JOC Article

First Total Synthesis of Cyrmenin B_1

Narayan S. Chakor, Loana Musso, and Sabrina Dallavalle*

Dipartimento di Scienze Molecolari Agroalimentari, Universita' di Milano, via Celoria 2, 20133 Milano, Italy

sabrina.dallavalle@unimi.it

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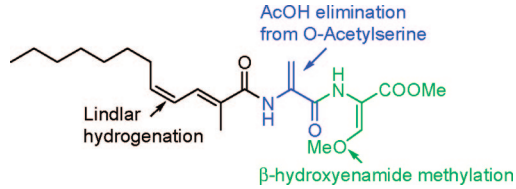


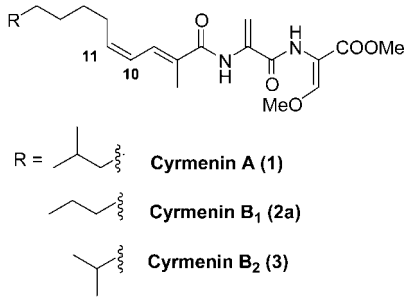
A short and efficient synthesis of cyrmenin B_1, an antifungal metabolite of myxobacteria *Cystobacter armeniaca* and *Archangium gephyra,* is described. The crucial steps of the synthesis included the formation of the dehydroalanine moiety from the corresponding serine acetate and the formation of the β-methoxyacrylate system via trimethylsilyldiazomethane methylation of the corresponding β-hydroxy enamide.

Introduction

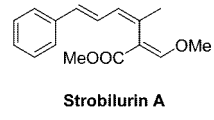
The agrochemical industry is continuously searching for new active pesticide compounds. The main goal of this research is to develop substances with lower application doses, increased selectivity, and reduced resistance, and without undesired ecological impact.[1]

Natural products have been and still are a large reservoir of new biologically active substances, and many pesticides have been developed from naturally occurring lead compounds. An outstanding example is the class of fungicides that has been generated from strobilurins, antifungal metabolites of myxobacteria.[2]

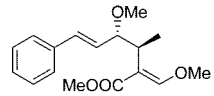
Recently, Sasse et al.[3] isolated novel antifungal metabolites, named cyrmenin A, B_1, and B_2, from the culture broth of strains of myxobacteria *Cystobacter armeniaca* and *Archangium gephyra.*



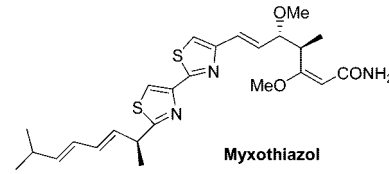
The cyrmenins are modified *N*-acyldipeptide esters containing a dehydroalanine, a 2-amino-3-methoxyacrylate moiety, and a (2*E*,4*Z*)-undecadienoic or dodecadienoic acid residue. With their two adjacent dehydro-amino acids, the cyrmenins represent a unique series of natural products. Although the substituted 2-amino-3-methoxyacrylate unit is not known to exist in other natural products, the β-methoxyacrylate system can be found in related families of natural fungicides such as strobilurins,[2] oudemansins,[4] and myxothiazol.[5]



Strobilurin A



Oudemansin



Myxothiazol

Like the compounds belonging to the aforementioned groups of fungicides, cyrmenins inhibit mitochondrial respiration by blocking electron transfer between cytochrome b and cytochrome c1.[3b] They exhibit high activity against *Botrytis cinerea*, *Pythium debaryanum*, *Hansenula anomala*, and *Metschnikowia pulcherrima*, showing at the same time an exceptionally low toxicity for animal cell cultures.[3b]

Although cyrmenins have attracted considerable attention, no total syntheses of these novel compounds have been reported

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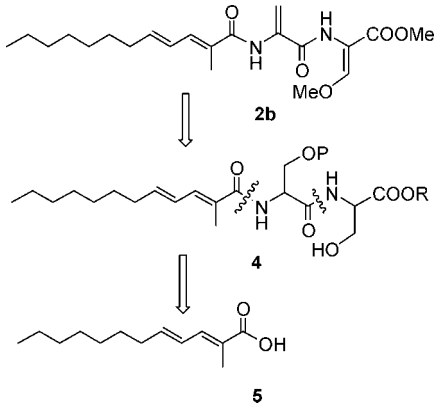
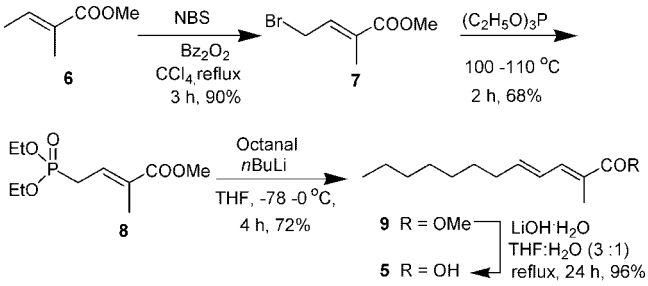
SCHEME 1. Retrosynthetic Analysis



SCHEME 2



so far. As part of a research program aimed at studying new antifungal compounds, we have developed a synthetic pathway which may, in principle, have value in the preparation of cyrmenins themselves as well as in synthesizing different analogues.

In this paper, we detail the efforts aimed at the preparation of cyrmenin B_1 (**2a**). The methodology developed could support future structure−activity relationship studies.

Results and Discussion

In order to check the feasibility of the synthesis, we decided to use as a model compound the unknown (8*E*,10*E*) isomer of cyrmenin B_1 (**2b**). The retrosynthetic analysis (Scheme 1) identified compound **4**, deriving from dienoic acid **5** and two units of serine, as possible precursors.

For the synthesis of the acid moiety of **2b** (Scheme 2) we started from commercially available methyl tiglate **6** and converted it into bromide **7** by NBS bromination. The Arbuzov reaction afforded phosphonate **8**,[6] which was subsequently condensed with octanal, to furnish all-*E* ester **9** in 72% yield. Hydrolysis with LiOH in THF/H_2O afforded acid **5**.

With diene acid **5** now prepared, we began to construct the complete carbon skeleton of cyrmenin by installing the two amino acid fragments. A first coupling with serine methyl ester hydrochloride, using BOP as a condensing agent, provided amide alcohol **10** in 96% yield. Mesylation, followed by eliminating the mesyl group with TEA (10 equiv), gave ester **11** that was hydrolyzed to give acid **12** in 20% yield. Even though this acid proved to be unstable (partial polymerization), it was coupled with *O*-(*tert*-butyldimethylsilyl)serine[7] using isobutyl chloroformate and 4-methylmorpholine as a base to afford compound **13** in 83% yield. Deprotection of the *O*-(*tert*-butyldimethylsilyl) group afforded alcohol **14** in 52% yield. However, many attempts to oxidize the alcohol with a variety of oxidizing reagents to the corresponding aldehyde for further functionalization failed, giving decomposition products (Scheme 3).

Reasoning that this instability was due to the dehydroalanine moiety, we postponed the introduction of the double bond until a later stage in the synthetic pathway. Therefore, amide alcohol **10** was protected with TBDPSCl to give ester **15** that was hydrolyzed to afford the acid **16**. This acid was coupled with serine methyl ester using BOP and $i\text{Pr}_2\text{NEt}$ to give **17** in 53% yield, thus assembling the complete carbon skeleton. Several trials for oxidation using PCC, PDC, and TEMPO gave decomposition of starting material, while with Dess-Martin periodinane and Swern oxidation no reaction occurred. Finally, the use of IBX for 7 h at reflux in ethyl acetate afforded aldehyde **18** in quantitative yield.

One of the critical structural features of cyrmenin is the β-methoxyacrylate group. On the basis of the existing literature for related substructures,[8] we reasoned that a useful method for constructing this key unit could involve the formation of the dimethylacetal of aldehyde **18** that, via elimination of methanol, could give the required β-methoxyacrylate. Accordingly, we prepared the dimethylacetal of **18**, but the elimination of methanol under either acidic or basic conditions was unsuccessful, even after several attempts. However, taking into account the possible enolization of **18**, we treated it with $TMSCHN_2$ in MeOH/toluene[9] to obtain a crude product that was purified by flash chromatography. The desired methyl β-methoxyacrylate derivative **19** was isolated as a single isomer (*Z*, 63% yield) together with decomposition products (Scheme 4).

The *Z*-configuration of the newly introduced β-methoxyacrylate moiety in **19** was elucidated by inspection of the ^{1}H NMR chemical shift of the proton at the β-position. In fact, the chemical shift of the H-2′ proton (7.35 ppm) is in agreement with the reported value for the *Z*-isomer of 2-benzoylamino-3-methoxyacrylic acid methyl ester (7.31 ppm), which is used as a model compound.[3b] The chemical shifts of the corresponding proton in the *E* isomer of 2-benzoylamino-3-methoxyacrylic acid methyl ester, strongly deshielded by the carbonyl group, was shifted to 8.08 ppm. Moreover, in natural cyrmenins, this signal is located at 7.32−7.33 ppm.[3b]

Deprotection of the silyl ether by treatment with TBAF gave the free dipeptide alcohol **20** in 75% yield. A crucial step in this synthesis was the formation of the dehydroalanine moiety. There is ample literature[10] to prepare dehydro-amino acids from the corresponding alcohols via mesyl formation followed by use of a base-like TEA or DBU. However, with alcohol **20** we observed the predominant formation of oxazoline **21**, most probably because of the proximity of the amido carbonyl that made formation of an intramolecular five-membered ring a favorable process.[11] Other methods reported in the literature

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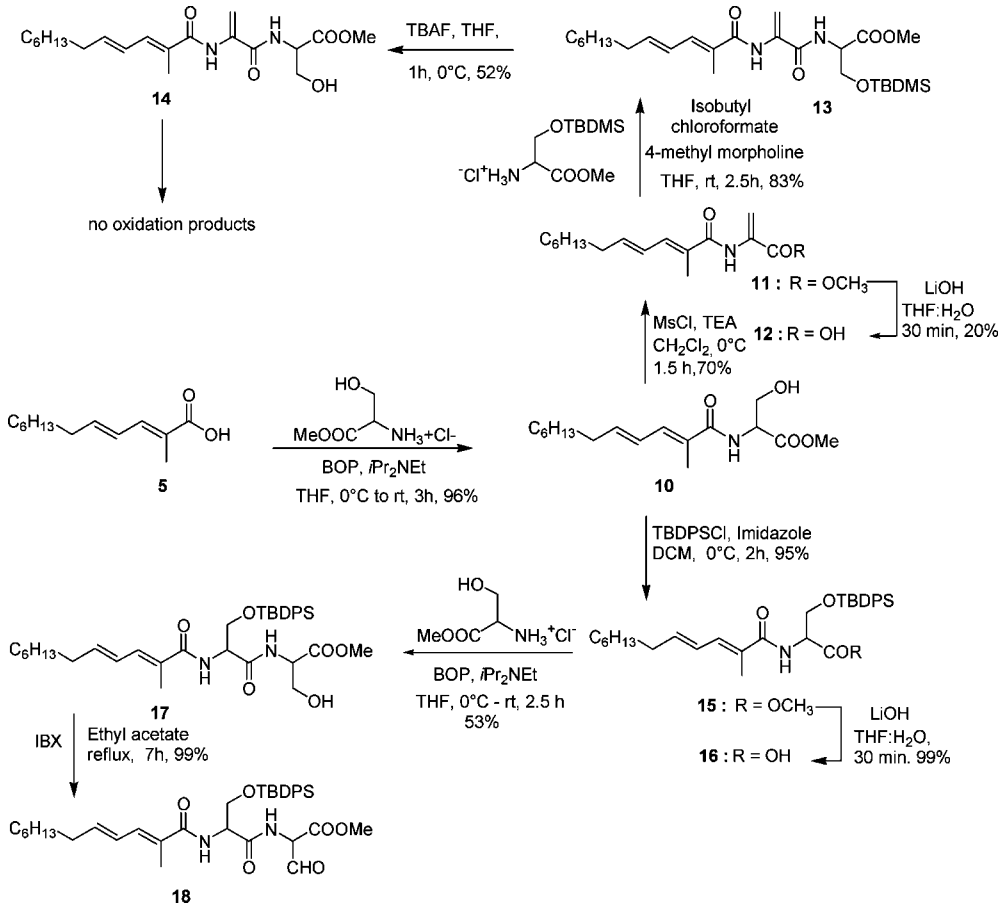
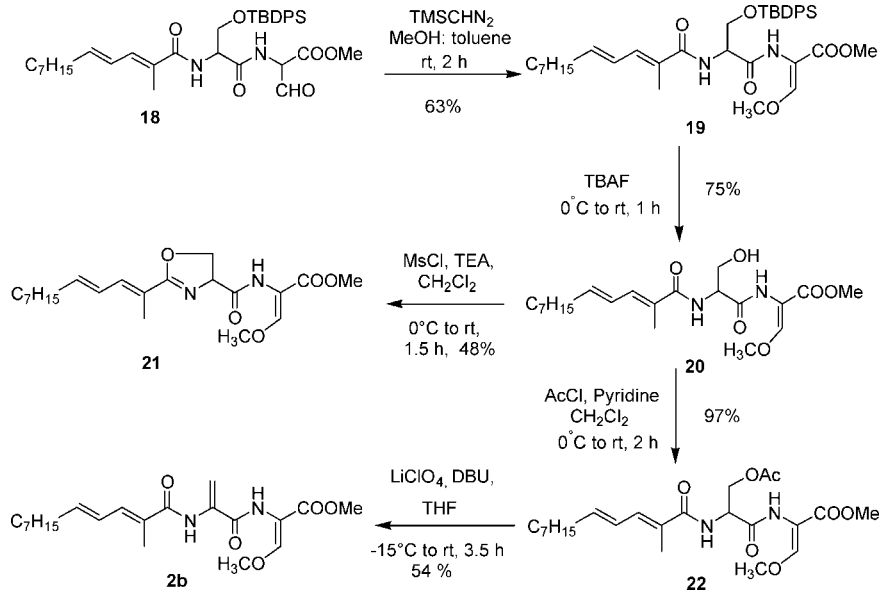
SCHEME 3



SCHEME 4



such as the use of oxalyl chloride and TEA[12] or $SOCl_2$/DBU[13] gave decomposition products, while the starting material remained unreacted with Martin sulfurane.[14] Finally, it was found that treatment of the acetyl derivative **22** with DBU at −15 °C in the presence of $LiClO_4$[15] afforded (8*E*,10*E*)-cyrmenin B_1 (**2b**) in 54% yield.

Having developed a flexible methodology for the synthesis of the geometrical isomer of cyrmenin B_1, we focused on the synthesis of the natural compound. We decided to follow the

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(13) Stohlmeyer, M. M.; Tanaka, H.; Wandless, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 6100–6101.
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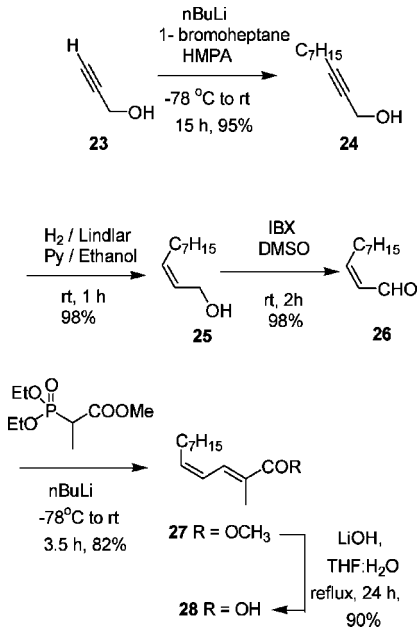
SCHEME 5



same pathway starting from acid **28**, with the 2*E*,4*Z*-configuration. A stereocontrolled approach was developed to prepare this intermediate (Scheme 5).

Alkylation of the dianion of propargyl alcohol with 1-bromoheptane gave dec-2-yn-1-ol **24**,[16] which was hydrogenated in the presence of the Lindlar catalyst to afford quantitatively (2*Z*)-dec-2-en-1-ol **25** as a single product. Oxidation with IBX to aldehyde **26** (ratio *E*/*Z*, 1:10) followed by stereoselective Horner−Wadsworth−Emmons olefination gave (2*E*,4*Z*) ester **27** in 82% yield, after column purification. The ester then was hydrolyzed to the expected acid **28**. The remaining steps of the synthesis followed the pathway already described for the 8*E*,10*E*-isomer of cyrmenin B_1 (Scheme 6).

No stereomutation of the olefinic bond of the original dienoate **28** had occurred at any stage of the synthesis, as confirmed by ^{1}H spectroscopy. The final compound, obtained in 14 steps with an overall yield of about 5%, completely matched natural cyrmenin B_1 in all spectroscopical properties and in the antifungal activity against some selected fungal strains. Evaluation of the antifungal activity of cyrmenin isomer **2b** is in progress.

In summary, the first total synthesis of cyrmenin B_1 was designed and carried out. Crucial steps for our strategy included the formation of the dehydroalanine moiety from the corresponding serine acetate and the formation of the β-methoxyacrylate moiety via trimethylsilyldiazomethane methylation of the corresponding β-hydroxy enamide. Because of the modular nature of our synthetic strategy, ready access to partial structures and preparation of congeners and analogues is available.

Experimental Section

(*Z*)-Dec-2-en-1-ol (25). A mixture of dec-2-yn-1-ol (**24**) (4 g, 1.0 mmol), EtOH (78 mL), pyridine (13 mL), and Lindlar catalyst (444 mg) was stirred at rt under a hydrogen gas atmosphere for 1 h. The mixture was filtered through a Celite pad. The filtrate was concentrated to obtain crude product which was purified by column chromatography (20% EtOAc/ hexane) to afford **25** (3.96 g, 98%) as a yellow oil. R_f = 0.53 (30% EtOAc in hexane). ^{1}H NMR ($CDCl_3$) δ: 5.45−5.65 (m, 2H), 4.16 (d, J = 6.1 Hz, 2H), 2.35 (brs, 1H), 2.05 (dt, J = 6.7, 7.0 Hz, 2H), 1.12−1.45 (m, 10H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 133.0, 128.5, 58.5, 31.9, 29.7, 29.3, 29.2, 27.5, 22.7, 14.1. HRMS (ESI$^+$) calcd for $C_{10}H_{20}ONa$ [M + Na]$^+$ 179.1406; found 179.1403.

(*Z*)-Dec-2-enal (26). Alcohol **25** (2.5 g, 15.9 mmol) was dissolved in DMSO (41 mL), and IBX (6.71 g, 23.9 mmol) was added. The resulting mixture was stirred for 2 h at rt. Water was added (30 mL), and the mixture was stirred for 5 min. The precipitate was filtered through a Celite pad, and the filtrate was extracted with Et_2O (3 × 75 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to afford **26** (2.43 g, 98%) as a yellow liquid, which was used for the next reaction without purification. R_f = 0.7 (10% EtOAc in hexane). ^{1}H NMR showed the presence of about 10% *E* isomer. ^{1}H NMR ($CDCl_3$) δ: 10.08 (d, J = 8.2 Hz, 1H), 6.62 (dt, J = 8.9, 7.2 Hz, 1H), 5.92 (dd, J = 8.2, 8.9 Hz, 1H), 2.58 (dt, J = 7.2, 7.1 Hz, 2H), 1.40−1.50 (m, 2H), 1.20−1.40 (m, 8H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 191.1, 153.7, 130.3, 31.8, 29.3, 29.1, 28.1, 22.7, 14.2. HRMS (ESI$^+$) calcd for $C_{10}H_{18}ONa$ [M + Na]$^+$ 177.1250; found 177.1255.

(2*E*,4*Z*)-3-Hydroxy-2-(2-methyldodeca-2,4-dienoylamino)-propionic Acid Methyl Ester (29). Compound **28** (Supporting Information, 1.70 g, 8.09 mmol) was dissolved in THF (150 mL), BOP (3.94 g, 8.90 mmol), and serine methyl ester hydrochloride (1.25 g, 8.09 mmol), and the resulting suspension was treated with *i*Pr_2NEt (3.05 mL, 17.82 mmol) and stirred for 3.5 h at rt. The organic solvent was removed under reduced pressure. The residue was dissolved in EtOAc (200 mL) and washed with 1 N HCl, water, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated, and then the residue was purified by flash chromatography to afford **29** (2.39 g, 95%) as a pale yellow solid. Mp: 38 °C. R_f = 0.55 (75% EtOAc in hexane). ^{1}H NMR ($CDCl_3$) δ: 7.29 (d, J = 10.9 Hz, 1H), 6.82 (d, J = 5.91 Hz, 1H), 6.25 (dd, J = 10.9, 10.4 Hz), 5.78 (dt, J = 10.4, 8.9 Hz, 1H), 4.62−4.70 (m, 1H), 3.90−4.10 (m, 2H), 3.76 (s, 3H), 2.25 (dt, J = 8.77, 7.44 Hz, 2H), 1.95 (s, 3H), 1.30−1.50 (m, 10H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 171.3, 169.6, 139.8, 130.1, 128.4, 123.3, 63.2, 55.2, 52.7, 31.8, 29.5, 29.2, 28.2, 22.7, 14.1, 12.6. HRMS (ESI$^+$) calcd for $C_{17}H_{29}NO_4Na$ [M + Na]$^+$ 334.1989; found 334.1985.

2-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2-((2*E*,4*Z*)-2-methyl-dodeca-2,4-dienoylamino)-propionylamino]-3-hydroxy-propionic Acid Methyl Ester (32). Ice-cooled aqueous LiOH·H_2O (0.426 g, 10.1 mmol) in water (24 mL) was added dropwise to the rapidly stirred solution of ester **30** (Supporting Information, 2.80 g, 5.09 mmol) in THF (73 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, then warmed to rt and stirred for 1 h. The reaction mixture was cooled to 0 °C, and ice-cooled 1 M HCl was added dropwise to the rapidly stirred solution causing the solution to become cloudy. The reaction mixture was partitioned between aqueous NaCl (30 mL) and EtOAc (40 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to afford **31** as white crude solid (2.69 g, 99%), which was used for the next reaction without purification. R_f = 0.59 (50% EtOAc in hexane). A mixture of **31** (1.74 g, 3.25 mmol) and serine methyl ester hydrochloride (0.60 g, 3.91 mmol) in THF (90 mL) was treated with BOP (1.73 g, 3.91 mmol) and *i*Pr_2NEt (1.22 mL, 7.17 mmol) at 0 °C. The resulting reaction mixture was stirred for 3 h at rt. The organic solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (250 mL) and washed with aqueous HCl (pH ≈ 5), water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated, and the residue was purified by flash chromatography (43% EtOAc in hexane) to give **32** (1.10 g, 53%) as a white solid. Mp: 126 °C. R_f = 0.67 (70%

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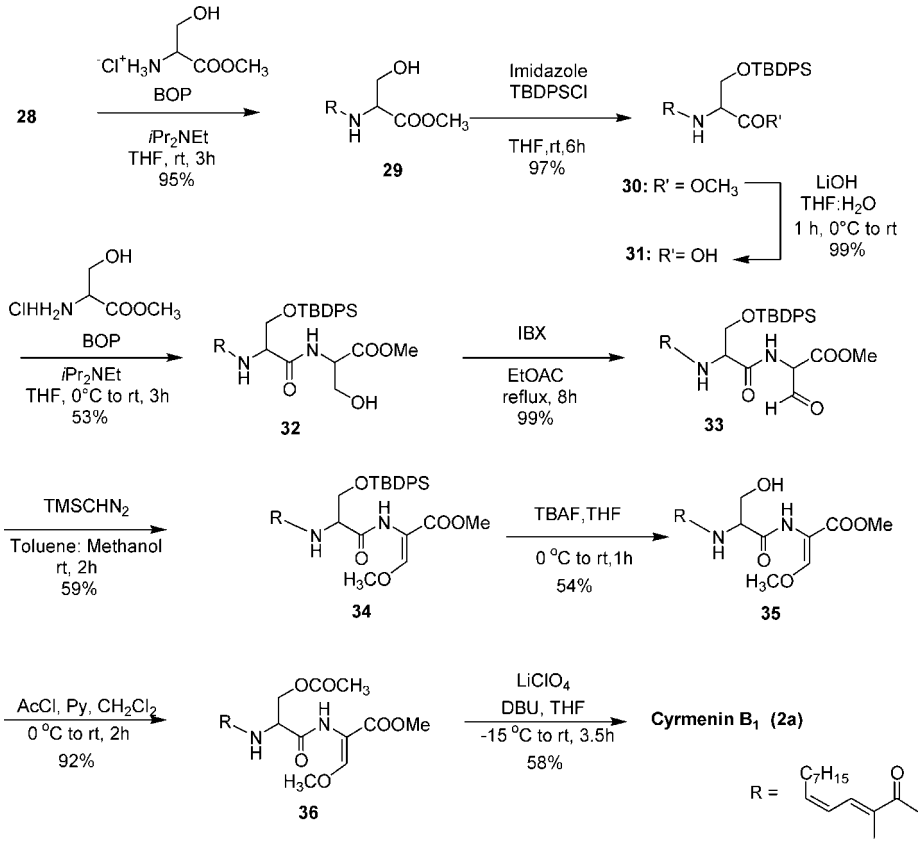
SCHEME 6



EtOAc in hexane). ^{1}H NMR ($CDCl_3$) δ: 7.56−7.67 (m, 4H), 7.37−7.47 (m, 7H), 7.18 (d, J = 7.4 Hz, 1H), 6.75 (d, J = 6.5 Hz, 1H), 6.23 (dd, J = 10.7, 7.4 Hz, 1H), 5.80 (dt, J = 10.7, 7.6 Hz, 1H), 4.55−4.65 (m, 2H), 3.75−4.20 (m, 4H), 3.76 (s, 3H), 2.25 (dt, J = 7.6, 6.7 Hz, 2H), 2.12 (brs, 1H), 1.94 (s, 3H), 1.20−1.50 (m, 10H), 1.10 (s, 9H), 0.86 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 170.1, 169.6, 169.2, 139.5, 135.0, 134.9, 134.3, 132.2, 131.8, 129.6, 127.7, 127.4, 122.7, 63.1, 62.2, 54.8, 54.6, 52.3, 31.3, 29.0, 28.8, 28.7, 27.7, 26.3, 22.1, 18.7, 13.6, 12.0. HRMS (ESI$^+$) calcd for $C_{36}H_{52}N_2O_6SiNa$ [M + Na]$^+$ 659.3487; found 659.3490.

2-[3-(*tert*-Butyl-diphenyl-silanyloxy)-2-((2*E*,4*Z*)-2-methyl-dodeca-2,4-dienoylamino)-propionylamino]-3-methoxyacrylic Acid Methyl Ester (34). A solution of **32** (1.20 g, 1.88 mmol) in EtOAc (130 mL) was treated with IBX (1.056 g, 3.77 mmol), and the reaction mixture was warmed at reflux for 8 h. The reaction mixture was cooled to rt and filtered. The filtrate was poured into 10% aqueous $Na_2S_2O_4$ (10 mL), and the mixture was stirred for 1 h. The mixture was extracted with EtOAc (4 × 50 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford **33** as a crude unstable product (1.18 g, 99%), which was immediately used for the next reaction without purification. R_f = 0.42 (20% EtOAc in hexane). Compound **33** (1.10 g, 1.73 mmol) in MeOH/toluene (1:1, 200 mL) at rt was treated with trimethylsilyldiazomethane (2 M in hexane, 2.15 mL, 4.33 mmol), and the reaction mixture was stirred for 2 h at rt. The organic solvents were removed under reduced pressure, and the residue was purified by flash chromatography (38% EtOAc/hexane) to afford **34** (0.67 g, 59%) as a yellow oil. R_f = 0.53 (60% EtOAc in hexane).^{1}H NMR ($CDCl_3$) δ: 7.60−7.78 (m, 5H), 7.30−7.49 (m, 8H), 6.90 (d, J = 11.2 Hz, 1H), 6.82 (d, J = 6.1 Hz, 1H), 6.25 (dd, J = 10.9, 11.1 Hz, 1H), 5.80 (dt, J = 10.9, 7.4 Hz, 1H), 4.75−4.85 (m, 1H), 4.15−4.25 (m, 1H), 3.85 (s, 3H), 3.80−3.90 (m, 1H), 3.72 (s, 3H), 2.29 (m, 1H), 1.93 (s, 3H), 1.20−1.50 (m, 10H), 1.10 (s, 9H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 171.2, 169.1, 165.3, 155.4, 135.6, 133.0, 132.4, 130.1, 129.6, 129.0, 128.0, 107.0, 63.7, 60.5, 54.2, 52.0, 31.9, 29.6, 29.3, 28.3, 26.9, 22.7, 21.3, 20.9, 14.4. HRMS (ESI$^+$) calcd for $C_{37}H_{52}N_2O_6SiNa$ [M + Na]$^+$ 671.3487; found 671.3497.

2-[3-Hydroxy-2-((2*E*,4*Z*)-2-methyl-dodeca-2,4-dienoylamino)-propionylamino]-3-methoxy-acrylic Acid Methyl Ester (35). To a solution of **34** (0.460 g, 0.709 mmol) in THF (40 mL) was added TBAF (1.0 M in THF, 0.85 mL, 0.851 mmol) at 0 °C, and then the mixture was stirred for 1 h at rt. The reaction was quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (70% EtOAc/hexane) to afford **35** (0.159 g, 54% yield) as a yellow liquid. R_f = 0.32 (EtOAc). ^{1}H NMR ($CDCl_3$) δ: 7.87 (s, 1H), 7.30 (s, 1H), 7.26 (m, 1H), 6.93 (d, J = 6.3 Hz, 1H), 6.23 (dd, J = 11.2, 10.8 Hz, 1H), 5.79 (dt, J = 10.8, 8.6 Hz, 1H), 4.62−4.69 (m, 1H), 4.16−4.20 (m, 1H), 3.87 (s, 3H), 3.50−3.75 (m, 5H), 2.26 (dt, J = 8.6, 7.1 Hz, 2H), 1.96 (s, 3H), 1.30−1.50 (m, 10H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 170.3, 170.0, 165.4, 156.2, 140.0, 130.2, 128.5, 123.4, 106.8, 63.2, 62.4, 54.3, 52.1, 31.9, 29.8, 29.6, 29.3, 20.3, 22.8, 14.2, 12.7. HRMS (ESI$^+$) calcd for $C_{21}H_{34}N_2O_6Na$ [M + Na]$^+$ 433.2309; found 433.2307.

2-[3-Acetoxy-2-((2*E*,4*Z*)-2-methyldodeca-2,4-dienoylamino)-propionylamino]-3-methoxy-acrylic Acid Methyl Ester (36). To a solution of **35** (0.112 g, 0.272 mmol) in CH_2Cl_2 (12 mL), was added pyridine (0.039 mL, 0.487 mmol) dropwise at 0 °C followed by AcCl (0.028 mL, 0.40 mmol). The resulting solution was stirred for 2 h at rt, and then it was cooled to 0 °C and quenched with 1 M HCl (2 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (47% EtOAc/hexane) to afford **36** (113 mg, 92%). R_f = 0.48 (80% EtOAc in hexane).

^{1}H NMR ($CDCl_3$) δ: 7.50 (s, 1H), 7.20−7.30 (m, 2H), 6.78 (d, J = 7.1 Hz, 1H), 6.23 (dd, J = 11.6, 10.9 Hz, 1H), 5.79 (dt, J = 10.9, 7.8 Hz, 1H, 1H), 4.92−4.96 (m, 1H, 1H), 4.54 (dd, J = 11.6, 6.5 Hz, 1H), 4.34 (dd, J = 11.6, 5.15 Hz, 1H), 3.86 (s, 3H), 3.70 (s, 3H), 2.27 (dt, J = 7.8, 7.1 Hz, 2H), 2.07 (s, 3H), 1.95 (s, 3H), 1.15−1.50 (m, 10H), 0.86 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 171.4, 169.5, 167.7, 165.2, 155.7, 139.9, 130.1, 128.5, 123.4, 106.7, 63.9, 62.4, 52.8, 52.0, 31.9, 29.8, 29.6, 29.4, 29.3, 28.3, 22.8, 21.0, 14.2, 12.7. HRMS (ESI$^+$) calcd for $C_{23}H_{36}N_2O_7Na$ $[M + Na]^+$ 475.2415; found 475.2418.

Cyrmenin B_1 (2a). Compound **36** (90 mg, 0.199 mmol) and $LiClO_4$ (0.211 g, 1.98 mmol) were dissolved in THF (7 mL) and cooled to −15 °C, and then DBU (0.033 mL, 0.218 mmol) was added dropwise. The resulting reaction mixture was stirred for 3.5 h in the same cooling bath. After dilution with EtOAc (20 mL), the organic layer was washed with 10% citric acid. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (7% Et_2O in CH_2Cl_2) to afford cyrmenin B_1 (**2a**) (45 mg, 58%) as a colorless oil. R_f = 0.41 (15% Et_2O in CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 8.50 (brs, 1H), 7.33 (s, 1H), 7.29 (d, J = 11.1 Hz, 1H), 7.08 (brs, 1H), 6.67 (d, J = 1.7 Hz, 1H), 6.24 (dd, J = 11.1, 11.4 Hz, 1H), 5.80 (dt, J = 11.4, 7.4 Hz, 1H), 5.39 (d, J = 1.7 Hz, 1H), 3.91 (s, 3H), 3.76 (s, 3H), 2.28 (dt, J = 7.4, 6.1 Hz, 2H), 1.99 (s, 3H), 1.25−1.40 (m, 2H), 1.10−1.30 (m, 8H), 0.86 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 167.9, 165.2, 162.8, 155.3, 140.1, 134.3, 130.1, 129.6, 123.5, 106.8, 102.4, 62.6, 52.2, 31.9, 29.8, 29.6, 29.3, 28.3, 22.8, 14.2, 12.6. HRMS (ESI$^+$) calcd for $C_{21}H_{32}N_2O_5Na$: $[M + Na]^+$ 415.2203; found 415.2200.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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