Communication

A Short and Efficient Synthesis of a Novel Diarylheptanoid Isolated from *Pleuranthodium Racemigerum*

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The first total synthesis of the linear diarylheptanoid 1-(4″-methoxyphenyl)-7-(4′-hydroxyphenyl)-(*E*)-hept-2-ene, which has a uniquely nonconjugated olefin, was achieved. The synthetic route employed an olefin cross-metathesis as a key step. Beginning with commercially available 3-(4-hydroxyphenyl)propan-1-ol, the final product was made in three steps with a 52% yield.

Keywords: Diarylheptanoid; Cytotoxic activity; Prostaglandin E_2; Olefin cross-metathesis.

INTRODUCTION

Diarylheptanoids are a family of natural plant metabolites that possess potent anti-inflammatory and antioxidant properties and have the characteristic feature of two aromatic rings tethered by a linear seven-carbon chain.[1] The best known example of this family is curcumin **1** (diferuloylmethane), which has been studied extensively for its wide-ranging pharmacological properties (Fig. 1).[2] In a program aimed to discover novel compounds from the *Pleuranthodium* species, the Wohlmuth group reported the isolation of a new diarylheptanoid **2**, 1-(4″-methoxyphenyl)-7-(4′-hydroxyphenyl)-(*E*)-hept-2-ene, which showed high potency for the inhibition of prostaglandin E_2 (PGE_2) production in 3T3 murine fibroblasts with an IC_{50} value of 34 μM.[3] The diarylheptanoid **2** was also tested for cytotoxic activity against four human cancer cell lines (Caco-2 colonic adenocarcinoma, PC3 prostate adenocarcinoma, HepG2 hepatocyte carcinoma, and MCF7 mammary adenocarcinoma). The cytotoxicity of diarylheptanoid **2** closely resembled that of curcumin, both in terms of the IC_{50} values and the dose-response curves in vitro. In this report, we describe the first total synthesis of diarylheptanoid **2** from the readily available starting material 3-(4-hydroxyphenyl)-propan-1-ol (**3**).

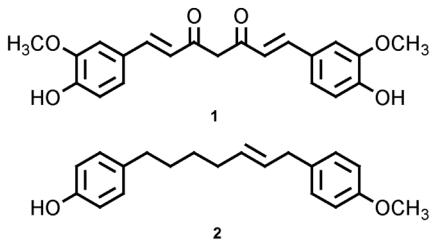


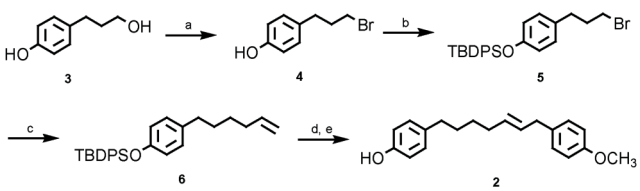
Fig. 1. Chemical structures of curcumin **1** and diarylheptanoid **2**.

RESULTS AND DISCUSSION

Our synthesis of diarylheptanoid **2** started from the commercially available 3-(4-hydroxyphenyl)propan-1-ol (**3**). The hydroxyl group at C(1) of **3** was transformed to a bromide by the Appel reaction giving 3-(4-hydroxyphenyl)propyl bromide (**4**) with an excellent yield (95%).[4] Protecting the phenol group with *tert*-butyldiphenylsilyl chloride (TBDPSCl) afforded compound **5** with a 97% yield as a white solid.[5] The desired olefin **6** was obtained from the displacement of the bromine atom by allylmagnesium chloride in toluene with a 93% yield.[6]

Subsequently, olefin **6** was treated with 4-allylanisole in the presence of the Grubbs' second-generation catalyst in CH_2Cl_2 at ambient temperature.[7] After 2 hours, the ex-

Scheme I

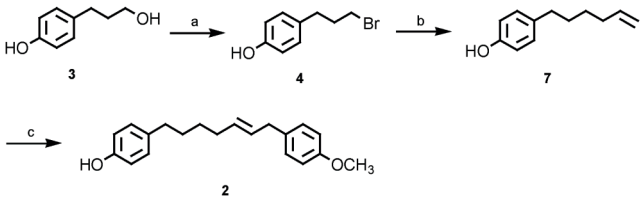


Reagents and conditions: (a) CBr_4, PPh_3, CH_2Cl_2, 0 ºC, 95%; (b) TBDPSCl, *tert*-BuOK, THF, 0 ºC, 97%; (c) allylmagnesium chloride, toluene, 95 ºC, 93%; (d) Grubbs' 1st generation catalyst, 4-allylanisole, CH_2Cl_2, reflux; (e) TBAF, THF, rt, 62% (E/Z = 83/17) over two steps.

pected product was not detected and a complex mixture of products was formed. Fortunately, the desired olefin cross-metathesis (CM) product can be obtained with the Grubbs' first-generation catalyst in CH_2Cl_2 at reflux for 18 hours.[8] The protecting group was removed by TBAF *in situ* to give an 83:17 mixture of (*E*)-diarylheptanoid **2** and its (*Z*)-isomer with a 62% yield.[9] These alkene isomers could be separated by flash column chromatography on silica gel impregnated with silver nitrate to give the desired diarylheptanoid **2** in a 50% isolated yield (Scheme I).[10-12]

In addition, a short and efficient synthesis of diarylheptanoid **2** was realized, as shown in Scheme II. The bromine atom at C(1) of compound **4** was efficiently substituted by allylmagnesium chloride (6 equiv.) in toluene at 95 ºC to afford olefin **7** with an excellent yield (95%). Olefin **7** reacted with 4-allylanisole catalyzed by the Grubbs' first-generation catalyst in CH_2Cl_2 at reflux to afford a mixture of (*E*)-diarylheptanoid **2** and its (*Z*)-isomer in an 85:15 ratio with a 70% yield. Similarly, these isomers could be separated to afford diarylheptanoid **2** in a 58% purified yield. The obtained spectral data are in agreement with those reported in the literature.[3]

Scheme II



Reagents and conditions: (a) CBr_4, PPh_3, CH_2Cl_2, 0 ºC, 95%; (b) allylmagnesium chloride, toluene, 95 ºC, 95%; (c) Grubbs' 1st generation catalyst, 4-allylanisole, CH_2Cl_2, reflux, 70% (E/Z = 85/15).

CONCLUSION

In summary, we report on a concise and expedient route for the total synthesis of 1-(4″-methoxyphenyl)-7-(4′-hydroxyphenyl)-(*E*)-hept-2-ene **2** in overall yields of 43% (5 steps) and 52% (3 steps). The synthetic sequence is based on an olefin cross-metathesis with the Grubbs' first-generation catalyst to establish the olefin as a key step. Notably, we have used silica gel impregnated with silver nitrate to achieve the successful separation of **2** and its (*Z*)-stereoisomer. Further studies are underway for the synthesis of linear diarylheptanoid analogues.

EXPERIMENTAL

3-(4-Hydroxyphenly)propyl bromide (4)

A magnetically stirred solution of 3-(4-hydroxyphenyl)propan-1-ol (**3**) (2.17 g, 14.3 mmol) and carbon tetrabromide (9.61 g, 28.9 mmol) in CH_2Cl_2 (60 mL) was added triphenylphosphine (9.3 g, 35.5 mmol) in portions with ice-bath cooling. After addition was completed, the mixture was stirred for an additional 10 min, whereupon the solvent was removed *in vacuo* to afford a glutinous mixture. The crude product was purified by flash column chromatography eluting with hexane/EtOAc (5:1) to obtain **4** (2.88 g, 95%) as a colorless liquid. IR (KBr) 3073, 2894, 2857, 1610, 1510, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 4.82 (br, 1H), 3.38 (t, *J* = 6.6 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.16-2.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.60, 132.69, 129.60, 115.31, 34.22, 33.14, 32.91; MS (EI): *m/z* 214 (M^+); HRMS (EI) *m/z* calcd for $C_9H_{11}BrO$ 213.9993, found 213.9995. Anal. Calcd for $C_9H_{11}BrO$: C, 50.22; H, 5.00. Found: C, 49.96; H, 5.03.

3-(4-(*tert*-Butyl)diphenylsiloxy)phenyl)propyl bromide (5)

A solution of compound **4** (2.32 g, 10.8 mmol) in dried THF (90 mL) was added potassium *tert*-butoxide (2.92 g, 25.9 mmol) in portions at 0 ºC. The mixture was stirred for another 20 min and then *tert*-butyldiphenylsilyl chloride (7.0 mL, 26.9 mmol) was added slowly. After stirred for another 30 min, the reaction mixture was then quenched by addition of a saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (3 × 50 mL). The extracts were combined and dried over anhydrous magnesium sulfate, filtered, then concentrated *in vacuo* to obtain a yellowish solid (10.2 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (100:1) to give **5** (4.72 g, 97%) as a white solid. Mp. 52-53 ºC; IR (KBr) 3069, 2894, 2858, 1608, 1510, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72-7.70 (m, 4H), 7.44-7.34 (m, 6H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 3.33 (d, *J* = 6.8 Hz, 2H), 2.63 (d, *J* = 7.2 Hz, 2H), 2.09-2.04 (m, 2H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.93, 135.53, 133.09, 132.86, 129.82, 129.17, 127.71, 119.63, 34.25, 33.08, 33.05, 26.56, 19.44; MS (EI): *m/z* 452 (M^+); HRMS (EI) *m/z* calcd for $C_{25}H_{29}SiBrO$ 452.1172, found 452.1179; Anal. Calcd for $C_{25}H_{29}SiBrO$: C, 66.00; H, 6.00. Found: C, 66.24; H, 5.87.

6-(4-(*tert*-Butyl)diphenylsiloxy)phenyl)hex-1-ene (6)

A solution of compound **5** (4.72 g, 10.4 mmol) in toluene (50 mL) was added allylmagnesium chloride (2.0 M solution in THF, 15.6 mL, 31.2 mmol) at 0 ºC. The reaction solution was stirred at 95 ºC for 36 h, while the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was quenched with cold saturated ammonium chloride solution (20 mL) at 0 ºC and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to award a yellowish liquid (5.12 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (100:1) to give **6** (4.02 g, 93%) as a colorless liquid. IR (KBr) 3072, 2931, 2858, 1644, 1510, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72-7.70 (m, 4H), 7.41-7.34 (m, 6H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 5.83-5.72 (m, 1H), 4.99-4.90 (m, 2H), 2.47 (t, *J* = 7.8 Hz, 2H), 2.06-2.01 (m, 2H), 1.56-1.50 (m, 2H), 1.40-1.34 (m, 2H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.49, 138.89, 135.54, 135.06, 133.23, 129.77, 128.97, 127.68, 119.37, 114.29, 34.89, 33.59, 30.95, 28.45, 26.58, 19.46; MS (EI): *m/z* 414 (M^+); HRMS (EI) *m/z* calcd for $C_{28}H_{34}SiO$ 414.2379, found 414.2386; Anal. Calcd for $C_{28}H_{34}SiO$: C, 81.00; H, 8.00. Found: C, 81.03; H, 8.03.

Diarylheptanoid 2

A solution of olefin **6** (0.42 g, 1.0 mmol) and 4-allylanisole (0.31 mL, 2.0 mmol) in dry CH_2Cl_2 (5 mL) was added via syringe to a stirred solution of Grubbs' first-generation catalyst (0.04 g, 0.05 mmol) in dry CH_2Cl_2 (5 mL) at ambient temperature. The reaction mixture was stirred at reflux for 18 h under a nitrogen atmosphere. The solvent was removed *in vacuo* and THF (10 mL) was added followed by a tetrabutylammonium fluoride solution (1.0 M solution in THF, 2.0 mL, 2.0 mmol) at ambient temperature. After stirring for another 2 h, the reaction mixture was concentrated *in vacuo* to obtain a dark liquid (1.12 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (10:1) to afford a mixture of 2 and its (*Z*)-isomer (0.184 g, 62%). The mixture of alkenes was separated further by flash column chromatography on $AgNO_3$-doped silica gel using hexane/EtOAc (10:1) as the eluent to give the desired diarylheptanoid 2 as a colorless liquid (0.15 g, 50%) and the (*Z*)-isomer (0.029 g, 10%). IR (KBr) 3744, 3028, 2931, 2857, 1648, 1510, 1251, 1111, 921 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 5.54 (dt, *J* = 14.4, 6.0 Hz, 1H), 5.46 (dt, *J* = 14.4, 6.0 Hz, 1H), 4.76 (br, 1H), 3.79 (s, 3H), 3.26 (d, *J* = 6.0 Hz, 2H), 2.52 (t, *J* = 7.6 Hz, 2H), 2.06-2.01 (m, 2H), 1.60-1.54 (m, 2H), 1.43-1.34 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.64, 153.50, 134.76, 133.21, 131.41, 129.37, 129.35, 129.33, 115.04, 113.75, 55.26, 38.09, 34.77, 32.24, 31.14, 28.92; MS (EI): *m/z* 296 (M^+); HRMS (EI) *m/z* Calcd for $C_{20}H_{24}O_2$ 296.1777, found 296.1785. Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.00; H, 8.00. Found: C, 80.73; H, 8.12.

6-(4-Hydroxyphenyl)hex-1-ene (7)

A solution of compound **4** (1.62 g, 7.5 mmol) in toluene (40 mL) was added allylmagnesium chloride (2.0 M solution in THF, 22.0 mL, 44.0 mmol) at 0 ºC. The reaction solution was stirred at 95 ºC for 42 h, while the reaction was monitored by TLC. The reaction mixture was quenched with cold saturated ammonium chloride solution (20 mL) at 0 ºC and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to award a yellowish liquid (2.32 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (15:1) to afford **7** (1.26 g, 95%) as a colorless liquid. IR (KBr) 3546, 3073, 2927, 2854, 1641, 1610, 1513, 1362 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 10.8 Hz, 2H), 6.75 (d, *J* = 10.8 Hz, 2H), 5.85-5.75 (m, 1H), 5.02-4.92 (m, 2H), 4.69 (br, 1H), 2.54 (t, *J* = 7.6 Hz, 2H), 2.10-2.04 (m, 2H), 1.63-1.55 (m, 2H), 1.45-1.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.31, 138.86, 134.86, 129.38, 115.13, 114.31, 34.79, 33.55, 31.05, 28.39; MS (EI): *m/z* 176 (M^+); HRMS (EI) *m/z* calcd for $C_{12}H_{16}O$ 176.1202, found 176.1193. Anal. Calcd for $C_{12}H_{16}O$: C, 81.82; H, 9.00. Found: C, 81.63; H, 9.10.

Synthesis of Diarylheptanoid 2 from olefin 7

As the previous procedure, a reaction solution of olefin **7** (0.176 g, 1.0 mmol), 4-allylanisole (0.31 mL, 2.0 mmol), and Grubbs' first-generation catalyst (0.04 g, 0.05 mmol) in dry CH_2Cl_2 (10 mL) was stirred at reflux for 18 h under a nitrogen atmosphere. The solvent was removed *in vacuo* to obtain the crude product (0.23 g). The crude product was purified by flash column chromatography using hexane/EtOAc (10:1) as the eluent to afford a mixture of **2** and its (*Z*)-isomer (0.207 g, 70%). The mixture of alkenes was separated further by flash column chromatography on $AgNO_3$-doped silica gel using hexane/EtOAc (10:1) as the eluent to afford the desired diarylheptanoid **2** as a colorless liquid (0.172 g, 58%) and the (*Z*)-isomer (0.027 g, 9%).

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11. The $AgNO_3$-doped silica gel was prepared as follows. A solution of $AgNO_3$ (20 g) in CH_3CN (200 mL) was added to silica gel (100 g). The silica gel solution was mixed thoroughly for 10 min, after which the vessel was covered with aluminum foil and dried in a hot oven (65 ºC for 24 h). The prepared $AgNO_3$-doped silica gel was stored in the dark prior to use.
12. The (*Z*)-isomer was identified by ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 5.53 (dt, J = 11.6, 6.4 Hz, 1H), 5.47 (dt, J = 11.6, 6.4 Hz, 1H), 3.78 (s, 3H), 3.32 (d, J = 6.4 Hz, 2H), 2.55 (t, J = 7.6 Hz, 2H), 2.18-2.13 (m, 2H), 1.62-1.58 (m, 3H), 1.46-1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.76, 153.65, 134.65, 133.27, 130.39, 129.37, 129.17, 128.54, 115.08, 113.84, 55.27, 34.84, 32.53, 31.24, 29.18, 27.00; MS (EI): *m/z* 296 (M^+).