Total synthesis of a lignanamide from *Aptenia cordifolia*

Yamu Xia[a,*], Chenchen Li[a], Huaizheng Zhang[a], Jiao Lin[a] and Chen Chai[b]

[a]*College of Chemical Engineering, Qingdao University of Science and Technology, Qingdao 266042,P.R.China*
[b]*The First Affiliated Hospital of Lanzhou University, Gansu 730000, P.R.China*

(*E,E*)-*N,N*-Dityramin-4,4'-dihydroxy-3,5'-dimethoxy-ß,3'-bicinnamamide, a lignanamide isolated from *Aptenia cordifolia*, was synthesised from vanillin and tyramine. The key 8-5′-neolignan intermediate diacid was formed efficiently using oxidative coupling of the ferulic acid derivatives and the ring-opening reaction of a dihydrobenzofuran.

Keywords: lignanamide, vanillin, tyramine, oxidative coupling, ring-opening reaction

Lignanamides are widely distributed in plants, and have been isolated from *Cannabis sativa,*[1–3] *Mitrephora thorelii,*[4] *Porcelia macrocarpa,*[5] *Aptenia cordifolia,*[6] *Commelina communis,*[7] *Solanum melongena L.,*[8] *Piper wallichii,*[9] *etc.* Within this general class, aryl-naphthalene and acyclic bis-phenylpropane derivatives have been identified. Because of the wide range of structures[10] as well as biological activities,[8–16] such as anti-inflammatory,[8] antitumour[16] and insecticide properties,[8] the total synthesis of several members of the lignanamide family attracted considerable attention. However, not many synthetic approaches to the lignanamides have been reported. In 2010, we reported the first total synthesis of lignanamide Cannabisin G by Stobbe reaction to construct the skeleton of lignan (C6–C4–C6),[17] followed by condensation with tyramine, and Hou *et al.*[18] successfully employed oxidative coupling.[18] After that, Uwe's group[19] reported a reaction using the laccase/O_2 catalyst system to synthesise a number of lignanamide skeletons.

We have discovered that, in an alkaline media, the dihydrobenzofuran ring could be opened in high yield, leading to a 8-5′-neolignan as outlined in Fig. 1. Furthermore, we found the final product has the skeleton of lignanamide (*E,E*)-*N,N*-dityramin-4,4'-dihydroxy-3,5'-dimethoxy-ß,3'-bicinnamamide (**1**, Fig. 2), which was first isolated by Marina *et al.*[6] in 2005 from the leaves of *Aptenia cordifolia,* possessing a roots elongation inhibitory activity against *Lactuca sativa* at 10^{-4}M.

We now report full details of the total synthesis of the lignanamide (*E,E*)-*N,N*-dityramin-4,4'-dihydroxy-3,5'-dimethoxy-ß,3'-bicinnamamide. The ring-opening reaction of the dihydrobenzofuran was studied in various conditions in a series of experiments, such as the use of diverse bases and solvents at different temperatures and we studied the different products. The skeleton of lignanamide **1** was synthesised in alkaline media through this short route. It relies on the synthesis of the dihydrobenzofuran lignan from a ferulic acid derivative with Ag_2O as the oxidant. This leads to the skeleton of lignanamide **1** in high yield in the presence of NaOH and alcohol. Finally, we obtained the desired lignanamide efficiently following a condensation reaction with tyramine. Compared with the earlier route, the strategy is novel and concise.

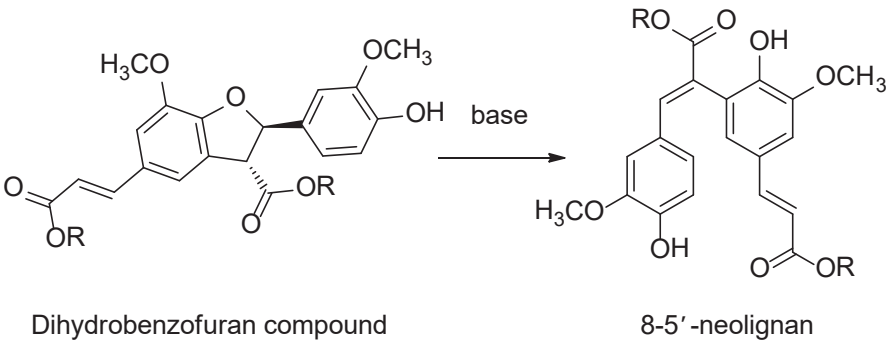

Fig. 1 The opening of the dihydrobenzofuran ring.

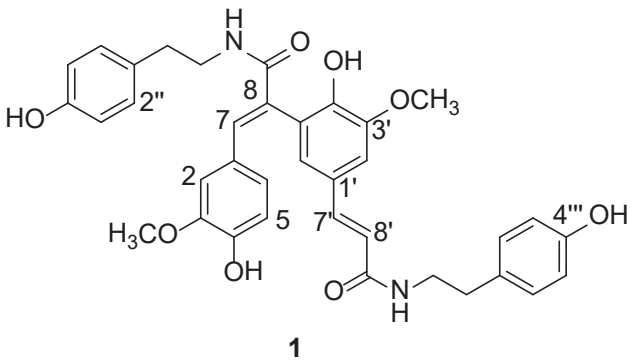

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Fig. 2 The lignanamide **1**.

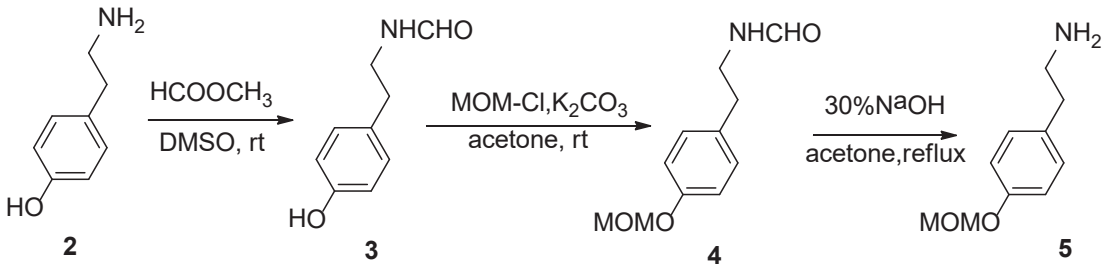
* Correspondent. E-mail: xiaym@qust.edu.cn

Result and discussion

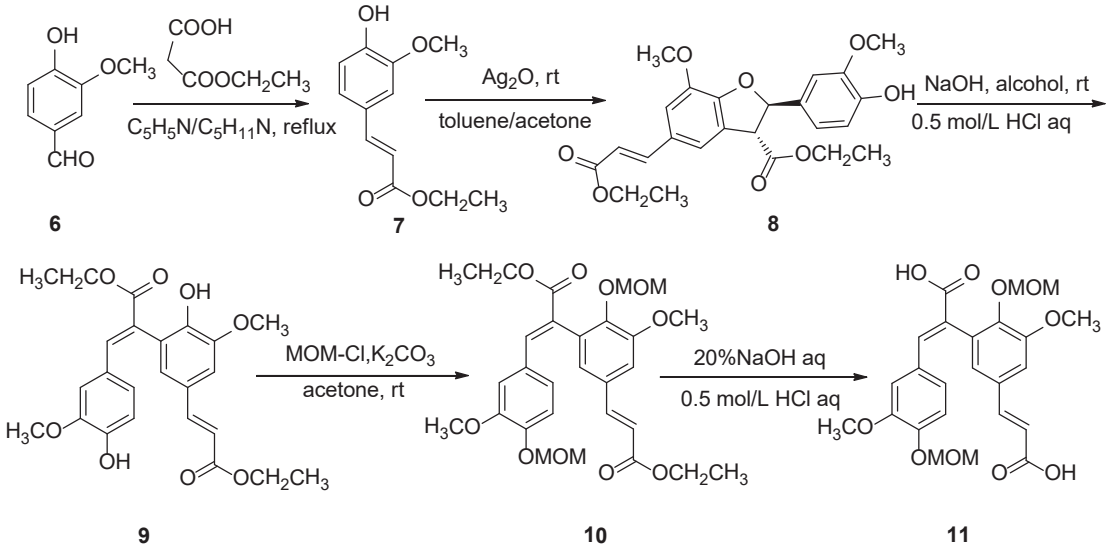
As shown in Scheme 1, the synthesis of the required tyramine intermediate began from compound **2**. Because both hydroxyl and amino groups of tyramine can react with the diacid, it is necessary to protect the hydroxyl group before the condensation reaction. First, the amino group of tyramine was protected to afford the product **3**. Then, the hydroxyl group of **3** was protected with MOMCl to give the intermediate **4**. Finally, selective removal of the formyl group afforded the desired key intermediate **5**.

As shown in Scheme 2, the required ferulic acid ethyl ester **7** could easily be prepared by Knoevenagel condensation between vanillin and the corresponding monoethyl malonate with yields ranging from 80 to 95%. The skeleton of the dihydrobenzofuran lignan **8** was obtained from the ferulic acid ethyl ester **7** through oxidative coupling by using Ag_2O. By comparison of the spectral data reported elsewhere,[23,24] the configuration of compound **8** was determined to be a threo-racemic compound. Then, by the opening of the dihydrobenzofuran ring using an alkaline catalytic system in the key step in this synthesis, we obtained compound **9** efficiently. The protection of the hydroxyl group and subsequent hydrolysis of these ester groups afforded through **10** the key intermediate compound **11**. According to literature spectral data,[25] the configuration of compounds **9, 10, 11** and **12** was determined to be *E,E*. In our short synthetic route, we took advantage of the opening of the dihydrobenzofuran ring to obtain the lignanamide skeleton simply and efficiently.

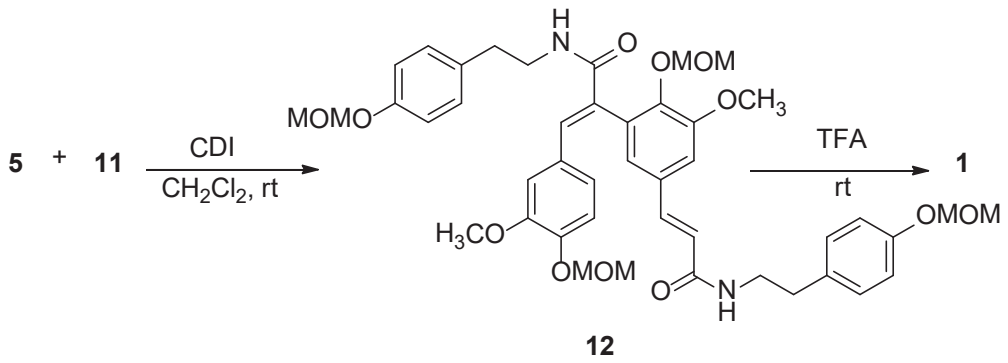
As shown in Scheme 3, compound **12** was successfully prepared from diacid **11** with tyramine using CDI as the reagent. Finally, the removal of the protecting groups using TFA at ambient temperature afforded the desired (*E*,*E*)-*N*,*N*-dityramin-4,4'-dihydroxy-3,5'-dimethoxy-ß,3'-bicinnamamide.



Scheme 1 Synthesis of tyramine ligand (**5**).



Scheme 2 Synthesis of 8-5′-neolignan diacid (**11**).



Scheme 3 Synthesis of lignanamide (**1**).

Conclusions

In summary, a new and concise strategic approach toward synthesising the natural product lignanamide (*E,E*)-*N,N*-dityramin-4,4'-dihydroxy-3,5'-dimethoxy-ß,3'-bicinnamamide (**1**, Fig. 2) has been developed. The synthesis of diferulic acid **11** from precursor **6** was achieved in an overall yield of 30% in five steps involving Knoevenagel reaction, oxidative coupling, the opening of the dihydrobenzofuran ring, MOMCl protection and hydrolysis. The lignanamide was finally prepared in good yield by condensing the diferulic acid **11** with a derivative of tyramine. We are continuing to examine the bioactivity of lignanamide **1** and the synthesis of related derivatives in our laboratory.

Experimental

All reagents and the solvents used in this study were of analytical grade and were used as-received. Dry solvents were prepared by literature methods and stored over molecular sieves. Flash column chromatography and TLC were performed on silica gel (200–300 mesh) and silica gel GF254 plates, respectively. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker AM-500 MHz spectrometer. HRMS spectra were obtained on a Bruker Daltonics APEXII47e spectrometer. Melting points were taken on a Gallenkamp melting point apparatus and are uncorrected.

N-[2-(4-Hydroxyphenyl) ethyl] formamide (**3**), N-{2-[4-(methoxymethoxy) phenyl] ethyl} formamide (**4**), 2-[4-(methoxymethoxy) phenyl] ethan-1-amine (**5**) and (E)-ferulic acid ethyl ester (**7**) were synthesised according to procedures that have been described previously.

N-*[2-(4-Hydroxyphenyl) ethyl] formamide* (**3**):[21] White solid; m.p. 95–97°C (lit.[20] 96–97°C); yield 11.8 g (98 %). ^{1}H NMR ($CDCl_3$), δ 2.79 (t, *J* = 7.0 Hz, 2H, $ArCH_2$), 3.55 (t, *J* = 7.0 Hz, 2H, CH_2NH), 5.03 (s, NH, 1H), 5.65 (s, 1H, OH), 6.79 (d, *J* = 8.5 Hz, 2H, ArH), 7.08 (d, *J* = 8.5 Hz, 2H, ArH), 8.15 (s, 1H, CH=O).^{13}C NMR ($CDCl_3$), δ 31.1, 39.5, 116.9, 129.8, 156.0, 161.3, 207.2 (CH=O).

N-*{2-[4-(Methoxymethoxy) phenyl] ethyl} formamide* (**4**):[21] Yellowish liquid; yield 11.2 g (75 %). ^{1}H NMR ($CDCl_3$), δ 2.62 (t, *J* = 7.0 Hz, 2H, $ArCH_2$), 3.29 (s, 3H, CH_3O), 3.33 (t, *J* = 7.0 Hz, 2H, CH_2NH), 4.98 (s, 2H, OCH_2O), 6.83 (d, *J* = 8.5 Hz, 2H, ArH), 6.97 (d, *J* = 8.5 Hz, 2H,ArH), 7.86 (s, H, CH=O). ^{13}C NMR ($CDCl_3$), δ 33.9, 38.9, 55.1, 93.7, 115.8, 129.1, 131.5, 155.3, 161.2. *2-[4-(Methoxymethoxy) Phenyl] ethan-1-amine* (**5**):[21] Yellowish liquid; yield 9.0 g (94.5 %). ^{1}H NMR ($CDCl_3$), δ 2.64 (t, *J* = 7.0 Hz, 2H, $ArCH_2$), 2.87 (t, 2H, CH_2NH_2), 3.41 (s, 3H, CH_3O), 5.09 (s, 2H, OCH_2O), 6.84–7.06 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$), δ 38.9, 43.5, 55.9, 94.5, 116.3, 129.8, 133.0, 155.7.

*(*E*)-Ferulic acid ethyl ester* (**7**):[22] White powder; m.p. 77°C (lit.[22] 77–78°C). ^{1}H NMR ($CDCl_3$), δ 1.34 (t, *J* = 12.0 Hz, 3H, CH_2CH_3), 3.91 (s, 3H, OCH_3), 4.25 (q, *J* = 12.0 Hz, 2H, CH_2CH_3), 5.91 (s, 1H, OH), 6.29 (d, *J* = 16.0 Hz, 1H, =CHCO), 6.91–7.06 (m, 3H, ArH), 7.61 (d, *J* = 16.0 Hz, 1H, ArCH). ^{13}C NMR ($CDCl_3$), δ 14.4, 55.9, 60.4, 109.4, 114.8, 115.7, 123.1, 127.1, 144.7, 146.8, 147.9, 167.3(C=O).

*Threo(±)-ethyl 5-[(*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-2,3-dihydrobenzofuran-3-carboxylate* (**8**): Fresh Ag_2O (6.57 g, 28.47 mmol) was added to a dry acetone (30 mL) and toluene (40 mL) solution of compound **7** (12.64 g, 56.93 mmol) under a nitrogen atmosphere at -20℃. The reaction mixture was stirred until complete disappearance of compound **7**, and then it was filtered and evaporated under reduced pressure. The residue was purified by column chromatography (petroleum/ethyl acetate = 3: 1) to afford the compound **8**: white solid; m.p. 151–152°C (lit.[23] 152.8-153.1°C); yield 5.68 g (45.2 %). ^{1}H NMR ($CDCl_3$), δ: 1.34–1.37 (m, 6H, 2×CH_3), 3.88 (s, 3H, Ar-OCH_3), 3.96(s, 3H, Ar-OCH_3), 4.25–4.30 (m, 4H, 2×OCH_2), 4.33 (d, *J* = 8.0 Hz, 1H, H-3), 6.11 (d, *J* = 8.0 Hz, 1H, H-2), 6.32 (d, *J* = 15.9 Hz, 1H, H-2′), 6.90–7.27 (m, 5H, ArH), 7.65 (d, *J* = 15.9 Hz, 1H, H-1′). ^{13}C NMR ($CDCl_3$), δ 14.3, 55.5, 56.3, 56.1, 60.4, 61.8, 87.5, 108.7, 111.7, 114.5, 115.9, 117.9, 119.5, 125.8, 128.6, 131.4, 144.5, 144.7, 145.9, 146.6,149.9, 167.2 (C=O), 170.2 (C=O). HRMS calcd. for $C_{24}H_{26}O_8$ 442.1628, found 442.1632. The spectral data are consistent with the literature.[24]

*Ethyl (*E,E*)-4,4'-dihydroxy-3,5'-dimethoxy-ß,3'-bicinnamate* (**9**): Compound **8** (5.68 g, 12.85 mmol) was suspended in ethyl alcohol (50 mL), and NaOH (0.62 g, 15.5 mmol) was added. The mixture was stirred vigorously for 4 h at room temperature. The solution was acidified with HCl (1 M) and evaporated under reduced pressure to remove EtOH. The residue was extracted with EtOAc (2×20 mL) and the organic layer washed with saturated NaCl aq. (2×20 mL) followed by drying over $MgSO_4$. The filtrate was concentrated and purified by column chromatography (petroleum/ ethyl acetate = 5: 3) to afford compound **9**: yellow solid; m.p. 138–139°C; yield 5.40 g (95 %). ^{1}H NMR ($CDCl_3$), δ 1.21 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 1.23 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 3.42 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.17 (q, *J* = 12.0 Hz, 2H, OCH_2CH_3), 4.20(q, *J* = 12.0 Hz, 2H, OCH_2CH_3), 5.84 (s, 1H, OH), 6.06 (s, 1H, OH), 6.19 (d, *J* = 16.0 Hz, 1H, H-8'), 6.51–7.00 (m, 5H, ArH), 7.51 (d, *J* = 16.0 Hz, 1H, H-7'), 7.76 (s, 1H, H-7). ^{13}C NMR ($CDCl_3$), δ 14.3, 55.3, 56.2, 60.4, 61.1, 108.7, 111.6, 114.3, 116.1, 123.3, 124.8, 125.8, 126.9, 127.0, 141.5, 144.3, 145.9, 146.0, 147.1, 147.3, 167.1 (C=O), 167.4 (C=O). HRMS calcd for $C_{24}H_{26}O_8$ 442.1628, found 442.1634. The data are consistent with that reported in ref. 25.

*Ethyl (*E,E*)-4,4'-dimethoxymethyl-3,5'-dimethoxy-ß,3'-bicinnamate* (**10**): Compound **9** (5.40 g, 12.2 mmol) was dissolved in dry acetone (30 mL), and potassium carbonate (8.43 g, 61.1 mmol) was added at room temperature. After 10 h of vigorous stirring, MOMCl (2.36 g, 29.3 mmol) was added dropwise. Stirring was continued for 3 h. The mixture was extracted with ethyl acetate and the organic layer was dried over $MgSO_4$. Then, it was concentrated under reduced pressure. The residual oil was purified by column chromatography (petroleum/ ethyl acetate = 3/1) to give the compound **10**: yellow solid; m.p. 55–57°C; yield 5.30 g (81.8 %). ^{1}H NMR ($CDCl_3$), δ 1.21 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 1.27 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 3.38 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.23 (q, *J* = 7.5 Hz, 2H, OCH_2CH_3), 4.25(q, *J* = 7.5 Hz, 2H, OCH_2CH_3), 5.21 (s, 2H, OCH_2OCH_3), 5.22 (s, 2H, OCH_2OCH_3), 6.28 (d, *J* = 16.0 Hz, 1H, H-8'), 6.65-7.10 (s, 5H, ArH), 7.57 (d, *J* = 16.0 Hz, 1H, H-7'), 7.85 (s, 1H, H-7). ^{13}C NMR ($CDCl_3$), δ 14.3, 55.2, 55.9, 56.3, 57.1, 60.5, 61.9, 95.1, 98.3, 110.9, 113.0, 115.3, 117.7, 123.9, 124.9, 128.6, 131.0, 132.2, 140.4, 143.8, 146.3, 147.7, 148.9, 153.1, 167.9 (C=O), 167.5 (C=O). HRMS calcd for $C_{28}H_{34}O_{10}$ 530.2152, found 530.2159.

*(*E,E*)-4,4'-Dimethoxymethyl-3,5'-dimethoxy-ß,3'-bicinnamic acid* (**11**): 20% NaOH aq. (20 mL) was added to an ethanol solution (5 mL) of **10** (5.3 g, 10 mmol), and the mixture was stirred at 40°C for 4 h. The solution was evaporated under reduced pressure to remove EtOH. Then, the mixture was poured into EtOAc (30 mL). The organic layer was separated, and the aqueous layer was back-extracted with EtOAc (3×10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure affording the crude product which was purified by recrystallisation (EtOAc/petroleum ether (3: 1)) to give compound **11**: yellow solid; m.p. 138–139°C; yield 4.6 g (97 %). ^{1}H NMR ($CDCl_3$), δ 3.39 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.02 (s, 2H, OCH_2OCH_3), 5.21 (s, 2H, OCH_2OCH_3), 6.30 (d, *J* = 16.0 Hz, 1H, H-8'), 6.68–7.26 (m, 5H, ArH), 7.64 (d, *J* = 16.0 Hz, 1H, H-7'), 7.93 (s, 1H, H-7). ^{13}C NMR ($CDCl_3$), δ 55.2, 56.0, 56.3, 57.2, 95.1, 98.4, 111.2, 113.1, 115.3, 116.9, 124.3, 125.5, 126.0, 128.2, 130.8, 131.7, 142.8, 146.1, 146.7, 148.2, 149.0, 153.1, 172.2 (C=O), 172.5 (C=O). HRMS calcd for $C_{24}H_{26}O_{10}$ 474.1526, found 474.1528.

*(*E,E*)-N,N-(4,4'-dimethoxymethyl)-dityramin-4,4'-dimethoxymethyl-3,5'-dimethoxy-ß,3'-bicinnamamide* (**12**): Diacid **11** (4.6 g, 9.7 mmol) was dissolved in dry CH_2Cl_2 (10 mL), and CDI (3.15 g, 19.4 mmol) was added under a nitrogen atmosphere at room temperature. After 3h of stirring, the reaction mixture was added dropwise to a stirred solution of **5** (3.85 g, 21.3 mmol) in dry CH_2Cl_2 (5 mL). The white precipitate, which formed, was filtered off and the solvent was evaporated under reduced pressure to afford a yellow oil. The residue was subjected to flash column chromatography (diethyl ether/petroleum ether (2:1)) to give compound **12**: white solid; m.p.

129–130°C; yield 4.8 g (62 %). ^{1}H NMR ($CDCl_3$), δ 2.72 (t, *J* = 7.0 Hz, 2H, $ArCH_2$), 2.82 (t, *J* = 7.0 Hz, 2H, $ArCH_2$), 3.34 (s, 3H, OCH_3), 3.43 (s, 3H, CH_3O), 3.45 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.48 (t, *J* = 7.0 Hz, 2H, CH_2NH), 3.51 (s, 3H, OCH_3), 3.62 (t, *J* = 7.0 Hz, 2H, CH_2NH), 3.91 (s, 3H, OCH_3), 5.00 (s, 2H, OCH_2O), 5.07 (s, 2H, OCH_2O), 5.16 (s, 2H, OCH_2O), 5.17 (s, 2H, OCH_2O), 6.17 (d, *J* = 16.0 Hz, 1H, H-8'), 6.57–7.14 (m, 13H, ArH), 7.50 (d, *J* = 16.0 Hz, 1H, H-7'), 7.81 (s, 1H, H-7). ^{13}C NMR ($CDCl_3$), δ 34.6, 34.9, 41.0, 41.3, 55.2, 55.9, 56.3, 57.3, 94.6, 95.2, 98.3, 112.2, 112.9, 115.6, 116.4, 116.7, 121.2, 122.3, 124.5, 129,2, 129.8, 131.8, 132.2, 132.4, 137.5, 139.6, 145.2, 147.2, 149.1, 153.5, 155.8, 156.1, 165.5, 166.5. HRMS calcd for $C_{44}H_{52}N_2O_{12}$ 800.3520, found 800.3529.

*(*E,E*)-*N,N*-dityramin-4,4'-dihydroxy-3,5'-dimethoxy-β,3'-bicinnamamide* (**1**): A mixture of compound **12** (0.1 g, 0.125 mmol), anhydrous CH_2Cl_2 (15 mL), and TFA (0.25 mL, 3.4 mmol) was stirred at ambient temperature for 6 h, then diluted with water (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on a short column of silica gel [eluent: $CHCl_3$/MeOH (1: 2)] to give (*E,E*)-*N,N*-dityramin-4,4'-dihydroxy-3,5'-dimethoxy-*β*,3'-bicinnamamide (**1**): amorphous powder; yield 67.2 mg (86.2 %). ^{1}H NMR ($CDCl_3$), δ 2.66 (t, *J* = 7.0 Hz, 2H, $ArCH_2$), 2.72 (t, *J* = 7.0 Hz, 2H, $ArCH_2$), 3.35 (s, 3H, OMe), 3.43 (t, *J* = 7.0 Hz, 2H, CH_2NH), 3.50 (t, *J* = 7.0 Hz, 2H, CH_2NH), 3.95 (s, 3H, OMe), 6.36 (d, *J* = 16.0 Hz, 1H, H-8'), 6.55–7.16 (m, 13H, ArH), 7.40 (d, *J* = 16.0 Hz, 1H, H-7'), 7.60 (s, 1H, H-7). ^{13}C NMR ($CDCl_3$), δ 36.1, 36.3, 43.0, 43.3, 56.3, 57.3, 112.2, 113.8, 115.6, 116.4, 116.8, 120.2, 125.3, 126.3, 127.2, 129.1, 131.8, 131.9, 132.1, 138.9, 141.9, 147.1, 148.2, 149.3, 151.6, 156.8, 168.8, 169.5. HRMS calcd for $C_{36}H_{36}N_2O_8$ 624.2472, found 624.2477. Physical and spectral data are in accordance with those previously reported.[6]

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Electronic Supplementary Information:

Copies of the original ^{1}H (500 MHz) NMR and ^{13}C (125 MHz) NMR spectra for compounds **3**, **4**, **5**, **8**, **9**, **10**, **11**, **12** and **1** are available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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