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Synthetic studies toward pondaplin: total synthesis of pondaplin analogues☆

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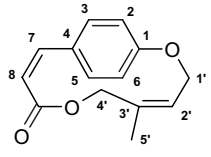
Abstract—Syntheses of synthetic analogues of pondaplin **1** have been achieved. Final macrolide construction was accomplished using a Keck macrolactonization reaction.

Pondaplin **1**,[1] a novel cyclic prenylated phenylpropanoid was recently isolated from *Annona glabra* L. (Annonaceae).[2,3] A number of bioactive Annonaceous acetogenins had been earlier isolated from this species.[2,4–6] Pondaplin **1** (Fig. 1) was reported to show selective cytotoxicities in six human solid tumor cell lines. Many related phenylpropanoids exhibit a broad range of biological activities such as antimicrobial, anticancer, and hypotensive properties.[7–9] Moreover, phenyl propanoid derivatives are known to inhibit enzymes such as cAMP phosphodiesterase and prostaglandin synthetase.[10,11]

The simple and interesting structure of pondaplin **1** and its significant biological profile against human solid tumor cell lines made it an intriguing target for total synthesis. We devised a strategy for the total synthesis of **1** starting from 4-hydroxybenzadehyde **2** using ring-closing metathesis (RCM)[12] as the key step (Scheme 1). Disappointingly **7** did not provide the target molecule but instead gave an oligomer. In order to access the core structure of pondaplin, diallyl ether **9** was prepared from **6** and subjected to RCM conditions. This attempt also failed to give the expected compound, an oligomer was isolated again (Scheme 1). After this work was completed, similar observations were published by Bressy and Piva.[13]



Pondaplin, 1

Figure 1. Structure of pondaplin.

Since the RCM strategy had failed, an alternative approach was established to achieve the total synthesis of pondaplin. Propargyl alcohol was protected as trityl ether **10**, which was subjected to methoxycarbonylation to afford **11** in 86% yield. The conjugate addition of lithium dimethylcuprate to **11** in ether at −100 to −85 °C provided *Z*-ester **12** as the sole product in 90% yield. The reduction of **12** with LAH/$AlCl_3$ afforded the corresponding *Z*-allylic alcohol **13** in 74% yield. Standard bromination conditions furnished bromide **14** in 62% yield.[14] Bromide **14** was used in an alkylation reaction with 4-hydroxybenzaldehyde **2** to give *O*-alkylated compound **15** in 63% yield. Modified Wadsworth–Emmons condensation[15] on 4-substituted benzaldehyde **15** using bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate in THF at −78 °C afforded *Z*-ethyl ester **16** in 88% yield. Removal of the trityl group followed by saponification of **17** afforded the corresponding *Z*-hydroxy acid **18**[16] in 99% yield. The olefinic protons in **16**–**18** (H-7 and H-8) showed coupling constants of 12.6 Hz. Subjecting hydroxy acid **18** to intramolecular Keck coupling conditions in the presence of

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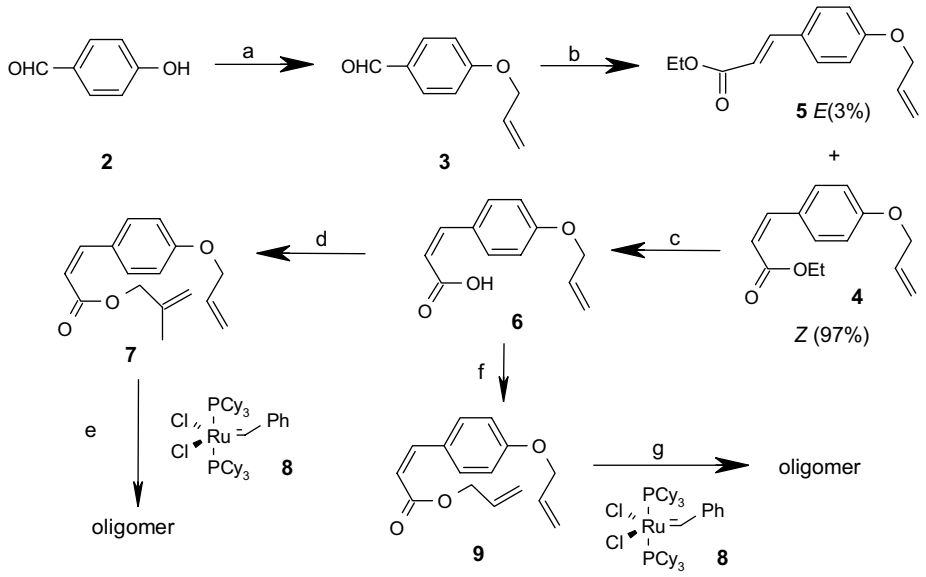
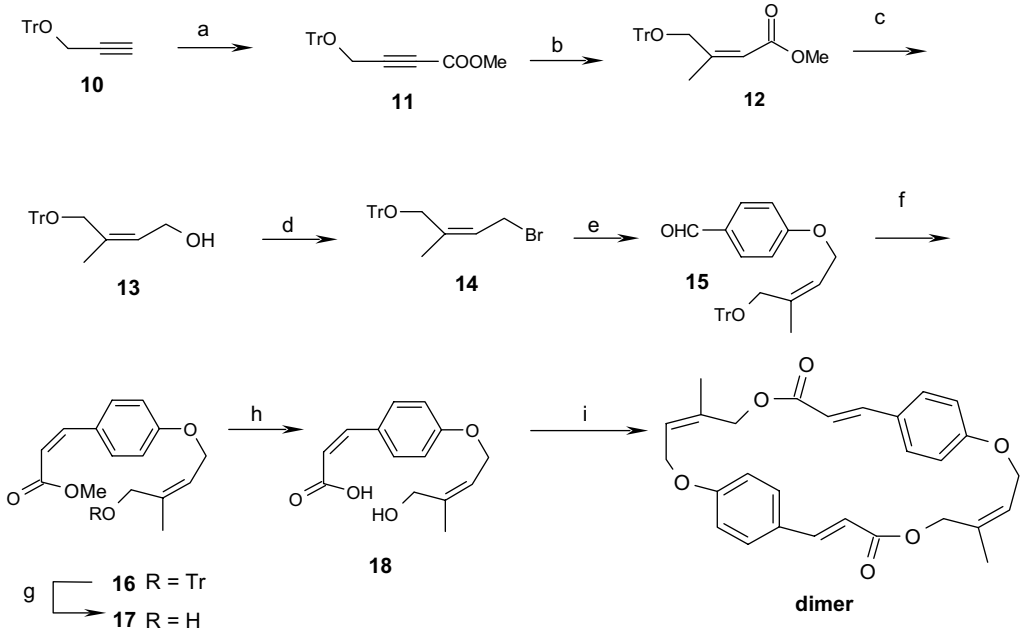


Scheme 1. Reagents and conditions: (a) allyl bromide, acetone, K_2CO_3, reflux, 1 h, 83%; (b) $Ph_3P{=}CHCOOEt$, MeOH, 0 °C, 6 h, 98%; (c) ethanol, 20% NaOH, 4 h, 96%; (d) 2-methyl-2-propen-1-ol, DCC, DMAP, ether, 20 °C, 79%; (e) benzene, reflux; (f) allyl alcohol, DCC, DMAP, ether, 20 °C, 90%; (g) benzene, reflux.

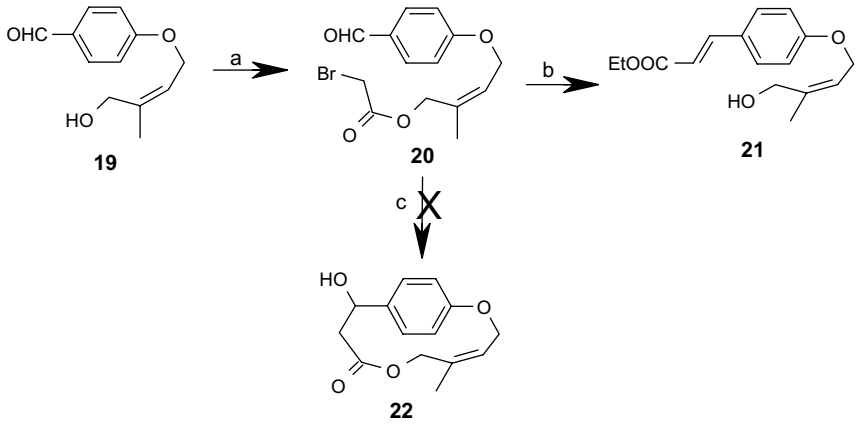


Scheme 2. Reagents and conditions: (a) EtMgBr, THF, 0 °C, 1 h, then ClCOOMe, 2 h, 86%; (b) Me_2CuLi, THF, −100 to −85 °C, 3 h, 90%; (c) LAH, $AlCl_3$, ether, 0 °C, 3 h, 74%; (d) MsCl, LiBr, Et_3N, MeCN, 0 °C, 2.5 h, 62%; (e) NaH, *p*-hydroxybenzaldehyde **2**, THF, 0 °C, 4 h, 63%; (f) NaH, $(CF_3CH_2O)_2P(O)CH_2COOMe$, 0 °C, 1 h, −78 °C, 2 h, 88%; (g) PPTS, 5:1 DCM–MeOH, rt, 2 h, 67%; (h) aq LiOH, MeOH, rt, 4 h, 99%; (i) DCC, DMAP, DCM, 0 °C–rt, 12 h, 55%.

1,3-dicyclohexylcarbodiimide and DMAP in DCM at 0 °C did not give the expected product **1**, instead a dimer[17] was formed (Scheme 2).

The ^{1}H NMR spectrum of the dimer showed the olefinic protons (H-7 and H-8) at 6.50 ppm ($J = 14.8$ Hz) and 7.60 ppm ($J = 15.6$ Hz), respectively, indicating a trans double bond. Our ^{1}H NMR data match with the dimer reported by Joullie and co-workers,[14b] but interestingly a recent paper[18] reports the total synthesis of pondaplin by intramolecular cyclization using Keck coupling conditions.

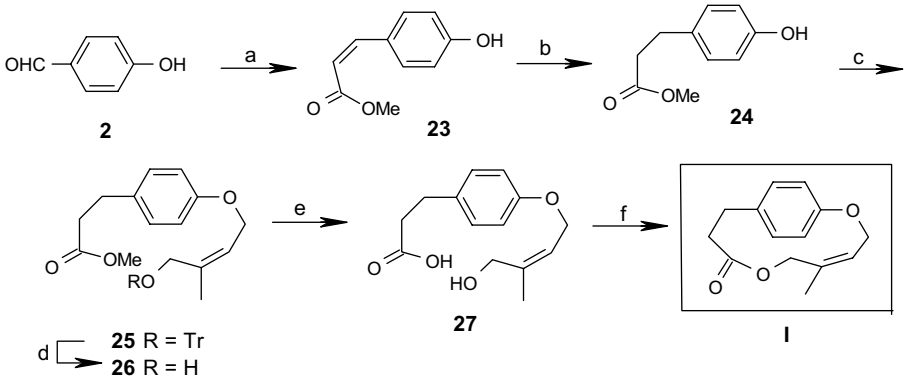
Since both these approaches gave unsatisfactory results in the final step, we next investigated an alternative strategy as shown in Scheme 3. Trityl ether **15** was deprotected to give alcohol **19**, which was acylated with bromoacetyl bromide to give the bromo ester **20**[19] in nearly quantitative yield. Further treatment of bromide **20** with $P(OEt)_3$ and an in situ Horner–Wadsworth–



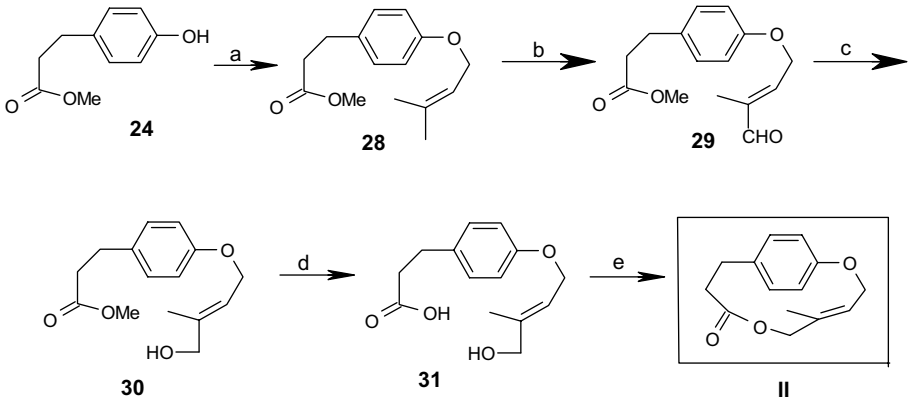
Scheme 3. Reagents and conditions: (a) $BrCOCH_2Br$, 2,6-lutidine, 0 °C, 99%; (b) NaH, $P(OEt)_3$, reflux, 2 h, 62%; (c) SmI_2, THF, 0 °C, 2 h.

Emmons reaction in the presence of NaH at reflux did not provide the required product **1** but instead gave an α,β-unsaturated ester **21**.[20] The coupling constants of the newly formed double bond in compound **21** were 15.8 Hz (H-7 and H-8), indicating the trans nature of the olefinic double bond. ^1H NMR, ^{13}C NMR, and mass spectroscopy support the assigned structure. Yet another alternative approach was employed on bromide **20**, but treatment with SmI_2 also failed to afford the natural product **1**.

We considered that the double bond reduction of the α,β-unsaturated ester might favor the cyclization. To examine this, the hydroxy ester **24** was prepared from 4-hydroxybenzaldehyde **2** in two steps. The two carbon Wittig olefination, followed by ester double bond reduction with Mg/MeOH afforded **24** in 94% overall yield for the two steps. *O*-Alkylation of **24** with bromide **14** followed by deprotection of the trityl ether afforded allyl alcohol **26**. Ester hydrolysis of **26** followed by intramolecular cyclization using Keck coupling conditions



Scheme 4. Reagents and conditions: (a) $Ph_3P{=}CHCOOMe$, MeOH, 6 h, 98%; (b) Mg/MeOH, reflux, 6 h, 90%; (c) NaH, THF, **14**, rt, 4 h, 60%; (d) PPTS, 5:1 DCM–MeOH, rt, 2 h, 67%; (e) aq LiOH, MeOH, rt, 4 h, 99%; (f) DCC, DMAP, DCM, 12 h, 55%.



Scheme 5. (a) Prenyl bromide, acetone, K_2CO_3, reflux, 1 h, 92%; (b) SeO_2, EtOH, reflux, 4 h, 50%; (c) $NaBH_4$, MeOH, 85%; (d) aq LiOH, MeOH, 4 h, 98%; (e) DCC, DMAP, DCM, 0 °C–rt, 12 h, 55%.

allowed macrolactonization to proceed to give the saturated analogue **I**[21] of pondaplin in good yield (Scheme 4).

Another pondaplin analogue **II** was synthesized from saturated ester **24** (Scheme 5). Compound **24** was subjected to alkylation with prenyl bromide to afford *O*-prenyl ether **28** in 92% yield. Further allylic oxidation was achieved using SeO_2 to afford *E*-aldehyde **29**. The aldehyde was reduced with $NaBH_4$ in MeOH to give the corresponding *E*-allylic alcohol **30** in 85% yield. Ester hydrolysis followed by intramolecular cyclization with DCC/DMAP in CH_2Cl_2 at 0 °C afforded the saturated analogue **II** (Scheme 5).[22]

In conclusion, syntheses of two pondaplin analogues have been achieved. Further studies directed toward the total synthesis of pondaplin **1** are currently underway in our laboratory and the results of these investigations will be reported in due course.

Acknowledgements

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16. Compound **18**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.88 (s, 3H, –CH_3), 4.18 (s, 2H, –OCH_2), 4.58 (d, $J = 6.7$ Hz, 2H, –OCH_2), 5.65 (t, 1H, $J = 6.8$ Hz), 5.82 (d, 1H, $J = 12.6$ Hz), 6.82 (d, 2H, $J = 8.9$ Hz, ArH), 6.92 (d, 1H, $J = 12.6$ Hz), 7.66 (d, 2H, $J = 8.9$ Hz, ArH).
17. Dimer: mp 142–146 °C; IR (KBr): 1710 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80 (s, 6H, –CH_3), 4.60 (br s, 8H, –OCH_2), 5.62 (t, 2H, $J = 6.8$ Hz), 6.50 (d, 2H, $J = 14.8$ Hz, H-8), 6.80 (d, 4H, $J = 8.8$ Hz, ArH), 7.39 (d, 4H, $J = 8.8$ Hz, ArH), 7.60 (d, 2H $J = 15.6$ Hz, H-7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 160.2, 143.3, 137.6, 127.5, 127.2, 122.6, 119.6, 114.0, 68.5, 65.8, 20.3. FAB Mass: 461 (M+1).
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19. Compound **20**: liquid, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.88 (s, 3H, –CH_3), 3.81 (s, 2H, –CH_2Br), 4.72 (d, 2H, $J =$ 6.7 Hz, –OCH_2), 4.78 (s, 2H, –OCH_2), 5.72 (t, 1H, $J = 6.8$ Hz), 6.98 (d, 2H, $J = 8.9$ Hz, ArH), 7.82 (d, 2H, $J = 8.9$ Hz, ArH), 9.89 (s, 1H, –CHO).
20. Compound **21**: mp. 67–70 °C, IR (KBr): 1709 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, 3H, $J = 7.1$ Hz, –CH_2CH_3), 1.88 (s, 3H, –CH_3), 4.21 (s, 2H, –OCH_2), 4.26 (q, 2H, $J = 7.1$, 14.2 Hz, –OCH_2CH_3), 4.60 (d, 2H, $J = 6.7$ Hz, –OCH_2), 5.6 (t, 1H, $J = 6.8$ Hz, olefinic), 6.25 (d, 1H, $J = 15.8$ Hz), 6.80 (d, 2H, $J = 8.7$ Hz, ArH), 7.42 (d, 2H, $J = 8.7$ Hz, ArH), 7.60 (d, 1H, $J = 15.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 167.29, 160.3, 144.1, 140.9, 129.6, 127.4, 122.2, 115.9, 115.0, 64.0, 61.9, 60.3, 21.3, 14.3; FAB Mass: 277 (M+1).
21. Preparation of saturated analogue I: To a stirred solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC) (1.4 mmol) and *N*,*N*-dimethylaminopyridine (DMAP) (1.4 mmol) in dry CH_2Cl_2 at 0 °C was added a solution of **27** in CH_2Cl_2 slowly and the mixture allowed to stir at rt for 12 h. Precipitated urea was then filtered off and the filtrate was washed twice with 0.5 N HCl and with saturated $NaHCO_3$ solution and then dried over $MgSO_4$. The solvent was removed by evaporation and the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 8:2) to afford saturated analogue **I** in 55% yield. mp 123–125 °C; IR (KBr): 1733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80 (s, 3H, –CH_3), 2.61 (t, 2H, $J = 7.5$ Hz, –CH_2CH_2), 2.90 (t, 2H, $J = 8.3$ Hz, –CH_2CO), 4.51 (d, 2H, $J = 6.6$ Hz, –OCH_2), 4.60 (s, 2H, –OCH_2), 5.65 (t, 1H, $J = 5.7$ Hz, olefinic), 6.78 (d, $J = 8.9$ Hz, 2H, ArH), 7.08 (d, 2H, $J = 8.9$ Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 157.0, 139.7, 132.5, 129.0, 119.8, 114.5, 70.8, 67.4, 35.7, 29.9, 19.3; FAB Mass: 233 (M+1).
22. Preparation of saturated analogue II: procedure same as above from **31**. Mp 119–121 °C; IR (KBr): 1733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (s, 3H, –CH_3), 2.61 (t, 2H, $J = 7.5$Hz, –CH_2CH_2), 2.90 (t, 2H, $J = 8.3$ Hz, –CH_2CO), 4.55 (d, $J = 6.0$ Hz, 2H, –OCH_2), 4.61 (s, 2H, –OCH_2), 5.65 (t, 1H, $J = 5.2$ Hz, olefinic), 6.78 (d, 2H, $J = 8.9$ Hz, ArH), 7.06 (d, 2H, $J = 8.9$ Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 157.0, 137.7, 132.5, 129.0, 119.8, 114.5, 75.1, 67.4, 35.7, 29.9, 13.7; FAB Mass: 233 (M+1).