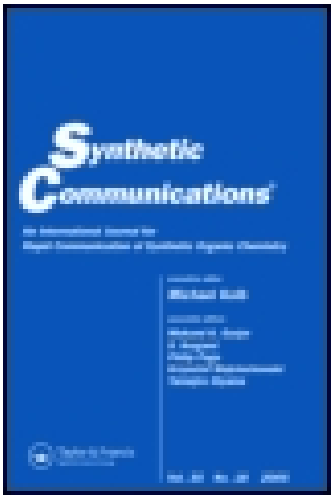

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Concise Synthesis of Pentenyl Phenyl Acrylic Acid

Dequn Sun [a], Pengxiang Lai [a], Weidong Xie [a], Jingen Deng [b] & Yaozhong Jiang [b]
[a] Marine College, Shandong University at Weihai, China
[b] Chengdu Institute of Organic Chemistry, CAS, China
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Concise Synthesis of Pentenyl Phenyl Acrylic Acid

Dequn Sun, Pengxiang Lai, and Weidong Xie
Marine College, Shandong University at Weihai, China

Jingen Deng and Yaozhong Jiang
Chengdu Institute of Organic Chemistry, CAS, China

Abstract: Pentenyl phenyl acrylic acid is a structural unit of pepticinnamin E, a natural product and a bisubstrate inhibitor of FPTase. In this article, a new synthetic strategy was developed to prepare pentenyl phenyl acrylic acid with high stereoselectivity and high overall yield of 78.6%. The method used in producing these effects involved the application of a five-step procedure. Pentenyl phenyl acrylic acid was synthesized starting from 2-iodo-benzyl alcohol through an *E*-selective Wittig–Horner reaction, and then the Sonogashira reaction was used to produce 2-(1-pentynyl)-E-ethyl-cinnamoylate, which was quantitatively hydrogenated, catalyzed by Lindlar catalyst.

Keywords: pentenyl phenyl acrylic acid, quantitative hydrogenation, Sonogashira reaction, stereoselectivity, Wittig–Horner reaction

INTRODUCTION

Pepticinnamin E[1] was isolated from *Sereptomyces OH*-4652, which was identified as the potent FPTase inhibitor and was first synthesized by Waldmann and his group.[2] Their research proved the *S* configuration at the central new 3,4-dihydroxy-D-L-phenylalanine (DOPA) analog and also showed that pepticinnamin E is a bisubstrate inhibitor. Until now, pepticinnamin E has been the only bisubstrate inhibitor produced from nature. There are two components in the structure of pepticinnamin E: one component is the

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Address correspondence to Dequn Sun, Marine College, Shandong University at Weihai, China. E-mail: dequn.sun@sdu.edu.cn

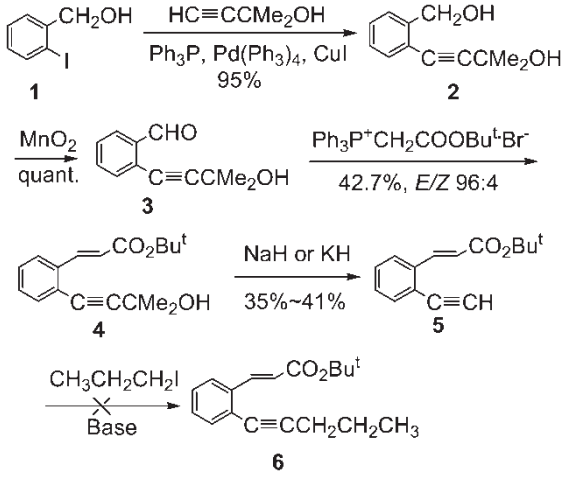
pentenyl phenyl acrylic acid, and the other is the new DOPA analog. Developing new methods to synthesize the two components is necessary to complete the synthesis of pepticinnamin E. These new methods are also important for the study of the structure–activity relationship between pepticinnamin E and the inhibitivity to FPTase. Our work emphasis was focused on the preparation of both DOPA analog and o-(Z-pentenyl)cinnamic acid **15**.

RESULTS AND DISCUSSION

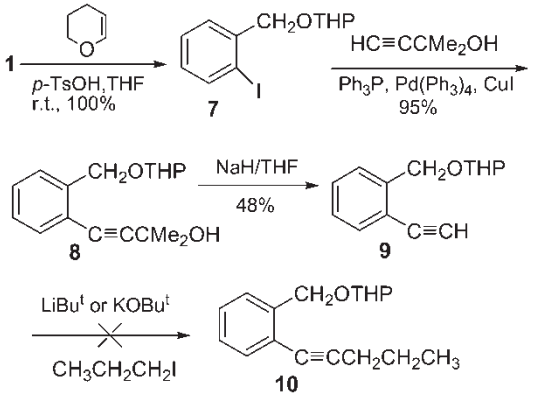
The synthesis of pentenyl phenyl acrylic acid reported by Waldmann started from benzoic acid, using a trans-selective Knoevenagel condensation and a *cis*- selective Wittig's reaction, which needed to be performed at $-100^{\circ}C$ to obtain diastereomerical purity (*de* = 84%). By using a five-step sequence, the target compound acrylic acid was synthesized with an overall yield of 38%.[2a]

In our study, we developed a new method for the preparation of pentenyl phenyl acrylic acid, which apparently improved the overall yield toward the target compound **15**. First, the key Sonogashira reaction was used for obtaining **2** quantitatively, followed by oxidation to yield aldehyde **3**. Wittig's reaction with phosphonium and butyllithium then gave a high *E*-selective product **4**, which was treated with a base to provide arylacetylene **5** with 35–41% yield. Alkylation of **5** was investigated under different conditions and was ultimately considered to be the steric effect of the *tert*-butoxycarbonylvinyl group as shown in Scheme 1.

The hydroxy group of 2-iodobenzyl alcohol **1** was then protected with the tetrahydropyran (THP) group to give **7**. Then **7** was coupled with 2-methyl-3-



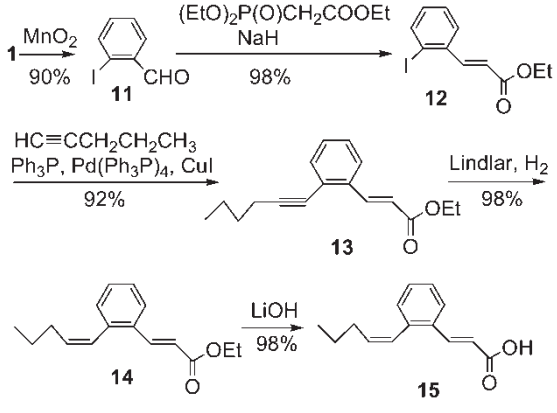
Scheme 1. Organic synthesis of control compounds.



Scheme 2. Organic synthesis of control compounds.

butyn-2-ol using the Sonogashira reaction catalyzed by palladium to give **8**, and the acetone was subsequently removed from **8** with sodium hydride to yield arylacetylene **9**. However, the propylation of **9** to afford the desired compound **10** was unfortunately unsuccessful under different basic conditions (Scheme 2).

Because the steric effect for propylation of **5** and **9** could not be avoided, the Sonogashira reaction was used to form the alkyne directly. Then, the synthetic route in Scheme 3 was developed to obtain the target compound **15**. The procedure started with an *E*-selective Wittig–Horner reaction[3] to obtain **12** with nearly quantitative yield and excellent stereoselectivity (>99%). Next, the key Sonogashira reaction[4] was used to form the alkyne **13**. After this, a quantitative hydrogen reduction was catalyzed by Lindlar catalyst[5] to give **14**. Finally, hydrolysis was used to afford the target compound **15** with an overall yield of 78.6%.



Scheme 3. Organic synthesis of target compound.

CONCLUSION

In summary, we reported a new synthetic route for the preparation of an important component of pepticinnamin E, the pentenyl phenyl acrylic acid, based on the Sonogashira reaction and quantitative hydrogen reduction catalyzed by Lindlar catalyst with an overall yield of 78.6% for five steps. This strategy permits the preparation of analogs of pentenyl phenyl acrylic acid from different alkynyl compounds.

EXPERIMENTAL

Melting points were determined with a Electrothermal digital melting-point apparatus and were uncorrected. Optical rotations were recorded on a Perkin-Elmer model 341 polarimeter, at the sodium D line. Elemental analyses were recorded on Carlo-1106 model automatic instrument. Infrared spectra (IR) were run on Nicolet MX-1 and Nicolet-560 Magna. ^{1}H NMR and spectra were run either on Bruker-200, Bruker-300, or Varian-400 instruments at 25°C; ^{13}C NMR was given by Bruker-200 instrument at 25°C. MS-EI mass spectra were obtained on a V.G. 7070E instrument.

All solvents were handled in the standard ways before use.

2-Iodo-E-ethyl-cinnamoylate (12)

To a solution of 2-iodobenzyl alcohol **1** (1.40 g, 6.0 mmol) in 50 ml of dry CH_2Cl_2, fresh MnO_2 (4.43 g, 51 mmol) was added. The reaction mixture was refluxed for 6 h, then filtered. The filtrate was concentrated in vacuo to give 2-iodobenzaldehyde **11** as a slightly yellow solid (1.25 g, yield 90%, mp 40–41°C). IR (KBr): $\nu = 1693, 1650, 1583, 1445, 1395, 1010, 760\ cm^{-1}$. To a suspension of NaH (0.3 g, 7.5 mmol) in 25 ml of dry CH_2Cl_2, $(EtO)_2P(O)CH_2COOEt$ (1.1 ml, 5.5 mmol) was added dropwise at 0°C. After stirring for 5 min, the solution of **11** (1.16 g, 5 mmol) in 20 ml of dry CH_2Cl_2 was added dropwise, and then the reaction mixture was kept stirring at 0°C for 30 min. Then the reaction mixture was carefully diluted with 10 ml of cold water. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organic phase was dried over Na_2SO_4 and concentrated in vacuo to give **12** as slightly yellow slurry (solidified under 0°C), (0.298 g, yield 98.7%). $C_{11}H_{11}IO_2$ (302.1): calcd. C, 43.73; H, 3.67; found C, 43.71; H, 3.64. IR (neat): $\nu = 1713, 1635, 1313, 1178\ cm^{-1}$. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.91$ (d, $J = 16$ Hz, 1H, CH═), 7.90 (d, $J = 9.4$ Hz, 1H, Ar-H), 7.55 (d, $J = 9.4$ Hz, 1H, Ar-H), 7.34 (t, $J = 7.6$ Hz, 1H, Ar-H), 7.04 (t, 1H, $J = 7.6$ Hz, Ar-H), 6.30 (d, $J = 16$ Hz, 1H, ═CH), 4.30 (q, $J = 7.2$ Hz, 2H, OCH_2), 1.34 (t, $J = 7.2$ Hz, 1H, CH_3) ppm. MS-EI (m/z): 302 (M^+).

2-(1-Pentynl)-E-ethyl-cinnamoylate (13)

To a suspension of Ph_3P (5.0 mg, 0.0191 mmol), $Pd(Ph_3P)_4$ (10 mg, 0.00865 mmol), CuI (0.906 g, 3.00 mmol), and **12** in 3 ml of dry THF, 6 ml of iPr_2NH and 1-pentyne (0.50 ml, 5.0 mmol) were added at room temperature; the reaction mixture was kept stirring for 10 min, then stirred at 53°C for 10 min. The reaction mixture was filtered to remove the white solid and washed with EtOAc. The filtrate was concentrated in vacuo, and the residue was diluted with EtOAc, then washed sequentially with cold 0.1 N HCl to pH < 7 (sat. NaCl to pH = 7). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give crude product, which was purified by chromatography (eluted with petr./ethyl acetate, 30:1) to afford **13** as a slightly yellow slurry (0.668 g, yield 92%). $C_{16}H_{18}O_2$ (242.3) calcd. C, 79.31; H, 7.49; found C, 79.34; H, 7.44. IR (neat): $\nu = 3040$, 2965, 2933, 2210, 1714, 1635, 1267, 1194, 1177 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.2$ (d, $J = 16$ Hz, 1H, CH═), 7.63–7.24 (m, 4H, Ar-H), 6.51 (d, $J = 16$ Hz, 1H, CH═), 4.27 (q, $J = 7.1$ Hz, 2H, OCH_2), 2.46 (t, $J = 7.0$ Hz, 2H, ≡CCH_2), 1.70 (m, 2H, CH_2), 1.34 (t, $J = 7.1$ Hz, 3H, CH_3), 1.13 (t, $J = 7.3$ Hz, 3H, CH_3) ppm. MS-EI (m/z): 242 (M^+).

2-(1-Z-Pentenyl)-E-ethyl-cinnamoylate (14)

To a solution of compound **13** (0.242 g, 1.0 mmol) in 12 ml of dry CH_3OH, Lindlar catalyst (0.242 g, 100% wt) was added. Then the equal molar of hydrogen was bubbled up into the reaction suspension with stirring at room temperature. The reaction process was monitored carefully by thin-layer chromatography (TLC) (n-hexane/ethyl acetate). The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give crude product, which was purified by chromatography (eluted gradually with n-hexane/ethyl acetate) to afford **14** as slightly yellow slurry (0.228 g, yield 98.3% based on recovered starting material, 12 mg of **13**). $C_{16}H_{20}O_2$ (244.3): calcd. C, 78.65; H, 8.25; found C, 78.69; H, 8.20. IR (neat): $\nu = 3010$, 2960, 2936, 1716, 1632, 1311, 1269, 1174 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.84$ (d, $J = 16$ Hz, 1H, CH═), 7.11–7.65 (m, 4H, Ar-H), 6.44 (d, $J = 12.0$ Hz, 1H, CH═), 6.29 (d, $J = 16$ Hz, 1H, CH═), 5.78 (d, $J = 12.0$ Hz, 1H, CH═), 4.18 (q, $J = 7.1$ Hz, 2H, OCH_2), 1.97 (m, 2H, CH_2), 1.39 (m, 2H, CH_2), 1.26 (t, $J = 7.1$ Hz, 3H, CH_3), 0.79 (t, $J = 7.2$ Hz, 3H, CH_3) ppm. MS-EI (m/z): 244 (M^+).

2-(1-Z-Pentenyl)-E-cinnamic Acid (15)

To a solution of compound **14** (152 mg, 0.622 mmol) in 2 ml of ethyl alcohol, $LiOH \cdot H_2O$ (111 mg, 2.5 mmol) was added at 0°C and then stirred for 19 h at

room temperature. The reaction mixture was acidified at 0°C with 0.1 N HCl to pH = 3.5 and extracted four times with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give crude white product, which was recrystallized two times from n-hexane/ethyl acetate to afford **15** as a white solid (132 mg, yield 97.8%). Mp 99–101°C. $C_{14}H_{16}O_2$ (216.3): calcd. C, 77.75; H, 7.46; found: C, 77.78; H, 7.41. IR (KBr): $\nu = 3500$, 3005, 2957, 2929, 1687, 1623, 1331, 1223 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.0$ (d, $J = 8.0$ Hz, 1H, CH═), 7.65–7.22 (m, 4H, Ar-H), 6.55 (d, $J = 11.6$ Hz, 1H, CH═), 6.41 (d, $J = 16.0$ Hz, 1H, CH═), 5.86 (m, 1H, CH═), 2.02 (m, 2H, CH_2), 1.38 (m, 2H, CH_2), 0.86 (t, $J = 6.8$ Hz, 3H, CH_3) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 172.5$ (C═O), 145.5 (HC═), 138.8, 135.4, 132.4, 130.4, 130.1, 130.0 (Ar-C), 127.2, 126.7, 126.6, 117.9 (HC═), 31.4 (CH_2), 22.6 (CH_2), 13.8 (CH_3) ppm. MS-EI (m/z): 216 (M^+).

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