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# Convergent synthesis of Carpatamide-A: Cytotoxic arylamine derivative from marine derived *Streptomyces* sp.

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**ABSTRACT**

First total synthesis of carpatamide-A **7a**, cytotoxic arylamine derivative isolated from marine derived *Streptomyces* sp., was achieved in twelve steps with overall yield of 24% with seven longest linear steps. In the penultimate step, dienoic acid **13** and an amino-phenylpropionic acid methyl ester core **21** were coupled to synthesize methylated derivative of carpatamide-A **22** followed by demethylation of the intermediate with $BBr_3$ to accomplish carpatamide-A **7a**. Both precursors **13** and **21** were synthesized from readily available starting materials i.e. isovaleraldehyde **8** and 2, 4-dihydroxy benzaldehyde **14**.


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Convergent synthesis; arylamine; Carpatamide-A; isovaleraldehyde; Horner-Wadsworths-Emmons reaction

## 1. Introduction

Marine natural products are an important source of lead compounds in medicine because of their variety and novel architecture. The isolation of cytotoxic arylamine derivatives carpatamide-A from marine derived *Streptomyces* sp (Fu et al. 2014) also accompanied the isolation of two other derivatives namely carpatamide-B and carpatamide-C. These compounds possess a novel core structure consisting of an amino-phenylpropionic acid, and an unsaturated fatty acid chain i.e. dienoic acid chain joined to the amine moiety of amino-phenyl propionic acid via an amide bond. Such aromatic substitution pattern has previously been encountered only in manumycin **1** (Kohno et al. 1996) and derivatives (Hwang et al. 1996) from *Streptomyces parvulus*. There are a large number of phenylpropionic acid-containing natural products reported in the literature (Figure 1). Compound **2**, a major

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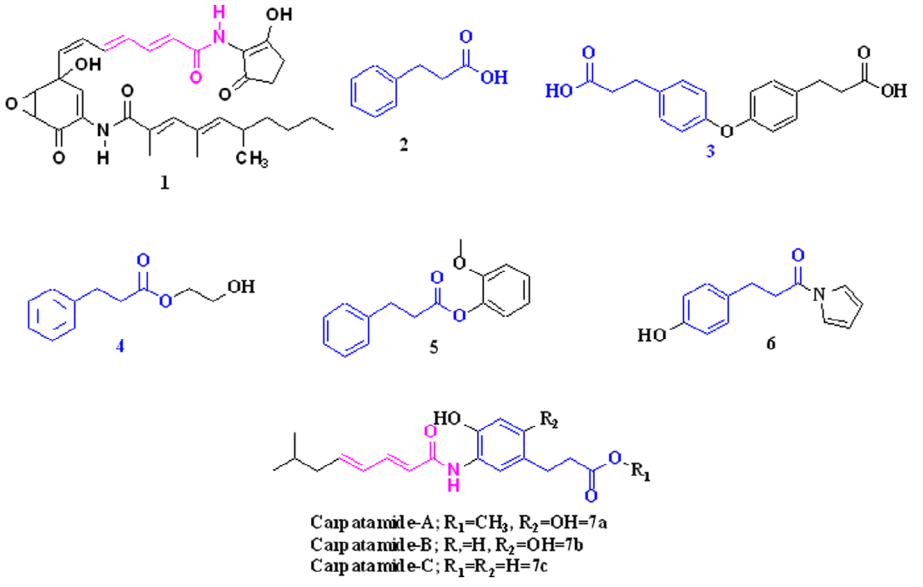



**Figure 1.** Structural analogues of carpatamides.

metabolite from the crude extract of *Bacillus licheniformis* SAB1, showed significant antifungal activity against *Rhodotorula* sp. and moderate antifungal activity against *Candida albicans* and *Aspergillus niger*. Bioactive compound **3** (Apteniol-A), an oxyneolignan from the Leaves of *Aptenia cordifolia* a terrestrial perennial herb belonging to the family *Aizoaceae* also produced by marine bacterium *B. licheniformis* SAB1, showed significant antifungal activity against *Aspergillus fumigates* and moderate antibacterial activity against *Vibrio cholerae* and *Salmonella typhi* (Devi et al. 2010). Compounds **4** and **5**, noroxyneolignan isolated from *Oxalis pescaprae* (Greca et al. 2009) showed phytotoxic activity on germination, root elongation and shoot elongation of *Lactuca sativa*. Compound **6** (Piperlotine-E), isolated from the leaves of *Piper lolot,* showed potent inhibitory activity on platelet aggregation induced by arachidonic acid (AA) and platelet activating factor (PAF). Compounds **7a, 7b** and **7c** (Carpatamides-A, B and C), respectively, were recently isolated and evaluated for cytotoxic activity. **7a** and **7c** have shown moderate cytotoxicity against non-small-cell lung cancer cell lines HCC366, A549, and HCC44 but no activity against H2122 (Fu et al. 2014). These were also evaluated for their cytotoxic activity specially against NSCLC cell lines HCC366, A549, and HCC44 with $IC_{50}$ values ranging from 2.2 to 8.4 µM, but **7b** did not show any activity against cancer cell lines due to its inability to penetrate cancer cells, as the studies have demonstrated that methyl ester of **7a** acts as a prodrug and is cleaved in cells to give the active pharmacophore (Fu et al. 2014).

To the best of our knowledge, this intriguing molecular architecture of carpatamide-A and related compounds comprising of unsaturated fatty acid with arylamine propionic acid esters have not been synthesized in laboratory to date. The low natural abundance of these compounds with impressive biological properties prompted us to explore concise and scalable total synthesis of these molecules. In continuation of our program involving synthesis of natural products of therapeutically importance, herein a concise approachtowards total

synthesis of carpatamides-A is described. This flexible synthetic strategy could be utilized to synthesize other members of carpatamides.

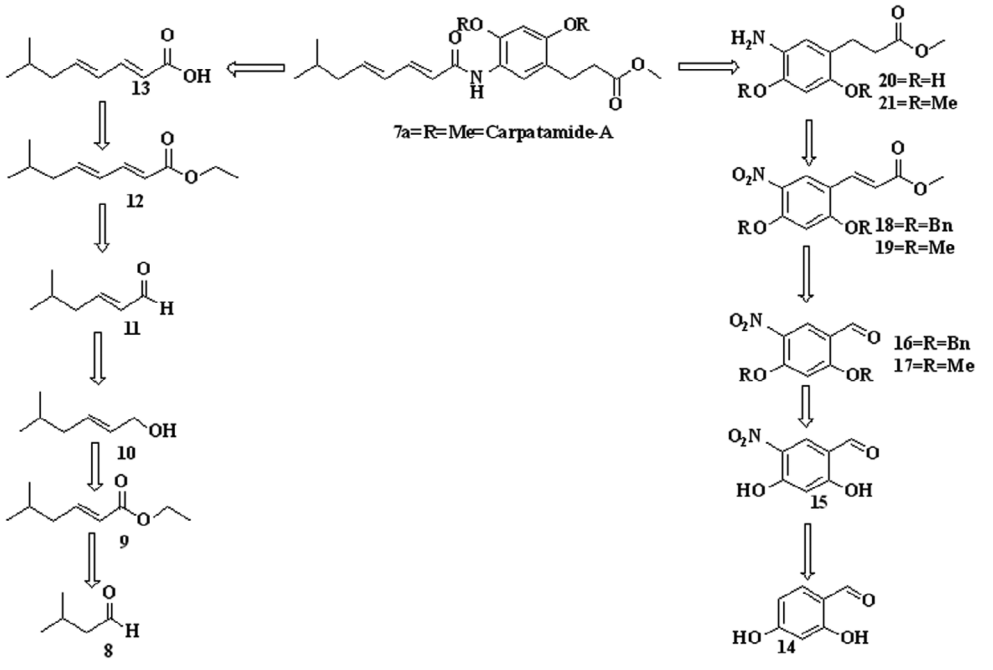
A retrosynthetic route to carpatamide-A has been depicted in Scheme 1. As shown, amide linkage could be accomplished by coupling of the corresponding unsaturated fatty acid **13** with amine derivative **20** or **21**. The unsaturated fatty acid can be synthesize from readily available isovaleraldehyde **8**, and arylamine derivative **20** or **21** from commercially available 2, 4-dihydroxy benzaldehyde **14** in a set of reactions involving nitration, Horner-Wadworth-Emmons, catalytic hydrogenation, oxidation and hydrolysis.

## 2. Results and discussion

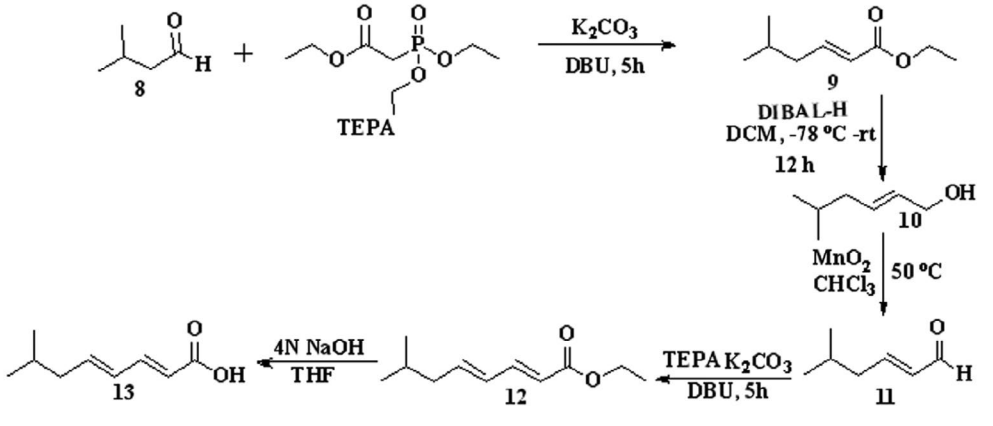
As envisaged in Scheme 2, synthesis of unsaturated fatty acid **13** was commenced with HWE (Ando and Yamada 2011) reaction of isovaleraldehyde **8** with triethylphosphonoacetate readily produced corresponding selective (*E*) α,β-unsaturated ester **9** with an isolated yield of 89% in the presence of DBU and $K_2CO_3$ under solvent free reaction conditions. Retrosynthetically reduction of **9** with DIBAL-H (Weiß et al. 2012) produced desired alcohol **10** in an yield of 79% at −78 °C addition followed by warming up to room temperature. The metallic oxidation of **10** with $MnO_2$ (Sharma et al. 2008) conferred the corresponding aldehyde **11** in an isolated yield of 68% after column chromatography. The aldehyde **11** was further subjected to HWE (Ando and Yamada 2011) reaction with triethylphosphonoacetate to yield the selective (*E*) α,β- unsaturated fatty acid ester **12** as a clear oil with an isolated yield of 87% under solvent free reaction conditions. The (*E*) α,β- unsaturated fatty acid ester **12** has proved to be low boiling point, which required attentive operation during work-up in order to prevent loss on evaporation. The ester **12** was further hydrolyzed in aqueous NaOH solution (4 N) (Ueno et al. 2005) at reflux condition to obtain desired dienoic acid **13** quantitatively as monitored by TLC, which was also a low boiling clear oil.

With unsaturated fatty acid **13** secured, we then focused on the synthesis of other precursor the pivotal arylamines (Scheme 3), **20** and **21**. Treatment of commercially available 2,4-dihydroxybenzaldehyde **14** with concentrated $HNO_3$ (Selvaraju et al. 2015) regioselectively produced 5-nitro 2,4-dihydroxybenzaldehyde **15** in 84% yield. Retrosynthetically we needed to protect free hydroxyls of **15** by using benzyl bromide and $K_2CO_3$ at refluxed conditions to produce 2,4-bis (benzyloxy)-5-nitrobenzaldehyde **16** in 65% isolated yield. Aldehyde **16** underwent HWE olefination (Ando and Yamada 2011) to yield the (*E*) α,β-unsaturated ester **18** with a yield of 89% under solvent free reaction conditions. Using **18** then we performed catalytic hydrogenation (Wilford et al. 1996) at refluxed conditions led to three synthetic transformation i.e. reduction of nitro group to desired amino group, reduction of the conjugated double bond and deprotection of benzyl ethers to give pivotal **20** as an orange fluoresce compound in an isolated yield of 72%.

With two desired fragments **13** and **20** retrosynthetically, we then aimed to furnish carpatamide-A by coupling of **13** and **20** using EDCI (Hausler et al. 2012) as a coupling agent with a catalytic amount of DMAP under reflux conditions. Unfortunately, the reaction mixtures obtained during number of attempts showed multiple close moving spots on thin layer chromatography, which were difficult to purify. The reason for this outcome could very well be due to the presence of free hydroxyl group on the intermediate **20** and these can also participate in coupling leading to ester formation, and ester are prone to hydrolysis, the presence of corresponding acids can also not be ruled out.

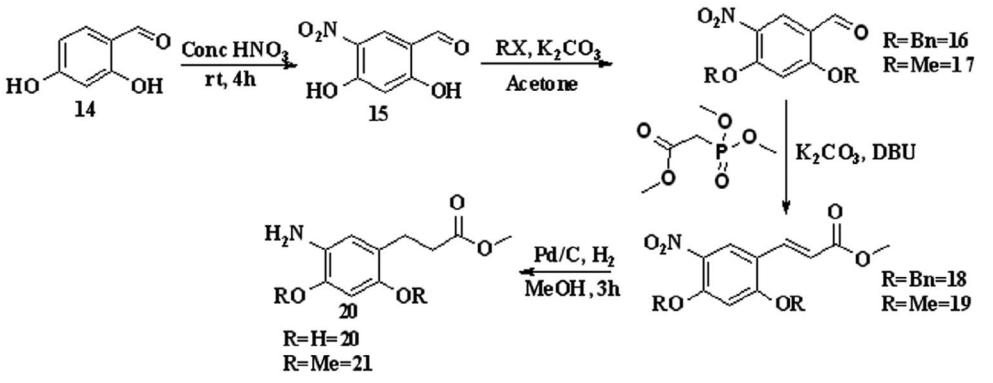



Scheme 1. Retrosynthetic approach to carpatamide-A.

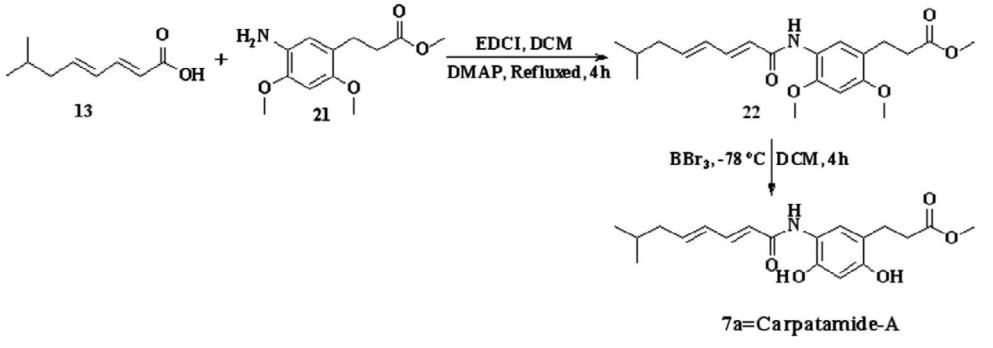



Scheme 2. Synthesis of unsaturated fatty acid **13**.

Consequently, we diverted the benzyl to methyl group. Following the preparation of the corresponding compound **21**, We prepared 2,4-dimethoxy-5-nitrobenzaldehyde **17** with 84% yield using **15**, methyl iodide and $K_2CO_3$ (Gudipudi et al. 2014) in acetone at refluxed conditions. The HWE (Ando and Yamada 2011) reaction of aldehyde **17** with triethylphosphonoacetate readily produced corresponding selective (*E*) α,β-unsaturated ester **19**. Upon catalytic hydrogenation (Wilford et al. 1996) of **19** using palladium on charcoal under refluxed condition compound **21** was afforded as brown oil in 77% yield (Scheme 3).




Scheme 3. Synthesis of amino-phenyl propionic acid methyl esters **20** and **21**.




Scheme 4. Synthesis of carpatamide-A, **7a**.

Upon successfully synthesis of two retrosynthetically desired fragments **13** and **21** were subjected to coupling reaction using EDCI, catalytic amount of DMAP (Hausler et al. 2012) under refluxed to yield the desired methyl precursor **22** of carpatamide-A with an isolated yields of 68%, which was also synthesized and reported by Fu et al. as derivative of carpatamide-A, but they have synthesized compound **22** in a biosynthetic manner, in which they have firstly isolated the carpatamide-A **7a** followed by methylation of carpatamide-A **7a** was carried out using TMS-$CHN_2$ to yield compound **22**.

Finally demethylation of **22** with boron tribromide (Bergman et al. 1999) at −78 °C resulted target molecule carpatamide-A **7a** with an isolated yield of 90% (Scheme 4). Spectroscopic data of **7a** and **22** were in agreement with those reported for the natural and synthetic product respectively (Fu et al. 2014).

## 3. Experimental section

### *3.1. Preparation of dienoic acid fragment*

#### *3.1.1. Synthesis of ethyl (E)-5-methylhex-2-enoate* (9)

To a stirred suspension of triethyl phosphonoacetate (10.90 mL, 55 mmol), potassium carbonate (13.82 g, 100 mmol) and DBU (2.23 mL, 1.5 mmol), isovaleraldehyde **8** (5.48 mL,

50 mmol) was added at room temperature and reaction mixture was allowed to stirred at same temperature and monitored by TLC, after completion of reaction (5 h) to a yellow mass of reaction mixture was added DCM (3 × 50 mL). The combined organic extract were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (9:1 petroleum ether/EtOAc) gave ester **9** as a clear oil: (6.9 mL, 89%); $^1$H NMR (400 MHz, DMSO): $\delta$ 0.93 (6H, d, $J$ = 6.64 Hz), 1.28 (3H, t, $J$ = 7.12 Hz), 1.78 (1H, m), 2.10 (2H, t, $J$ = 6.92 Hz), 4.19 (2H, q, $J$ = 7.16 Hz), 5.78 (1H, d, $J$ = 16.24 Hz), 6.94 (1H, q, $J$ = 7.88 Hz); $^{13}$C NMR (100 MHz DMSO) 14.20, 22.27, 27.73, 41.39, 60.03, 122.25, 148.12, 166.58; IR (KBr) $\nu_{max}$ 2959, 2879, 1691, 1641, 1469, 1381, 1361, 1280 cm-$^1$; HRMS (ESI): *m/z*: calcd for $C_9H_{16}NaO_2$: [M + Na]+ 179.1048, Found 179.1041.

### *3.1.2. (E)-5-methylhex-2-en-1-ol* (10)

To a stirred solution of ester **9** (6.24 mL, 40 mmol) in dry DCM (40 mL) was added slowly DIBAL-H (1 M in THF) (100 mL, 100 mmol) over 15 min dropwise under argon at −78 °C. The reaction mixture was gradually warmed to room temperature for 12 h and cooled again to 0 °C and quenched by the cautious addition of MeOH. A saturated solution of potassium sodium tartrate (Rochelle salt) was added and mixture left to stirr for several hours until the organic and aqueous layers had completely separated. The combined organic extract were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (8:2 petroleum ether/EtOAc) gave alcohol **10** as clear viscous oil, (3.6 mL, 79%); $^1$H NMR (DMSO, 400 MHz): $\delta$ 0.85 (6H, d, $J$ = 6.68 Hz), 1.59 (1H, m), 1.89 (2H, t, $J$ = 6.48 Hz), 3.89 (2H, t, $J$ = 5.20 Hz), 4.62 (1H, t, $J$ = 5.48 Hz), 5.54 (2H, m); $^{13}$C NMR (DMSO, 100 MHz) 27.29, 33.03, 46.30, 66.67, 133.69, 136.92; IR (KBr) $\nu_{max}$ 3614, 3441, 2899, 1469, 1389, 1361 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_7H_{14}NaO$: [M + Na]$^+$ 137.0942, Found 137.0936.

### *3.1.3. (E)-5-methylhex-2-enal* (11)

To a stirred solution of alcohol **10** (2.85 mL, 25 mmol) in $CHCl_3$ (30 mL) was added $MnO_2$ (17.38 g, 200 mmol). The mixture was heated at 50 °C overnight. The mixture was filtered through a bed of Celite, solvent was carefully removed under reduced pressure and purified by silica gel chromatography to give the product **11** as clear volatile oil (1.9 mL, 68%), $^1$H NMR (DMSO, 400 MHz): $\delta$ 0.92 (6H, d, $J$ = 6.68 Hz), 1.79 (1H, m), 2.21 (2H, dt, $J$ = 1.08 Hz), 6.12 (1H, m), 7.01 (1H, m), 9.50 (1H, d, $J$ = 8 Hz); $^{13}$C NMR (DMSO, 100 MHz) 22.03, 22.08, 27.16, 41.12, 133.59, 158.43, 194.43; IR (KBr) $\nu_{max}$ 3606, 3491, 2910, 1772, 1469, 1389, 1361 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_7H_{12}NaO$: [M + Na]$^+$ 135.0786, Found 135.0774.

### *3.1.4. Ethyl (2E,4E)-7-methylocta-2,4-dienoate* (12)

To a stirred suspension of triethyl phosphonoacetate (3.05 mL, 15.4 mmol), potassium carbonate (3.86 g, 28 mmol) and DBU (0.63 mL, 0.42 mmol) was added (*E*)-5-methylhex2-enal **11** (1.57 mL, 14 mmol) at room temperature and reaction mixture was allowed to stirred at room temperature and monitored by TLC, after completion of reaction (5 h) reaction mixture was partitioned between DCM and water, organic layer was separated and allowed to concentrate at reduced pressure carefully and purified by silica gel column chromatography by using 5% ethyl acetate in petroleum ether to give ester **12** (1.94 mL, 87%), as a clear oil, $^1$H NMR (DMSO, 400 MHz): d 0.85 (6H, d, $J$ = 6.60 Hz), 1.20 (3H, t, $J$ = 7.08 Hz), 1.66 (1H, m), 2.02 (2H, t, $J$ = 6.36 Hz), 4.09 (2H, t, $J$ = 7.12 Hz), 5.82 (1H, d, $J$ = 15.32 Hz), 6.23 (2H, m), 7.20 (1H,

m); $^{13}$C NMR (DMSO, 100 MHz) 14.52, 22.48, 28.15, 42.17, 60.05, 119.50, 129.74, 143.87, 145.22, 166.62; IR (KBr) $\nu_{max}$ 2955, 2869, 1721, 1641, 1514, 1475, 1376, 1355, 1320 cm$^{-1}$; HRMS (ESI): *m/z*: calcd for $C_9H_{16}NaO_2$: $[M + Na]^+$ 205.1204, Found 205.1225.

#### *3.1.5. (2E,4E)-7-methylocta-2,4-dienoic acid*

To a stirred solution of ester **12** (1.50 mL, 8.25 mmol) in THF (10 mL) was added NaOH solution (4 N) (5 mL) slowly and allowed to stirred at room temperature and monitored by TLC, upon completion of reaction (5 h), reaction mixture was partitioned between DCM and water, organic layer was separated and allowed to concentrate under reduced pressure to obtained dienoic acid **13** (Quantitatively, on the basis of conversion in TLC) which require additional care in order to avoid evapouration due to its low boiling point and moved to the coupling step without further purification. HRMS (ESI): *m/z* calcd for $C_9H_{14}NaO_2$: $[M + Na]^+$ 177.0891, Found 177.0893.

### *3.2. Preparation of amino aryl propionic acid methyl ester fragment*

#### *3.2.1. 2,4-dihydroxy-5-nitrobenzaldehyde* (15)

To a stirred nitric acid (0.834 mL, 20 mmol) at ice bath 2,4-dihydroxybenzaldehyde **14** (1.38 g, 10 mmol) was added slowly in period of 15 min and reaction mixture allowed to stirred at room temperature and monitored by TLC, upon completion of reaction (3 h) ice cold water was added with stirring to precipitate the titled compound **15** as creamish crystalline solid, (1.53 g, 84%); $^1$H NMR (DMSO, 400 MHz): $\delta$ 6.63 (1H, s), 8.29 (1H, s), 10.09 (1H, s), 11.87 (2H, s); $^{13}$C NMR (DMSO, 100 MHz) $\delta$ 104.83, 116.08, 129.90, 130.21, 159.72, 166.14, 190.46; IR (KBr) $\nu_{max}$ 3426, 1764, 1469, 1389, 1361 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_7H_4NNaO_5$: $[M + Na]^+$ 206.0065, Found 206.0071.

#### *3.2.2. 2,4-bis(benzyloxy)-5-nitrobenzaldehyde* (16)

To a stirred suspension of 2,4-dihydroxy-5-nitrobenzaldehyde **15** (1.062 g, 5.8 mmol), potassium carbonate (2.004 g, 14.5 mmol) in acetone (20 mL), benzyl bromide (1.55 mL, 13.05 mmol) was added dropwise and allowed to refluxed and monitored by TLC, workup was done with ethyl acetate and water, organic layer was concentrated under reduced pressure to obtained crude which was purified by recrystallizaion to obtain **16** (65%), yellow soild $^1$H NMR (DMSO, 400 MHz): $\delta$ 5.43 (2H, s), 5.44 (2H, s), 7.23 (1H, s), 7.50 (10H, m), 8.28 (1H, s), 10.18 (1H, s); $^{13}$C NMR (DMSO, 100 MHz) $\delta$ 71.05, 71.41, 100.43, 117.24, 126.77, 127.50, 127.73, 128.33, 128.35, 128.61, 128.65, 132.76, 135.15, 135.34, 157.91, 164.59, 186.69; IR (KBr) $\nu_{max}$ 3426, 3410, 2829, 2810, 1764, 1690 1469, 1389, 1361 cm$^{-1}$; HRMS (ESI): *m/z*: calcd for $C_{21}H_{17}NNaO_5$ $[M + Na]^+$ 386.1004, Found 386.1003.

#### *3.2.3. 2,4-dimethoxy-5-nitrobenzaldehyde* (17)

To a stirred suspension of 2,4-dihydroxy 5-nitrobenzaldehyde **15** (2.76 g, 20 mmol) and potassium carbonate (6.91 g, 50 mmol) in acetone (30 mL) at ice cooled condition, methyl iodide (2.73 mL, 44.4 mmol) was added and reaction mixture allowed to stirred at room temperature and monitored by TLC, upon completion of reaction (6 h), workup was done using ethyl acetate and water, organic layer was concentrated under reduced pressure to obtain **17**, (2.79 g, 84%), brown crystalline solid, $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 4.07 (3H, s), 4.08 (3H, s), 6.55 (1H, s), 8.50 (1H, s), 10.28 (1H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 56.49, 56.97, 95.93,

127.99, 159.53, 165.83, 186.54; IR (KBr) $\nu_{max}$ 2981, 2970, 2892, 1702, 1671, 1580, 1420, 1302 $cm^{-1}$; HRMS (ESI): *m/z*: calcd for $C_9H_9NNaO_5$ $[M + Na]^+$ 234.0378, Found 234.0376.

### *3.2.4. Methyl (E)-3-(2,4-bis(benzyloxy)-5-nitrophenyl)acrylate* (18)

To a stirred suspension of trimethylphosphono acetate, potassium carbonate (3.31 g, 24 mmol) and DBU (0.54 mL, 0.36 mmol) was added 4-bis (benzyloxy)-5-nitrobenzaldehyde **16** (7.20 mL, 66 mmol) at room temperature and reaction mixture was allowed to stirred at room temperature and monitored by TLC, after completion of reaction (5 h) reaction mixture was partitioned between DCM and water, organic layer was separated and allowed to concentrate at reduced pressure carefully and purified by silica gel column chromatography by using 5% ethyl acetate in petroleum ether to give titled compound **18** (1.94 mL, 89%), yellow solid, $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 3.81 (3H, s), 5.18 (4H, s), 6.54 (1H, d, $J$ = 16.12 Hz), 6.58 (1H, s), 7.43 (10H, m), 7.93 (1H, d, $J$ = 16.16 Hz), 8.24 (1H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 51.79, 71.20, 71.43, 99.47, 116.71, 118.93, 126.86, 127.11, 127.15, 128.48, 128.69, 128.87, 129.01, 133.08, 134.96, 134.98, 137.50, 155.33, 165.50, 167.46; IR (KBr) $\nu_{max}$ 3468, 3422, 1761, 1456, 1469, 1332, 1261 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{24}H_{21}NNaO_6$ $[M + Na]^+$ 442.1267, Found 442.1237.

### *3.2.5. Methyl (E)-3-(2,4-dimethoxy-5-nitrophenyl)acrylate* (19)

To a stirred suspension of trimethylphosphonoacetate (1.43 mL, 8.8 mmol), potassium carbonate (2.21 g, 16 mmol) and DBU (0.32 mL, 0.24 mmol) was added 2,4-dimethoxy-5-nitrobenzaldehyde **17** (1.68 g, 8 mmol) at room temperature and reaction mixture was allowed to stirred and monitored by TLC, after completion of reaction (5 h), reaction mixture was partitioned between DCM and water, organic layer was separated and allowed to concentrate at reduced pressure carefully and purified by silica gel column chromatography by using 5% ethyl acetate in petroleum ether to give titled compound **19** (1.73 g, 81%), as yellow solid; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 3.81 (3H, s), 4.01 (3H, s), 4.03 (3H, s), 6.51 (1H, d, $J$ = 16.12 Hz), 6.52 (1H, s); 7.85 (1H, d, $J$ = 16.12 Hz), 8.21 (1H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 51.76, 56.29, 56.74, 95.96, 116.07, 118.72, 127.27, 132.40, 137.52, 156.78, 162.92, 167.47; IR (KBr) $\nu_{max}$ 3020, 2972, 2810, 1700, 1610, 1590, 1440, 1320 $cm^{-1}$: HRMS (ESI): *m/z*: calcd for $C_{12}H_{13}NNaO_6$ $[M + Na]^+$ 290.0641, Found 290.0602.

### *3.2.6. Methyl 3-(5-amino-2,4-dihydroxyphenyl)propanoate* (20)

To a stirred Suspension of methyl (*E*)-3-(2,4-bis(benzyloxy)-5-nitrophenyl)acrylate **18** (2.30 g, 5.5 mmol) and ammonium formate (1.47 g, 23.27 mmol) in methanol, Pd/C (20 mol %) was added and reaction mixture was allowed to refluxed and monitored by TLC, after completion of reaction (3 h), reaction mixture was passed through the celite bed and washed with methanol and filtrate was concentrated under reduced pressure to obtain crude, which was purified by column chromatography using 15% EtOAc: hexane to obtain desired methyl 3-(5-amino-2,4-hydroxyphenyl)propanoate **20** (832 mg, 72%), light brown oil; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 2.74 (2H, t, $J$ = 6.88 Hz), 2.96 (2H, t, $J$ = 7.00 Hz), 3.71 (3H, s), 6.56 (1H, s), 7.39 (1H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 22.71, 25.04, 52.17, 104.70, 113.44, 122.40, 122.69, 125.64, 131.59, 146.91, 148.23, 148.75, 174.60; IR (KBr) $\nu_{max}$ 3420, 2994, 2872, 2860, 1740, 1691, 1540 $cm^{-1}$: HRMS (ESI): *m/z* calcd for $C_{10}H_{13}NNaO_4$ $[M + Na]^+$234.0742, Found 234.0753.

### 3.2.7. Methyl 3-(5-amino-2,4-dimethoxyphenyl)propanoate (21)

To a stirred solution of methyl (*E*)-3-(2,4-dimethotxy-5-nitrophenyl)acrylate **19** (1.33 g, 5 mmol) and ammonium formate (1.33 g, 21.25 mmol) in methanol, Pd/C (20 mol %) was added and reaction mixture was allowed to refluxed and monitored by TLC, after completion of reaction (3 h), reaction mixture was passed through the celite bed and washed with methanol and filtrate was concentrated under reduced pressure to obtain crude, which was purified by column chromatography using 10% EtOAc: hexane to obtain desired methyl 3-(5-amino-2,4-dimethoxyphenyl)propanoate **21** (861 mg, 72%), light brown oil; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 2.50 (2H, t, $J$ = 7.96 Hz), 2.76 (2H, t, $J$ = 7.64 Hz), 3.59 (3H, s), 3.70 (3H, s), 3.76 (3H, s), 6.36 (1H, s), 6.48 (1H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 24.38, 33.51, 50.47, 54.76, 55.28, 95.83, 116.20, 119.88, 128.00, 145.38, 149.43, 172.93; IR (KBr) $\nu_{max}$ 3480, 2980, 2972, 2960, 2820, 1980, 1720, 1690, 1580, 1410, 1390, 1220 cm$^{-1}$: HRMS (ESI): *m/z* calcd for $C_{12}H_{17}NNaO_4$ $[M + Na]^+$ 262.1055, Found 262.1038.

## 3.3. Coupling of two fragments

### 3.3.1. Methyl 3-(2,4-dimethoxy-5-((2E,4E)-7-methylocta-2,4-dienamido)phenyl) propanoate 22

To a stirred suspension of methyl 3-(5-amino-2,4-dimethoxyphenyl)propanoate **21** (478.54 mg, 2 mmol), EDCI.HCl (341.55 mg, 2.2 mmol) and DMAP (24.4 mg, 0.2 mmol) in dichloromethane (5 mL), (2*E*,4*E*)-7-methylocta-2,4-dienoic acid **13** (339.25 mg, 2.2 mmol) was added and reaction mixture was allowed to stirred at refluxed condition and monitored by TLC, after completion of reaction (5 h), work-up was done using dichloromethane and water, organic layer was concentrated under reduced pressure to obtain crude, which was purified by column chromatography using 15% EtOAc: hexane to yield title compound **22**, (510 mg, 68%), as yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.93 (6H, d, $J$ = 6.64 Hz), 1.76 (1H, m), 2.09 (2H, t, $J$ = 6.76 Hz), 2.61 (2H, t, $J$ = 8.32 Hz), 2.92 (2H, t, $J$ = 7.52 Hz), 3.69 (3H, s), 3.82 (3H, s), 3.89 (3H, s), 5.95 (1H, d, $J$ = 14.92 Hz), 6.22 (2H, m), 6.46 (1H, s), 7.30 (1H, m), 7.57 (1H, s), 8.25 (1H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 22.33, 25.53, 28.31, 34.44, 42.33, 51.49, 55.71, 55.92, 95.08, 114.06, 120.72, 121.81, 126.48, 129.35, 141.83, 142.38, 147.57, 153.79, 163.88, 173.80; IR (KBr) $\nu_{max}$ 3410, 2969, 2929, 1729, 1610, 1390, 1220, 1148, 1102, 1037 cm$^{-1}$: HRMS (ESI): *m/z* calcd for $C_{21}H_{29}NNaO_5$ $[M + Na]^+$ 398.1943, Found 398.1936.

### 3.3.2. Carpatamide-A (7a)

To a stirred solution of compound **22** (375.46 mg, 1 mmol), in dried dichloromethane at −78 °C, boron tribromide (2.5 mL, 2.5 mmol) in DCM (1 M) was added dropwise and reaction mixture was warmed to room temperature slowly and monitored by TLC, after completion of reaction (4 h), work-up was done using dichloromethane and water, organic layer was concentrated under reduced pressure to obtain crude, which was purified by column chromatography using 15% EtOAc: petroleum ether to yield title compound carpatamide-A **7a**, (315 mg, 90%), as yellow oil.$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.94 (6H, d, $J$ = 6.64 Hz), 1.77 (1H, m), 2.10 (2H, t, $J$ = 6.40 Hz), 2.67 (2H, t, $J$ = 6.60 Hz), 2.81 (2H, t, $J$ = 6.40 Hz), 3.69 (3H, s), 5.99 (1H, d, $J$ = 14.84 Hz), 6.20 (2H, m), 6.53 (1H, s), 6.75 (1H, s), 7.39 (1H, m), 7.67 (1H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 22.34, 22.66, 22.69, 24.29, 28.30, 34.80, 42.39, 52.17, 107.49, 114.07, 119.83, 123.89, 129.10, 139.29, 144.06, 144.27, 148.82, 153.43, 165.77, 175.73; IR (KBr) $\nu_{max}$ 3610, 3440,

2996, 2920, 2890, 2862, 2866, 1740, 1680, 1590, 1485, 1392, 1248, 1182, 1037 $cm^{-1}$: HRMS (ESI): *m/z*: calcd for $C_{19}H_{25}NNaO_5$ $[M + Na]^+$ 370.1630, Found 370.1628.

## 4. Conclusions

In summary, a potentially scalable, an efficient and convergent approach to carpatamide-A (**7a**) has been accomplished in twelve steps with overall yield of 24% with seven longest linear steps. The salient features of this synthetic approach are including Horner-Wadworth-Emmons reaction for the construction of the required *E*-double bond, metallic oxidation, nitration and incorporation of multiple transformations in catalytic hydrogenation step.

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## Disclosure statement

No potential conflict of interest was reported by the authors.

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