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An Expeditious Route for the Total Synthesis of Pondaplin Isolated from *Annona glabra*

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Abstract: A novel cyclic prenylated phenylpropanoid, pondaplin **1**, was first synthesized in 26% overall yields through an expeditious route (7 steps) that employed highly regio- and stereoselective phenyltellurenylation to arylacetylene and palladium (II) chloride-catalyzed carbonylation of hydroxy styryl phenyl telluride as key steps.

Keywords: Pondaplin, total synthesis, natural product.

Pondaplin **1**[1], was isolated recently in a trace amount from the bioactive ethanolic extracts of the leaves of *Annona glabra* which was obtained from trees native to Florida, USA and identified by its spectroscopic analysis as a cyclic prenylated phenylpropanoid depicted in **Figure 1**. The selective cyctotoxicities against six human solid tumor cell lines and particularly potent activity against MCF-7 breast and PC-3 prostate cancer cell lines[1], arose our interest to synthesize pondaplin and its analogs in reasonable amounts for its further medicinal studies and structure-activity relationship (SAR) studies. Very recently we have achieved the total synthesis of pondaplin through an expeditious access that employed highly regio- and stereoselective phenyltellurenylation to a 4-hydroxyphenylacetylene **5** followed by palladium (II) chloride-catalyzed carbonylation of (Z)-4-hydroxystyryl phenyl telluride **6** as the key steps.

The retrosynthetic analysis of pondaplin **1** in **Figure 1** showed that the key steps are to prepare the intermediates both containing Z-form double bond moeities that may be synthesized starting from 3-methyl-2(5H)-furanone **2** and 4-hydroxyphenylacetylene **5**, respectively. Thus, commercially available 3-methyl-2(5H)-furanone **2** was treated with hydrobromic acid in the presence of $MgBr_2$ and subsequently reduced by $LiAlH_4$ to produce the expected (Z)-form bromoalcohol **4** in good yield [2](**Scheme 1**).

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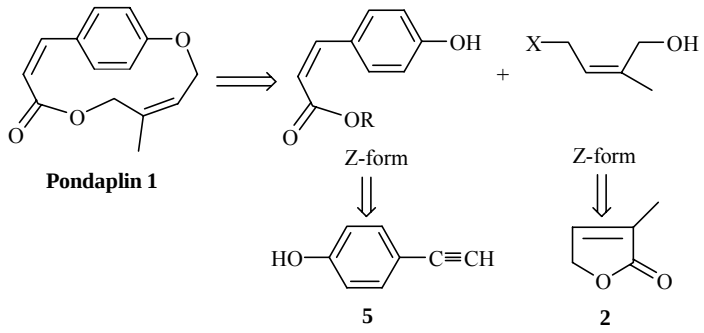
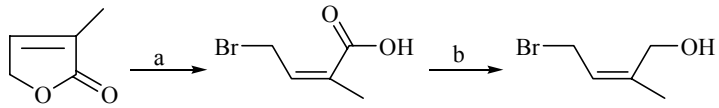
Figure 1 Retrosynthetic analysis of pondaplin **1**



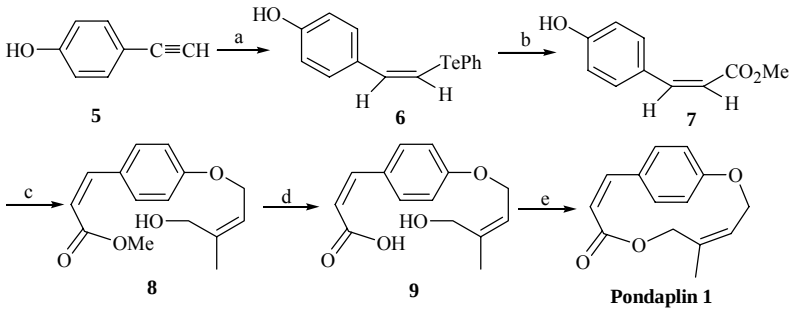
Scheme 1



a) 48% HBr, $MgBr_2$, rt, 4h, 78% b) $LiAlH_4$, ether, rt, 3h, 90%

Generally the *cis*-cinnamic acids or their esters were prepared essentially by the photolysis of their corresponding *trans*-compounds[3,4]. This method requires a separation from a mixture of *cis*- and *trans*-isomers and gives the expected *cis*-isomers in

Scheme 2



a) $(PhTe)_2$, $NaBH_4$, N_2, reflux, 20 h, 90% b) CO (1 atm), $PdCl_2/CuCl_2$, Et_3N, MeOH, rt, 3 days, 70% c) NaH, DMF, compound **4**, rt, 12 h, 91% d) NaOH, rt, 4 h, HCl e) DCC, DMAP, toluene, 75°C, 2 steps 65%

comparatively lower yields. However, palladium (II) chloride-catalyzed carbonylation of organic tellurides with carbon monoxide leads to the corresponding methyl carboxylates in good to excellent yields[5]. The combination of this carbonylation with phenyltellurenylation of arylacetylenes makes it possible to prepare ring-substituted *cis*-methyl cinnamates. As shown in **Scheme 2**, hydroxyphenylacetylene **5**[6] was reacted

with diphenyl ditelluride[7] to afford (Z)-4-hydroxystyryl phenyl telluride **6** as a sole product in 90% yield[8]. Treatment of **6** with atmospheric pressure of CO and a catalytic amount of palladium chloride in the presence of the re-oxidant cupper (II) chloride in methanol and triethylmine at room temperature for 3 days provided (Z)-methyl-4-hydroxy cinnamate **7** in 70% yield[9]. Subsequent coupling reaction of **7** with the intermediate **4** in *N,N*-dimethylformamide gave compound **8** in 91% yield. Hydrolysis of **8** with sodium hydroxide then acidified by HCl into acid **9** which was followed by intramolecular cyclization in the presence of 1,3-dicyclohexylcarbodiimide and 4-dimethylaminopyridine (DCC/DMAP) system in toluene affording the Pondaplin **1**[10] in overall yield 65% from **8**.

In conclusion, we have accomplished an effective design and expeditious route for the total synthesis of the title compound pondaplin. This concise synthetic plan may be utilized to rapidly prepare a variety of related analogs in a reasonable amount. This work is in progress in our group.

Acknowledgments

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Reference and Notes

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2. ^{1}H-NMR (300 MHz, $CDCl_3$) of compound **4**: 5.64-5.65 (m, 1H), 4.23(s, 2H), 3.97 (s, 2H), 1.68 (s, 3H). Only the Z-form **4** was obtained from the commercial starting material 3-metyl-2(5H)-furanone **2** through the Z-form immediate acid **3**. The Z-form of **4** was confirmed by 9% NOE observed between 5.64-5.65 ppm (m, C=CH) and 1.68 ppm (CH_3).
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7. Preparation procedure see: W. S. Haller, K. J. Irgolic, *J. Organomet. Chem*., **1972**, *38*, 97.
8. Preparation of (Z)-4-hydroxystyryl phenyl telluride **6**: Ethanol (5 mL) was added to a mixture of diphenyl ditelluride (1.02 g, 2.5 mmol) and $NaBH_4$ (0.24 g, 6.3 mmol) at 0^{o}C under nitrogen. The mixture became homogeneous after being stirred for 30 min and the color of solution turned from orange to pale yellow. A solution of 4-hydroxyphenylacetylene **5** (0.59 g, 5.0 mmol) in ethanol (5 mL) was added and then the resulting mixture was stirred for 20 h at reflux. After it was cooled to room temperature, the reaction mixture was treated with brine, extracted with $CHCl_3$ and dried over $MgSO_4$. After removal of solvent, the crude product (0.727 g, 90%) was further purified by column on silica gel (hexanes/ethyl acetate = 5/1) to give pure product **6** in 82% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.75-7.79 (m, 2H), 7.41 (d, 1H, J=10.3Hz), 7.24-7.35 (m, 3H), 7.19 (d, 2H, J=8.7Hz), 6.96 (d, 1H, J=10.3Hz), 6.94 (d, 2H, J=8.7Hz). HRMS (EI) Calcd. for $C_{14}H_{12}OTe$ (M^+) 323.6001, Found 323.5992.
9. Preparation of (Z)-methyl-4-hydroxy cinnamate **7**: Palladium (II) chloride (0.034 g, 0.2 mmol), copper (II) chloride (0.54 g, 4.0 mmol) and organic telluride **6** (0,646 g, 2.0 mmol) were placed in a flask. The system was flushed with CO (1 atm) and saturated with a CO balloon at room temperature. Dry methanol (20 mL) and triethylamine (0.84 mL, 6.0 mmol) were added by syringe. After the resulting mixture was stirred for 3 days, the brown solid was filtered off. The filtrate was poured into aqueous NH_4Cl solution, extracted with ether and dried over

$MgSO_4$. After removal of solvent, the left residue was chromatgraphed by column (hexanes/ethyl acetate = 5/1) to provide compound **7** (0.25 g, 70%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.19 (d, 2H, J=8.7Hz), 6.94 (d, 2H, J=8.7Hz), 6.88 (d, 1H, J=13Hz), 5.84 (d, 1H, J=13Hz), 3.87 (s, 3H). HRMS (EI) calcd. for $C_{10}H_{10}O_3$ (M^+) 178.0629, found 178.0631.

10. The synthetic Pondaplin was identified by its spectral data compared to that of natural product. Representative data of Pondaplin **1** are as follows: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.58 (d, 2H, J=8.8Hz), 6.87 (d, 1H, J=12Hz), 6.81 (d, 2H, J=8.8Hz), 5.82 (d, 1H, J=12Hz), 5.60-5.62(m, 1H), 4.54 (s, 2H), 4.16 (d, 2H, J=7Hz), 1.67 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 166.61, 158.02, 144.23, 132.21, 126.97, 126.46, 116.12, 114.96, 68.93, 58.65, 13.96.

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