The condensation of 4-(4-acetoxyphenyl)-butan-2-one (**7c**) (0.300 g, 1.45 mmol) and (**E**)-3-(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)acrylaldehyde

(**12b**) (0.320 g, 1.38 mmol) via the procedure described previously gave a mixture of **14a–c**. Without separation, the mixture was dissolved in MeOH (40 mL), and 0.060 g of p-TsOH was added. The resulting mixture was refluxed for 20 h. After the removal of MeOH under reduced pressure, CH_2Cl_2 (50 mL) was added, and the organic phase was washed with saturated $NaHCO_3$ and dried (Na_2SO_4). Removal of the solvent, and TLC on a silica-gel plate, eluting with $CHCl_3$–MeOH–H_2O (90:10:1) gave **3** as yellow oil (0.250 g, 59%).

^{1}H NMR (400 MHz, acetone-d_6) δ 7.44 (AA′ part of AA′XX′ system, d, 2H, H-2′ and H-6′, $J = 8.4$ Hz); 7.38 (dd, 1H, H-5, $J_{5,6} = 10.6$ Hz, $J_{4,5} = 15.4$ Hz); 7.07 (AA′ part of AA′XX′ system, d, 2H, H-2″ and H-6″, $J = 8.4$ Hz); 7.01 (A part of AB system, d, 1H, H-7, $J_{6,7} = 15.4$ Hz); 6.88 (B part of AB system, dd, H-6, $J_{6,7} = 15.4$ Hz, $J_{5,6} = 10.6$ Hz); 6.86 (XX′ part of AA′XX′ system, d, 2H, H-3″ and H-5″, $J = 8.4$ Hz); 6.74 (XX′ part of AA′XX′ system, d, 2H, H-3′ and H-5′, $J = 8.4$ Hz); 6.25 (d, 1H, H-4, $J = 15.4$ Hz); 2.90–2.78 (A_2B_2 system, m, 4H, 2 × H-1 and 2 × H-2). ^{13}C NMR (100 MHz, acetone-d_6) δ 198.6 (C-3); 159.1 (C-4″); 155.8 (C-4′) 143.2 (C-5); 141.4 (C-7); 132.5 (C-1′); 129.5 (C-2′ and C-6′); 129.2 (C-2″ and C-6″); 128.6 (C-4); 128.2 (C-1″); 124.3 (C-6); 116.0 (C-3″ and C-5″); 115.3 (C-3′ and C-5′); 42.2 (C-2); 29.5 (C-1). ^{1}H NMR and ^{13}C NMR spectra are in agreement with data given in the literature.[27]

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REFERENCES

1. Claeson, P.; Tuchinda, P.; Reutrakul, V. Naturally occurring 1,7-diaryheptanoids. *J. Indian Chem. Soc.* **1994**, *71*, 509–521.
2. Claeson, P.; Claeson, U. P.; Tuchinda, P.; Reutrakul, V. Occurrence, structure, and bioactivity of 1,7-diarylheptanoids. *Stud. Nat. Prod. Chem.* **2002**, *26*, 881–908.
3. (a) Flynn, D. L.; Rafferty, M. F.; Boctor, A. M. Inhibition of 5-hydroxyeicosatetraenoic acid (5-HETE) formation in intact human neutrophils by naturally occurring diarylheptanoids: Inhibitory activities of curcuminoids and yakuchinones. *Prostaglandins, Leukotrienes, Med.* **1986**, *22*, 357–360; (b) Lee, M. W.; Kim, J. H.; Jeong, D. W.; Ahn, K. H.; Toh, S. H.; Surh, Y. J. Inhibition of cyclooxygenase-2 expression by diarylheptanoids from the bark

of *Alnus hirsuta* var. Sibirica. *Biol. Pharm. Bull.* **2000**, *23*, 517–518; (c) Lee, S. L.; Huang, W. J.; Lin, W. W.; Lee, S. S.; Chen, C. H. Preparation and anti-inflammatory activities of diarylheptanoid and diarylheptylamine analogs. *Bioorg. Med. Chem*. **2005**, *13*, 6175–6181.

4. Araujo, C. A. C.; Leon, L. L. Biological activities of *Curcuma longa* L. *Memorias do Instituto Oswaldo Cruz* **2001**, *96*, 723–728.
5. Yang, Y.; Kinoshita, K.; Koyama, K.; Takahashi, K.; Kondo, S.; Watanabe, K. Structure–antiemetic activity of some diarylheptanoids and their analogues. *Phytomedicine*. **2002**, *9*, 146–152.
6. Hikino, H.; Kiso, Y.; Kato, N.; Hamada, Y.; Shioiri, T.; Aiyama, R.; Itokawa, H.; Kiuchi, F.; Sankawa, U. Antihepatatoxic actions of gingerols and diarylheptanoids. *J. Ethnopharmacol.* **1985**, *14*, 31–39.
7. Ali, M. S.; Banskota, A. H.; Tezuka, Y.; Saiki, I.; Kadota, S. Antiproliferative activity of diarylheptanoids from the seeds of *Alpinia blepharocalyx*. *Biol. Pharm. Bull.* **2001**, *24*, 525–528.
8. (a) Chun, K. S.; Sohn, Y.; Kim, H. S.; Kim, O. H.; Park, K. K.; Lee, J. M.; Lee, J.; Lee, J. Y.; Moon, A.; Lee, S. S.; Surh, Y. J. Anti-tumor promoting potential of naturally occurring diarylheptanoids structurally related to curcumin. *Mutat. Res.-Fund. Mol. M.* **1999**, *428*, 49–57; (b) Ishida, J.; Kozuka, M.; Tokuda, H.; Nishino, H.; Nagumo, S.; Lee, K. H.; Nagai, M. Chemopreventive potential of cyclic diarylheptanoids. *Bioorg. Med. Chem.* **2002**, *10*, 3361–3365.
9. (a) Claeson, P.; Panthong, A.; Tuchinda, P.; Reutrakul, V.; Kanjanapothi, D.; Taylor, W. C.; Santisuk, T. Three nonphenolic diarylheptanoids with antiinflammatory activity from *Curcuma xanthorrhiza*. *Planta Med.* **1993**, *59*, 451–454; (b) Claeson, P.; Pongprayoon, U.; Sematong, T.; Tuchinda, P.; Reutrakul, V.; Soontornsaratune, P.; Taylor, W. C. Non-phenolic linear diarylheptanoids from *Curcuma xanthorrhiza*: A novel type of topical anti-inflammatory agents: Structure–activity relationship. *Planta Med.* **1996**, *62*, 236–240.
10. Huang, W. Z.; Dai, X. J.; Liu, Y. Q.; Zhang, C. F.; Zhang, M.; Wang, Z. T. Studies on antibacterial activity of flavonoids and diarylheptanoids from *Alpinia katsumadai*. *J. Plant Resour. Environ.* **2006**, *15*, 37–40.
11. Yu, W.; Hu, X.; Tokuda, S. Novel medicine for antianaphylaxis, anti-asthma, and anti-inflammatory agent. Chinese Pat. CN1180065, 1998, *Chem. Abstr.* **2000**, *132*, 105480.
12. Kikuzaki, H.; Kawai, Y.; Nakatani, N. 1,1-Diphenyl-2-picrylhydrazyl radical-scavenging active compounds from greater cardamom (*Amomum subulatum* Roxb.). *J. Nutr. Sci. Vitaminol.* **2001**, *47*, 167–171.
13. Jang, D. S.; Park, E. J.; Hawthorne, M. E.; Vigo, J. S.; Graham, J. G.; Cabieses, F.; Santarsiero, B. D.; Mesecar, A. D.; Fong, H. H. S.; Mehta, R. G.; Pezzuto, J. M.; Kinghorn, A. D. Constituents of Musa × paradisiaca cultivar with the potential to induce the phase II enzyme, quinone reductase. *J. Agric. Food Chem.* **2002**, *50*, 6330–6334.
14. Moon, S. S.; Cho, S. C.; Lee, J. Y. Tsaokoarylone, a cytotoxic diarylheptanoid from Amomum tsao-ko fruits. *Bull. Korean Chem. Soc.* **2005**, *26*, 447–450.

15. Göksu, S.; Çelik, H.; Seçen, H. An efficient synthesis of alnustone, a naturally occurring compound. *Turk. J. Chem.* **2003**, *27*, 31–34.
16. Xu, G.; Li, S. Synthesis of 1,7-bis(hydroxyphenyl) hepta-4E,6E-dien-3-one. *Lanzhou Daxue Xuebao, Ziran Kexueban*. **2004**, *40*, 106; *Chem. Abstr.* **2006**, *146*, 337527.
17. Baranovsky, A.; Schmitt, B.; Fowler, D. J.; Schneider, B. Synthesis of new biosynthetically important diarylheptanoids and their oxa- and fluoro-analogues by three different strategies. *Synth. Commun.* **2003**, *33*, 1019–1045.
18. Itokawa, H.; Aiyama, R.; Ikuta, A. Synthesis of diarylheptanoids and assessment of their pungency. *Chem. Pharm. Bull.* **1983**, *31*, 2491–2496.
19. Tae, E. L.; Lee, S. H.; Lee, J. K.; Yoo, S. S.; Kang, E. J.; Yoon, K. B. A strategy to increase the efficiency of the dye-sensitized TiO_2 solar cells operated by photoexcitation of dye-to-TiO_2 charge-transfer bands. *J. Phys. Chem. B* **2005**, *109*, 22513–22522.
20. Liu, Y. G.; Li, S. B. Synthesis of 1-(3′,4′-dihydroxyphenyl)-7-(4″-hydroxyphenyl)-4-hepten-3-one. *Chin. Chem. Lett.* **2001**, *12*, 1069–1070.
21. Alexander, B. H.; Beroza, M.; Oda, T. A.; Steiner, L. F.; Miyashita, D. H.; Mitchell, W. C. The development of bait for the male melon fly. *J. Agric. Food Chem.* **1962**, *10*, 270–276.
22. Tanaka, H.; Kato, I.; Ito, K. Total synthesis of neolignans, Americanin A and Isoamericanin A. *Chem. Pharm. Bull.* **1987**, *35*, 3603–3608.
23. Van Dyck, S. M. O.; Lemiere, G. L. F.; Jonckers, T. H. M.; Dommisse, R. Synthesis of 4-O-methylcedrusin: Selective protection of catechols with diphenyl carbonate. *Molecules* **2000**, *5*, 153–161.
24. Galland, S.; Mora, N.; Abert-Vian, M.; Rakotomanomana, N.; Dangles, O. Chemical synthesis of hydroxycinnamic acid glucosides and evaluation of their ability to stabilize natural colors via anthocyanin copigmentation. *J. Agric. Food Chem.* **2007**, *55*, 7573–7579.
25. Tamada, S.; Nagami, K.; Teramoto, S.; Tanaka, T.; Nakagawa, K. Novel dihydropyridine derivatives and process for preparing the same. Eur. Pat. 1985, EP145434; *Chem. Abstr*. **1986**, *104*, 19517.
26. Kosaka, T.; Wakabayashi, T. Synthesis of 2-(4-aryl-1E,3E-butadienyl) benzoxazoles by the Horner–Wadsworth–Emmons reaction. *Heterocycles.* **1995**, *41*, 477–485.
27. Ali, M. S.; Tezuka, Y.; Awale, S.; Banskota, A. H.; Kadota, S. Six new diarylheptanoids from the seeds of *Alpinia blepharocalyx*. *J. Nat. Prod.* **2001**, *64*, 289–293.