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First total synthesis of mariamide A

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Abstract

Mariamide A, a lignanamide isolated from the seeds of *Silybum marianum*, has demonstrated potential utility as an antioxidant and antidiabetic agent and possesses an 8-O-4′ neolignan skeleton. Herein, a first total synthesis of mariamide A is presented that proceeds in nine steps using vanillin as the starting material. The key steps for the preparation of mariamide A involve an I_2-catalyzed bromomethoxylation of an alkene group, a nucleophilic substitution followed by a sequential elimination and a monoacylation reaction.

Keywords

8-O-4′ neolignans, I_2-catalyzed bromomethoxylation, lignanamides, mariamide A, lignans

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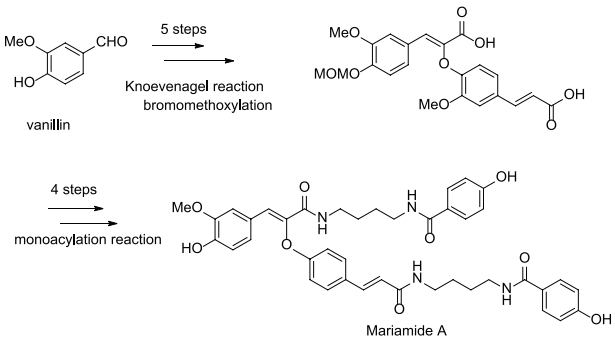

Introduction

Lignans are widely distributed in the plant kingdom and represent an enormous class of pharmacologically active secondary metabolites.[1,2] These compounds are derived from the oxidative coupling of two phenylpropanoid units by a β,β′-linkage with a different degree of oxidation in the side chain and a different substitution pattern on the aromatic moieties.[3] Therefore, lignans exhibit an enormous structural diversity originating from the various linking patterns of these phenylpropanoid units.

A small but significant subgroup within the lignans, lignanamides were first found in the roots of *Capsicum annuum var. grossum*,[4] and later were isolated from *Mitrephora thorelii*,[5] *Cannabis sativa*,[6] *Hyoscyamus niger*,[7] *Solanum melongena L*,[8] *Lycium chinense*,[9,10] and so on. Lignanamides possess significant pharmacological effects such as anti-inflammatory,[8,11] antihyperlipidemic,[9] radical-scavenging activity,[10] antiproliferative,[12] reduction of endoplasmic reticulum stress-induced cytotoxicity,[13] and phytotoxicity role.[7] Given their relative rarity in nature and the limited number of biological studies concerning these compounds, lignanamides are worthy of further investigation as desirable synthetic targets. Several elegant reports on lignanamide synthesis have been reported.[12,14,15] Motivated by these unusual structural features and significant biological activity, our laboratory accomplished the first total synthesis of cannabisin F in 2014[16] and cannabisin B in 2015,[17] both of which belong to the lignanamides.

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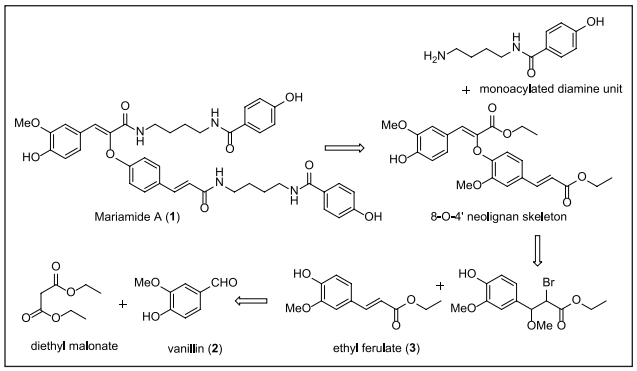
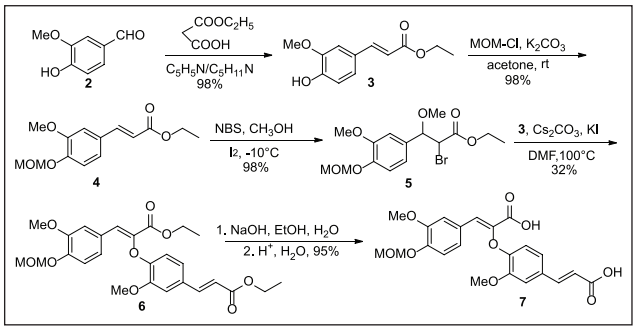


Scheme 1. Retrosynthetic analysis of mariamide A (**1**).



Scheme 2. Synthesis of 8-O-4′ neolignan intermediate (**7**).

Recently Qin et al.[18] was the first to report the lignanamide, mariamide A (**1**) from the seeds of *Silybum marianum*. Mariamide A (**1**) has demonstrated potential utility as an antioxidant and an antidiabetic agent and possesses an 8-O-4′ neolignan skeleton structurally, which attracted our interest. Based on our previous work, we set out to explore a new methodology for the synthesis of mariamide A (**1**) under more convenient and general conditions.

Herein, we describe a first synthetic route to mariamide A (**1**) in nine steps using vanillin as the starting material.

Results and discussion

Retrosynthetically, we envisaged that compound **1** could be accessed from an amidation reaction between an 8-O-4′ neolignan skeleton and a monoacylated diamine unit (Scheme 1). The 8-O-4′ skeleton intermediate could be traced back to ethyl ferulate (**3**) that in turn could be accessed from vanillin (**2**) via a Knoevenagel reaction.

As shown in Scheme 2, Knoevenagel reaction of vanillin (**2**) with monoethyl malonate easily afforded ethyl ferulate (**3**) in 98% yield. To obtain the desired 8-O-4′ neolignan intermediate **6** efficiently, protection of the phenolic group in **3** by using methoxymethyl chloride (MOM-Cl) to furnish compound **4** was necessary. With compound **4** in hand, our next task was to explore the bromomethoxylation of the alkene group in **4**. NBS is a common halogen source for bromomethoxylation reaction. However, a longer reaction time and low yield, especially with electron-deficient alkenes, are major drawbacks.[19] Inspired by Lodh et al.'s[20] and Bar's[19] work, we anticipated that iodine might catalyze the electrophilic halogen transfer from NBS to the olefin. An initial experiment was performed at −10°C using **4** as the substrate and iodine as the catalyst, which lead to the formation of **5** as the sole reaction product in 98% isolated yield. Further investigations revealed that a low reaction temperature was necessary. With precursor **5** in hand, we turn to the implementation of the coupling between **3** and **5** to form the crucial 8-O-4′ neolignan intermediate **6**. After screening various conditions (Table 1), compound **6** could be obtained by using Cs_2CO_3 and KI in DMF at 100°C in synthetically useful yields; no undesired compound **6′** was observed. We speculate that any compound **6′** formed in the reaction was converted into compound **6** immediately via elimination of CH_3OH (Scheme 3). Excess Cs_2CO_3, however, accelerated the elimination of HBr in **5** to form olefin compound **5′**, and a lower or higher reaction temperature provided a low yield of compound **6**. Dicarboxylic acid **7** could be prepared in 95% yield from compound **6**.

Having the 8-O-4′ neolignan intermediate **7** secured, the total synthesis of mariamide A (**1**) was completed in a few steps (Scheme 4; Figure 1). Thus, benzoic acid derivative **9**, which was obtained in two steps in 80% overall yield from commercially available ethyl 4-hydroxybenzoate (**8**), was coupled with 1,4-diaminobutane using Verma et al.'s[21] method to generate monoacylated diamine unit **10**. The presence of 20% NaCl solution was necessary to obtain a useful yield in the reaction, but the yield with further increase in NaCl concentration did not show improvement. Next, the dicarboxylic acid **7** was coupled with monoacylated diamine **10** to give the precursor **11**. The desired target **1** was obtained successfully by removal of the MOM protecting groups in precursor **11**.

The ^{1}H NMR spectrum of synthetic 1 (Table 2) showed the signals due to one E form 1,2-disubstituted and one trisubstituted olefin moieties (δ 7.41 (1H, d, J=15.5 Hz), 6.44 (1H, d, J=15.5 Hz); 7.23 (1H, s)), two methoxys (δ 3.94, 3.68), and a series of methylenes, which is similar with the isolated compound **1**. The presence of an ether bridge connecting between C-8′ and C-4‴ was supported by the data C-7′ signal δ 125.1 and C-8′ signal δ 141.9, as well as the H-7′ signal δ 7.23, which is similar with the isolated compound **1**.

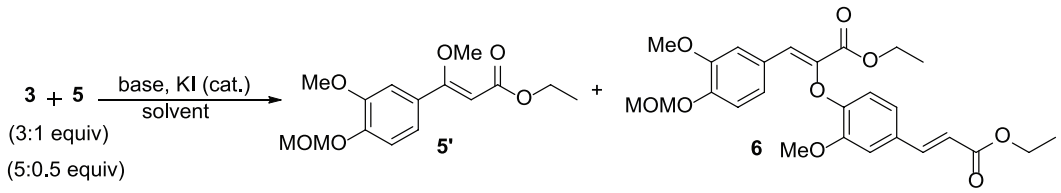
Conclusion

In summary, the lignanamide mariamide A (**1**) has been synthesized for the first time in nine steps from inexpensive commercially available starting materials (vanillin) using a concise I_2-catalyzed bromomethoxylation reaction of an alkene group, a nucleophilic substitution reaction followed by a sequential elimination reaction and a monoacylation reaction as key steps. The strategy may also be useful for the preparation of various 8-O-4′ neolignans or lignanamides and their derivatives, while potentially contributing to an improved and deeper understanding of bioactivities of related compounds.

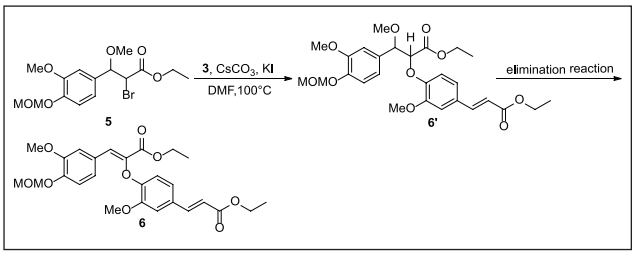
Experimental

All chemicals were purchased (Aladdin or Sinopharm Chemical Reagent Co., Ltd) for the reactions are analytical grade and were used without further purification. Solvents were dried and stored using standard procedures. Highly

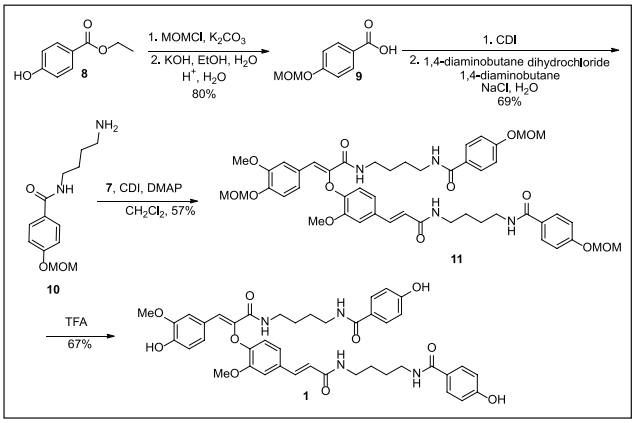
Table 1. Comparison of different reaction condition for the synthesis of compound **6**.



Entry	Condition	Base (equiv.)	Solvent	Yield of **5′** (%)	Yield of **6** (%)
1	KI, 10 h, reflux	K_2CO_3 (1)	Acetone	0	0
2	KI, 10 h, reflux	Cs_2CO_3 (1)	Acetone	91	Trace
3	KI, 10 h, 100°C	K_2CO_3 (1)	DMF	85	8
4	KI, 10 h, 100°C	Cs_2CO_3 (1)	DMF	78	12
5	KI, 10 h, 100°C	NaH (1)	DMF	89	Trace
6	KI, 10 h, 60°C	K_2CO_3 (1)	DMF	93	0
7	KI, 10 h, 60°C	Cs_2CO_3 (1)	DMF	92	Trace
8	KI, 10 h, 100°C	Cs_2CO_3 (0.5)	DMF	45	32
9	KI, 10 h, reflux	Cs_2CO_3 (0.5)	CH_3OH	0	0
10	KI, 10 h, 120°C	Cs_2CO_3 (0.5)	DMF	51	22



Scheme 3. A plausible mechanism for the synthesis of compound **6**.



Scheme 4. Completion of the total synthesis of mariamide A (**1**).

moisture- or oxygen- sensitive reactions were performed under a nitrogen atmosphere. Melting points were taken on a Gallenkamp melting point apparatus without calibration. Flash column chromatography and thin-layer chromatography (TLC) inspections were performed on Aladdin silica gel (200–300 mesh) and silica gel plates (GF_{254}), respectively. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-500 MHz, Bruker AM-600 MHz spectrometers. high-resolution mass spectra (HRMS) were obtained on a Bruker APEXII47e spectrometer.

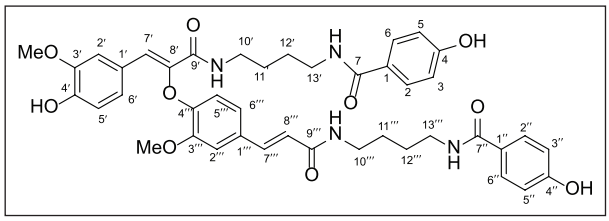


Figure 1. Mariamide A.[18]

*(E)-Ferulic acid ethyl ester (**3**)*

To an oven-dried round-bottom flask (500 mL) charged with vanillin (**2**) (38.48 g, 252.88 mmol), monoethyl malonate (50.11 g, 379.32 mmol) and piperidine (4.0 g, 50.58 mmol) was added pyridine (100 mL) under air at room temperature. The reaction solution was stirred for 24 h at 100°C. The resulting solution was cooled to 0°C and hydrochloric acid was added dropwise until pH was 1–2. The mixture was allowed to stand for 24 h at −10°C, and then filtered and dried. The residue was purified by flash column chromatography (petroleum/EtOAc = 6/1) to afford **3**: white solid: m.p. 60–61°C (Lit.[22] 59–61°C); yield: 55.08 g (98%); ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.61 (d, J = 16 Hz, 1H, ArCH=CH), 7.06 (dd, J = 8 Hz, 2 Hz, 1H, ArH), 7.03 (d, J = 2 Hz, 1H, ArH), 6.91 (d, J = 8 Hz, 1H, ArH), 6.29 (d, J = 16 Hz, 1H, ArCH=CH), 5.92 (s, 1H, ArOH), 4.25 (q, J = 7 Hz, 2H, CH_2CH_3), 3.92 (s, 3H, OCH_3), 1.33 (t, J = 7 Hz, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$), δ 167.5 (C=O), 147.8, 146.7, 145.0, 127.5, 123.1, 115.8, 114.6, 109.5, 60.4, 55.8, 14.40. The spectral data are consistent with the literature.[23]

*Ethyl (E)-3-(3-methoxy-4-(methoxymethoxy) phenyl)acrylate (**4**)*

To an oven-dried round-bottom flask (250 mL) charged with a solution of **3** (10 g, 45.0 mmol) in acetone (80 mL) was added anhydrous K_2CO_3 (18.66 g, 135.0 mmol) under

Table 2. Comparison of the spectroscopic data for the isolated compound in CD_3OD[18] and the synthetic compound in $CDCl_3$.

	Isolated compound **I**		Synthetic compound **I**	
	δ_H (400 MHz)	δ_C (100 MHz)	δ_H (500 MHz)	δ_C (500 MHz)
1		126.5		126.6
2,6	7.65, d (7.8)	130.2	7.66 d (8.0)	130.3
3,5	6.80, d (7.8)	116.1	6.81–6.79, m	116.2
4		161.9		161.9
7		170.0		170.0
1′		125.5		125.5
2′	7.30, s	113.7	7.30, s	113.7
3′		148.9		148.9
4′		149.5		149.6
5′	6.71, d (8.7)	116.2	6.70, d (8.5)	116.2
6′	7.03, d (8.7)	126.2	7.05, d (8.5)	126.3
7′	7.22, br s	125.1	7.23, s	125.1
8′		141.8		141.9
9′		165.7		165.7
10′	3.28, m	40.3	3.27–3.24, m	40.32
11′	1.50, m	27.8	1.49–1.40, m	27.80
12′	1.50, m	27.9	1.49–1.40, m	27.83
13′	3.28, m	40.4	3.27–3.24, m	40.4
1″		126.5		126.5
2″, 6″	7.68, d (7.8)	130.2	7.68, d (8.0)	130.2
3″, 5″	6.80, d (7.8)	116.0	6.81–6.79, m	116.1
4″		162.0		162.1
7″		170.1		170.1
1‴		131.9		132.0
2‴	7.22, br s	112.3	7.23, s	112.3
3‴		150.5		150.6
4‴		147.7		147.8
5‴	6.76, d (8.7)	115.3	6.75, d (8.5)	115.3
6‴	6.98, d (8.7)	122.2	6.96, d (8.5)	122.2
7‴	7.40, d (15.2)	141.0	7.41, d (15.5)	141.2
8‴	6.45, d (15.2)	121.0	6.44, d (15.5)	121.1
9‴		168.7		168.7
10‴	3.35, m	40.3	3.34–3.30, m	40.29
11‴	1.63, m	27.8	1.63–1.57, m	27.9
12‴	1.63, m	28.0	1.63–1.57, m	28.0
13‴	3.36, m	40.5	3.40–3.36, m	40.5
3′-OCH_3	3.66, s	56.0	3.68, s	56.0
3‴-OCH_3	3.95, s	56.4	3.94, s	56.5

air at room temperature. The reaction mixture was stirred for 1 h at room temperature and MOM-Cl (5.43 g, 67.49 mmol) was added dropwise at 0°C. After stirring for 6 h, the reaction was quenched with water and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (3 × 10 mL) and brine (3 × 10 mL), and dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified by flash chromatography (petroleum/EtOAc = 6/1) to give **4**: white solid; m.p. 50–53°C; yield 11.74 g (98 %); ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.62 (d, J = 16 Hz, 1H, ArCH=CH), 7.14 (d, J = 8 Hz, 1H, ArH), 7.08–7.06 (m, 2H, ArH), 6.32 (d, J = 16 Hz, 1H, ArCH=CH), 5.26 (s, 2H, CH_3OCH_2O), 4.25 (q, J = 7 Hz, 2H, CH_2CH_3), 3.91 (s, 3H, OCH_3), 3.51 (s, 3H, CH_3OCH_2O), 1.33 (t, J = 7 Hz, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$), δ 167.2 (C=O), 150.0, 148.4, 144.4, 128.8, 122.2, 116.5, 115.8, 110.2, 95.1, 60.4, 56.3, 55.9, 14.3. HRMS (ESI): M/Z $[M]^+$ calcd for $C_{14}H_{18}O_5$: 266.1154; found: 266.1159.

*Ethyl 2-bromo-3-methoxy-3-(3-methoxy-4-(methoxymethoxy)phenyl)propanoate (**5**)*

To an oven-dried round-bottom flask (100 mL) charged with a well-stirred solution of **4** (2.0 g, 7.51 mmol) in dry methanol (20 mL) was added NBS (1.47 g, 8.26 mmol) and iodine (0.19 g, 0.75 mmol) at −10°C under a nitrogen atmosphere. After stirring for 10 h, the resulting solution was quenched with saturated $NaHSO_3$ solution and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (3 × 20 mL) and brine (3 × 20 mL), and dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified by flash chromatography (petroleum/EtOAc = 3/1)

to yield **5**: yellowish oil; yield 2.77 g (98%); ^{1}H NMR (500 MHz, $CDCl_3$), δ 6.96 (d, J = 8 Hz, 1H, ArH), 6.76–6.72 (m, 2H, ArH), 5.05 (s, 2H, CH_3OCH_2O), 4.32 (d, J = 10 Hz, 1H, CHBr), 4.10 (q, J = 7 Hz, 2H, CH_2CH_3), 4.05 (d, J = 10 Hz, 1H, ArCH), 3.70 (s, 3H, OCH_3), 3.32 (s, 3H, CH_3OCH_2O), 3.03 (s, 3H, $ArCHOCH_3$), 1.34 (t, J = 7 Hz, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$), δ 168.5 (C=O), 149.7, 146.8, 130.8, 121.0, 115.6, 110.5, 95.2, 83.8, 61.7, 57.2, 55.9, 55.6, 47.4, 13.8; HRMS (ESI) calcd for $C_{15}H_{21}{}^{79}BrO_6$: 376.0522; found: 376.0535. The NMR data are similar with that reported in Bar's[19] work.

*Ethyl (Z)-3-methoxy-3-(3-methoxy-4-(methoxymethoxy)phenyl)acrylate (**5′**)*

To an oven-dried round-bottom flask (100 mL) charged with **3** (888.96 mg, 4.0 mmol) in dry DMF (3 mL) was added Cs_2CO_3 (1.30 g, 4.0 mmol) under a nitrogen atmosphere at room temperature. After stirring for 1 h, catalytic amounts of KI (10%) was added and a solution of **5** (754.46 mg, 2.0 mmol) in dry DMF (2 mL) was added dropwise at 40°C. The reaction mixture was stirred for 6 h at 40°C under a nitrogen atmosphere. The resulting mixture was treated with water (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with water (3 × 20 mL) and brine (3 × 20 mL), and dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified by flash chromatography (petroleum/EtOAc = 10/1) to yield **5′**: colorless oil; yield 533.35 mg (90%); ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.16–7.11 (m, 2H, ArH), 7.06 (s, 1H, ArH), 5.52 (s, 1H, CHC=O), 5.26 (s, 2H, CH_3OCH_2O), 4.20 (q, J = 7 Hz, 2H, CH_2CH_3), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, $ArCOCH_3$), 3.52 (s, 3H, CH_3OCH_2), 1.31 (t, J = 7 Hz 3H, CH_2CH_3). HRMS (ESI): M/Z $[M]^+$ calcd for $C_{15}H_{20}O_6$: 296.1260; found: 296.1268.

*Ethyl (Z)-2-(4-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(3-methoxy-4-(methoxymethoxy)phenyl)acrylate (**6**)*

To an oven-dried round-bottom flask (100 mL) charged with **3** (888.96 mg, 4.0 mmol) in dry DMF (3 mL) was added Cs_2CO_3 (651.64 mg, 2.0 mol) under nitrogen atmosphere at room temperature. After stirring for 1 h, a catalytic amount of KI of catalytic amounts (10%) was added and the solution of **5** (754.46 mg, 2.0 mmol) in dry DMF (2 mL) was added dropwise at 100°C. The reaction mixture was stirred for 10 h at 100°C under a nitrogen atmosphere. The resulting mixture was added water (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with water (3 × 20 mL) and brine (3 × 20 mL), and dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified by flash chromatography (petroleum/EtOAc = 20/1) to yield **6**: white solid; m.p. 91–93°C; yield 311.36 mg (32%); ^{1}H NMR (600 MHz, $CDCl_3$), δ 7.60 (d, J = 16.2 Hz, 1H, ArCH=CH), 7.42 (d, J = 1.8 Hz, 1H, ArH), 7.36 (s, 1H, ArCH=C), 7.18 (dd, J = 8.4 Hz, 1.8 Hz, 1H, ArH), 7.13 (d, J = 1.8 Hz, 1H, ArH), 7.09 (d, J = 8.4 Hz, 1H, ArH), 6.98 (dd, J = 8.4 Hz, 1.8 Hz, 1H, ArH), 6.76 (d, J = 8.4 Hz, 1H, ArH), 6.31 (d, J = 16.2 Hz, 1H, ArCH=C*H*), 5.23 (s, 2H, CH_3OCH_2O), 4.26–4.22 (m, 4H, 2 × CH_3CH_2), 3.98 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.48 (s, 3H, CH_3OCH_2O), 1.33 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.22 (t, J = 7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$), δ 167.1 (C=O), 164.4 (C=O), 161.8, 149.6, 149.4, 148.9, 148.2, 144.2, 129.6, 127.5, 121.9, 120.4, 116.9, 116.2, 115.6, 111.0, 109.9, 105.2, 95.1, 60.5, 60.2, 56.4, 56.1, 55.9, 14.3, 14.2; HRMS (ESI): M/Z $[M]^+$ calcd for $C_{26}H_{30}O_9$: 486.1890; found: 486.1898.

*2-[4-(2-Carboxyeth-1-en-1-yl)-2-methoxyphenoxy]-3-[3-methoxy-4-(methoxymethoxy)phenyl]prop-2-enoic acid (**7**)*

To an oven-dried round-bottom flask (50 mL) charged with a solution of ester **6** (50.0 mg, 0.103 mmol) in EtOH (1 mL) was added 3 M aqueous solution of NaOH (3 mL). The mixture was stirred and reflux for 6 h. After cooling and concentration, diethyl ether (10 mL) and 3.0 M aqueous acetic acid (6 mL) were added at 0°C. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with water (3 × 20 mL) and brine (3 × 20 mL), and dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified by recrystallization (EtOAc/petroleum ether = 3/1) to yield **7**: white solid; m.p. 187–189°C; yield 42 mg (95%); ^{1}H NMR (500 MHz, DMSO-d_6), δ 7.51 (d, J = 16 Hz, 1H, ArCH=CH), 7.49 (s, 1H, ArH), 7.43 (s, 1H, ArH), 7.38 (s, 1H, ArCH=C), 7.23 (d, J = 8 Hz, 1H, ArH), 7.12 (d, J = 8 Hz, 1H, ArH), 7.03 (d, J = 8 Hz, 1H, ArH), 6.68 (d, J = 8 Hz, 1H, ArH), 6.47 (d, J = 16 Hz, 1H, ArCH=CH), 5.16 (s, 2H, CH_3OCH_2O), 3.91 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.34 (s, 3H, CH_3OCH_2O); ^{13}C NMR (125 MHz, DMSO-d_6), δ 173.0 (C=O), 169.3 (C=O), 154.6, 153.9, 152.4, 152.1, 148.9, 143.8, 134.1, 131.6, 131.4, 128.9, 127.3, 122.9, 121.2, 118.6, 118.3, 116.8, 99.7, 61.1, 61.0, 60.4; HRMS (ESI): M/Z $[M]^+$ calcd for $C_{22}H_{22}O_9$: 430.1264; found: 430.1255.

*Ethyl 4-(methoxymethoxy)benzoate (**9**)*

To an oven-dried round-bottom flask (100 mL) charged with a solution of **8** (3.32 g, 20 mmol) in acetone (20 mL) was added anhydrous K_2CO_3 (8.30 g, 60 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature and MOM-Cl (3.22 g, 40 mmol) was added dropwise at 0°C. After stirring for 6 h, the reaction was quenched with water and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (3 × 10 mL) and brine, and dried ($MgSO_4$), and the solvent was removed in vacuo to give the corresponding protected ester.

To an oven-dried round-bottom flask (50 mL) charged with a solution of the protected ester in EtOH (20 mL) was added a 3.0 M aqueous solution of KOH (10 mL). The mixture was stirred at refluxed for 4 h. After cooling and concentration, 3.0 M aqueous acetic acid (25 mL) was added at 0°C. The crude white product was precipitated, filtered and washed with water, dried and recrystallized from ethanol to

yield compound **9**: white powder; m.p. 123–124°C (Lit.[24] 125–126°C); yield 2.91 g (80%); ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.09 (d, J = 8.7 Hz, 2H, ArH), 7.11 (d, J = 8.7 Hz, 2H, ArH), 5.24 (s, 2H, OCH_2OCH_3), 3.49 (s, 3H, OCH_2OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$), δ 170.2 (C=O), 161.3, 132.0, 122.7, 116.0, 94.2, 56.9.

*N-(4-Aminobutyl)-4-(methoxymethoxy) benzamide (**10**)*

To an oven-dried round-bottom flask (50 mL) was added **9** (182.18 mg, 1 mmol) and CDI (178.35 mg, 1.1 mmol), and the reaction mixture was mixed with a spatula to start the reaction. The reaction mixture was left at room temperature for 10 min until the solid reaction mixture turned to a pale yellow liquid. To separate round-bottom flask charged with a stirred solution of 1,4-diaminobutane (440.75 mg, 5.0 mmol) in deionized water (20 mL) was added 1,4-diaminobutane dihydrochloride (805.35 mg, 5.0 mmol), and after stirring for 20 min, NaCl (4.0 g, 68.446 mmol) was added. This brine solution was added to the flask containing the acyl imidazole and the mixture was stirred for 1 h at room temperature. The aqueous layer was washed with ethyl acetate to remove the diacylated product. Next 10 mL of a saturated solution of NaOH was added to the aqueous layer which was then extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with water (3 × 10 mL) and brine (3 × 20 mL), and dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified by flash chromatography (dichloromethane/methanol = 3/0.1) to yield **10**: yellowish oil; yield 174.08 mg (69%); ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.72 (d, J = 8.5 Hz, 2H, ArH), 6.94 (d, J = 8.5 Hz, 2H, ArH), 5.11 (s, 2H, CH_3OCH_2O), 3.39 (s, 3H, CH_3OCH_2O), 3.37–3.29 (m, 2H, $CONHCH_2$), 2.76–2.62 (m, 2H, CH_2NH_2), 1.65–1.42 (m, 4H, CH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$), δ 167.3 (C=O), 159.6, 128.8, 128.0, 115.7, 94.1, 56.1, 41.0, 39.7, 29.3, 26.9; HRMS (ESI): M/Z $[M]^+$ calcd for $C_{13}H_{20}N_2O_3$: 252.1470; found: 252.1469.

*N-(4-((E)-3-(3-methoxy-4-(((Z)-1-(3-methoxy-4-(methoxymethoxy)phenyl)-3-((4-(4-(methoxymethoxy)benzamido)butyl) amino)-3-oxoprop-1-en-2-yl)oxy)phenyl) acrylamido)butyl)-4-(methoxymethoxy) benzamide (**11**)*

To an oven-dried round-bottom flask (50 mL) charged with a solution of dicarboxylic acid intermediate **7** (40.0 mg, 0.093 mmol) in dry CH_2Cl_2 (5 mL) was added CDI (37.67 mg, 0.232 mmol) under a nitrogen atmosphere at room temperature. After stirring for 2 h, a solution of **10** (58.62 mg, 0.232 mmol) and DMAP (1.14 mg, 0.929% mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to the reaction mixture. The mixture was stirred under a nitrogen atmosphere at room temperature for 6 h. Water (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with water (3 × 10 mL) and brine (3 × 20 mL), and dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified by flash chromatography (dichloromethane/methanol = 3/0.1) to yield **11**: colorless oil; yield 47.62 mg (57%); ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.47 (d, J = 15.5 Hz, 1H, ArCH=CH), 7.36 (s, 1H, ArCH=C), 7.16 (d, J = 8.5 Hz, 1H, ArH), 7.07–7.02 (m, 7H, ArH), 6.92 (d, J = 8.5 Hz, 1H, ArH), 6.82 (d, J = 8.5 Hz, 1H, ArH), 6.77–6.40 (m, 4H, ArH), 6.33 (d, J = 15.5 Hz, 1H, ArCH=CH), 5.21 (s, 2H, CH_3OCH_2O), 5.20 (s, 2H, CH_3OCH_2O), 5.19 (s, 2H, CH_3OCH_2O), 3.95 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.48–3.44 (m, 9H, 3 × CH_3OCH_2O) 3.48–3.44 (m, 2H, $CONHCH_2$), 3.42–3.38 (m, 2H, $CONHCH_2$), 3.34–3.31 (m, 4H, 2 × $CONHCH_2$), 1.70–1.60 (m, 4H, CH_2CH_2), 1.52–1.39 (m, 4H, CH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$), δ 167.3, 167.1, 166.1, 163.3, 159.8, 149.5, 149.0, 147.6, 145.7, 141.7, 139.6, 131.1, 128.7, 127.9, 126.7, 124.2, 124.1, 121.3, 120.8, 115.9, 115.7, 115.6, 113.1, 111.2, 95.2, 94.2, 56.3, 56.2, 56.0, 55.6, 39.6, 39.3, 39.1, 27.2, 27.1, 26.8, 26.5; HRMS (ESI) calcd for $C_{48}H_{58}N_4O_{13}$: 898.4000; found: 898.4007.

*Mariamide A (**1**)*

To an oven-dried round-bottom flask (50 mL) charged with a solution of compound **11** (40.0 mg, 0.045 mmol) in dry CH_2Cl_2 (2 mL) was added TFA (0.11 mL, 1.35 mmol) at room temperature. After stirring for 8 h, the solvent was removed in vacuo. The crude product was purified by flash chromatography (dichloromethane/methanol = 3/0.1) to yield **1**: white amorphous powder; yield 22.86 mg (67%) ^{1}H NMR (500 MHz, CD_3OD), δ 7.68 (d, J = 8 Hz, 2H, ArH), 7.66 (d, J = 8 Hz, 2H, ArH), 7.41 (d, J = 15.5 Hz, 1H, ArCH=CH), 7.30 (s, 1H, ArH), 7.23 (s, 1H, ArCH=C), 7.23 (s, 1H, ArH), 7.05 (d, J = 8.5 Hz, 1H, ArH), 6.96 (d, J = 8.5 Hz, 1H, ArH), 6.81–6.79 (m, 4H, ArH), 6.75 (d, J = 8.5 Hz, 1H, ArH), 6.70 (d, J = 8.5 Hz, 1H, ArH), 6.44 (d, J = 15.5 Hz, 1H, ArCH=CH), 3.94 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.40–3.36 (m, 2H, $CONHCH_2$), 3.34–3.30 (m, 2H, $CONHCH_2$), 3.27–3.24 (m, 4H, 2 × $CONHCH_2$), 1.63–1.57 (m, 4H, 2 × CH_2CH_2), 1.49–1.40 (m, 4H, 2 × CH_2CH_2); ^{13}C NMR (125 MHz, CD_3OD), δ 170.1 (C=O), 170.0 (C=O), 168.7 (C=O), 165.7 (C=O), 162.1, 161.9, 150.6, 149.6, 148.9, 147.8, 141.9, 141.2, 132.0, 130.3, 130.2, 126.6, 126.5, 126.3, 125.5, 125.1, 122.2, 121.1, 116.21, 116.19, 116.1, 115.3, 113.7, 112.3, 56.5, 56.0, 40.5, 40.4, 40.32, 40.29, 28.0, 27.9, 27.83, 27.80; HRMS (ESI): M/Z $[M]^+$ calcd for $C_{42}H_{46}N_4O_{10}$: 766.3214; found: 766.3219.

Declaration of conflicting interests

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Supplemental material

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