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Asymmetric Total Synthesis of Hetiamacins A−F

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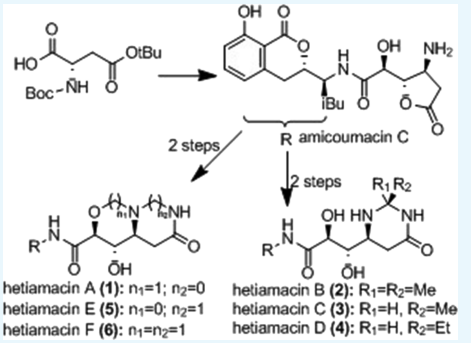
ABSTRACT: Herein, we report a concise and stereoselective approach for the asymmetric total synthesis of hetiamacins A−F on the basis of the total synthesis of amicoumacin C, which could be synthesized from a known L-aspartic acid derivative. The synthesis of hetiamacin A was accomplished by an 11-step sequence that featured 1,3-oxazinane ring formation of amicoumacin B followed by amidation in one pot. Hetiamacins B−F were synthesized from amicoumacin A in only one step.



INTRODUCTION

Hetiamacins A−F are new members of amicoumacin group antibiotics isolated from the cultured broth of *Bacillus subtilis* PJS by our group recently.[1] Amicoumacins are known to exhibit various biological properties such as antimicrobial, anticancer, antiulcer, and herbicidal activities.[2] This class of secondary metabolites produced structurally features a dihydroisocoumarin unit (left-hand amine segment) linked through an amide bond to an unusual amino acid of considerable structural diversity (right-hand acid segment), as exemplified by amicoumacins A−C.[3] The planar structures (Figure 1) of hetiamacins were elucidated by spectroscopic

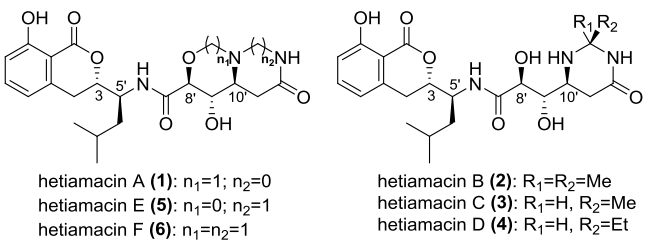


Figure 1. Structure of hetiamacins A−F

methods; however, the stereochemistry of all chiral centers on hetiamacins A−D was not originally determined. The structure of hetiamacin A was revised through the total synthesis of the initially proposed structure and the newly assigned one.[4] Also, for the other additional amicoumacin-type natural products hetiamacins B−D, their absolute configurations were unambiguously determined by Kuwahara and co-workers through their synthetic study.[5] Recently, full stereochemical assignments for hetiamacins E and F were determined by spectroscopic methods.[1c]

The synthesis of hetiamacins and other amicoumacin family members has attracted much attention due to their interesting biological activities.[6] An additional synthetic challenge involves controlling the configuration of the amino acid segment, which is susceptible to stereoisomerization. In our previous work, we succeeded in the first total synthesis of hetiamacin A, and then Kuwahara et al. accomplished the synthesis of hetiamacins A−D from a known L-aspartic acid derivative via Sharpless asymmetric dihydroxylation and Wittig reactions. Our ongoing research program that is focused on a more practical and shorter synthetic route, which allows to obtain scalable hetiamacins.

RESULTS AND DISCUSSION

Our retrosynthetic analysis of hetiamacins is outlined in Scheme 1. The hetiamacins A−F could be synthesized from amicoumacin C (**7**) as the common intermediate. The compound **7** could be obtainable via condensation of the amine segment **8** and the acid segment that would be derived from hydrolysis of N-protected lactam **9**. The lactam **9** was considered to be readily accessible by stereoselective dihydroxylation of unsaturated lactam **10** followed by protecting dihydroxy. The unsaturated lactam **10** would be traced back to N-Boc-protected aspartic acid derivative **11** by a route featuring condensation, reduction, and elimination.

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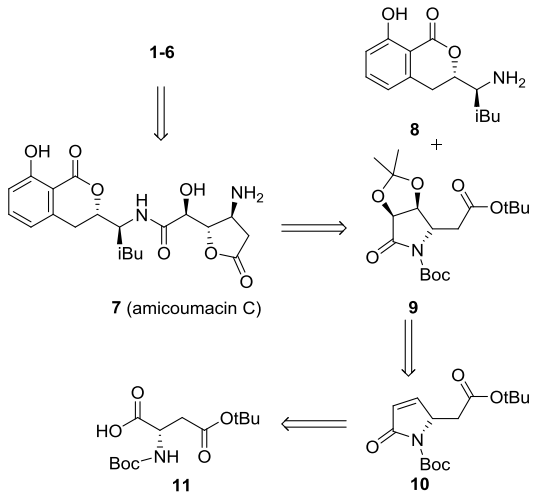
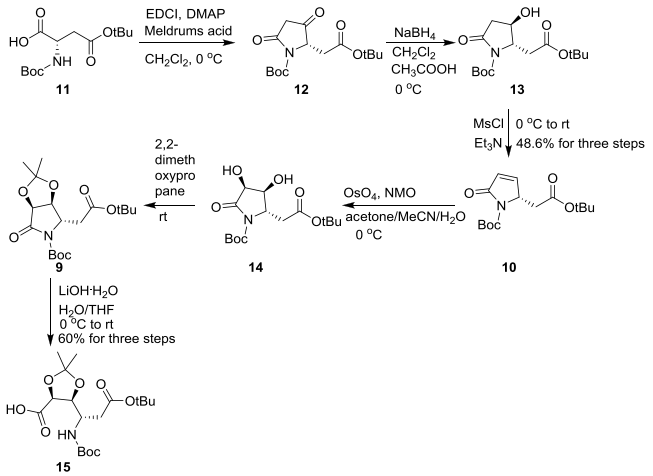
Scheme 1. Retrosynthetic Analysis of Compounds 1−6



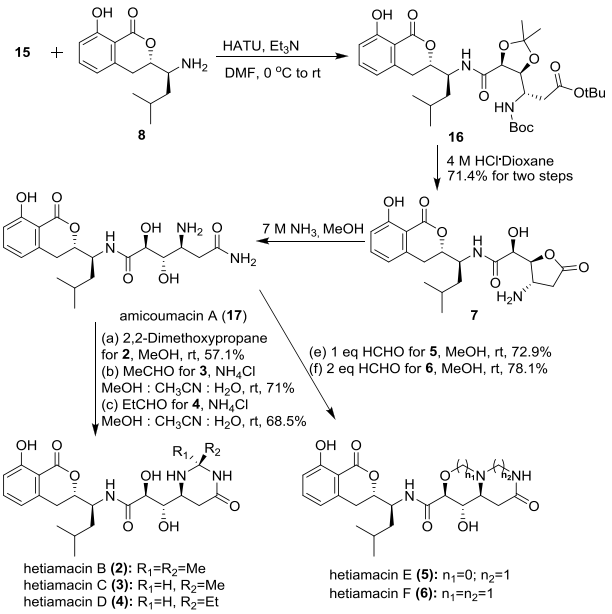
Based on the synthetic plan described above, our synthesis of hetiamacins A−F began with the conversion of **11** into *β*-hydroxy lactam **13** in 50% yield by involving the acylation of Meldrum's acid with **11** followed by deprotection and decarboxylation to produce tetramic acid **12** and then reduction by $NaBH_4$ to give *β*-hydroxy lactam **13**.[7] Subjection of **13** to a one-pot mesylation/elimination protocol quantitatively provided dehydration product **10**, which was then exposed to dihydroxylation conditions to give **14** with litter diastereomer, albeit in a moderate isolated yield of 58%. After protection of the diol **14** as its acetonide, the product **9** was hydrolyzed with $LiOH·H_2O$ in the presence of a catalytic amount of H_2O_2 to obtain the acid segment **15** (Scheme 2).[6j,h,8]

Scheme 2. Synthesis of Compound 15



The synthesis of hetiamacins B−F was performed as shown in Scheme 3. With the key intermediate **15** in hand, we proceeded to the final stage of the synthesis of compounds **1**−**6**. Coupling of the acid segment **15** with the known compound **8**, prepared according to a reported protocol,[6j] in the presence of HATU and DIEA gave compound **16** in 92% yield. Exposure of **16** to HCl in dioxane brought about deprotection of all of its three protecting groups to furnish the hydrochloride of amicoumacin C (**7**) $[\alpha]_D^{26} = -62.5$ (c = 0.024, MeOH); lit.[6c] $[\alpha]_D^{25} = -71.1$ (c = 0.34, MeOH)). Ammonolytic opening of

Scheme 3. Synthesis of Hetiamacins B−F



the *γ*-lactone moiety of compound **7** afforded amide **17** in equivalent yield, then treated with 2,2-dimethoxypropane to furnish hetiamacin B (**2**) in 57.1% yield ($[\alpha]_D^{25} = -120$ (c = 0.01, $CHCl_3$); lit.[5] $[\alpha]_D^{27} = -115$ (c = 0.08, $CHCl_3$)).[9] Application of the same step (*N*,*N*-acetal ring formation) to amide **17** (amicoumacin A) using acetaldehyde or propionaldehyde instead of 2,2-dimethoxypropane afforded compounds **3** and **4** and their epimers (14′-epi-hetiamacins C: 45%, 14′-epi-hetiamacins D: 43%) as byproducts. Therefore, we varied several factors in the reactions including temperature, additives, and solvents.[6g,10] Among the reaction conditions attempted, treatment of compound **17** with NH_4Cl and aldehyde in $MeOH:CH_3CN:H_2O$ (1:1:1) gave the best result (hetiamacin C: ($[\alpha]_D^{24} = -100$ (c = 0.02, $CHCl_3$); lit.[5] $[\alpha]_D^{26} = -99$ (c = 0.115, $CHCl_3$)) and hetiamacin D: ($[\alpha]_D^{27} = -90$ (c = 0.02, $CHCl_3$); lit.[5] $[\alpha]_D^{25} = -97$ (c = 0.155, $CHCl_3$))) and furnished the desired cyclization product up to 70% yield. The ^1H and ^{13}C NMR spectra of compounds **2**−**4** were also in good agreement with those of natural hetiamacins B−D.

The intermediate amicoumacin A (**17**) reacted with 1 equiv formaldehyde to form the *N*,*N*-acetal unit, providing hetiamacin E (**5**) in 72.9% yield and less isomer hetiamacin A with an *N*,*O*-acetal ring as products. Also, in the same process, reaction with 2 equiv formaldehyde to form the *N*,*N*-acetal unit and *N*,*O*-acetal ring gave hetiamacin F (**6**) in 78.1% yield. Based on the excellent agreement of the ^1H and ^{13}C NMR spectra of **5** and **6** with those of hetiamacins E and F from natural origin, respectively, we concluded that the relative stereostructures of hetiamacins E and F should be represented by **5** and **6** (see the Supporting Information for comparison of their ^{13}C NMR data with authentic data). The absolute configurations of hetiamacins E and F would be confirmed to be 3*S*,5′*S*,8′*S*,9′*S*,10′*S*.

The synthesis of hetiamacin A (**1**) was from the intermediate amicoumacin B (**17**), which hydrolyzed from amicoumacin C (**7**), reacted with formaldehyde to form the *N*,O-acetal unit, providing the 1,3-oxazinane derivative, and then coupled with NH_4Cl in the presence of HATU and DIEA

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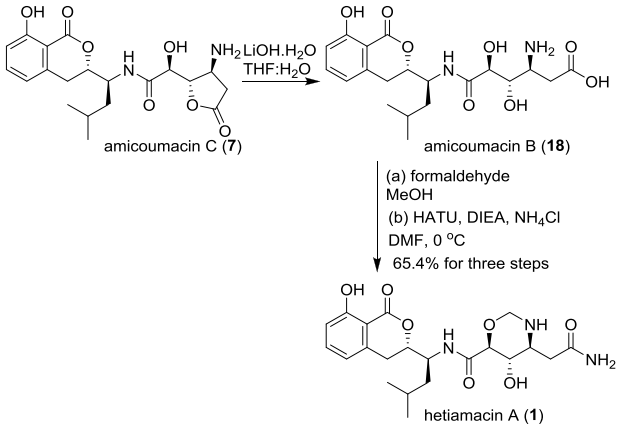
in 92% yield for three steps ($[\alpha]_D^{26}$ = −103.3 (c = 0.03, MeOH); lit.[5] $[\alpha]_D^{22}$ = −106 (c = 0.26, MeOH)) (Scheme 4).

Scheme 4. Synthesis of Hetiamacin A



CONCLUSIONS

In conclusion, the enantioselective total synthesis of hetiamacins A−F was achieved with the common intermediate amicoumacin C (**7**), which was accomplished from *N*-Boc-L-aspartic by the concise eight-step sequence of reactions. Based on the excellent agreement of the NMR spectra of the synthetic compounds with those of respective natural samples, the absolute configurations of hetiamacins E and F were concluded to be represented by structures **5** and **6**. Our efficient approach to hetiamacins would readily be applicable and economical to the synthesis of other members of amicoumacin-type natural products. Especially, the synthetic method will also facilitate the preparation of analogues for structure−activity relationship studies to develop new types of antibiotics.

EXPERIMENTAL SECTION

All reactions were carried out in oven-dried glassware under a nitrogen atmosphere employing standard techniques in handling air-sensitive materials. Chemicals were either used as received or purified according to the procedures outlined in Purification of Common Laboratory Chemicals. Glassware was dried in an oven at 160 °C or flame-dried under vacuum and cooled under an inert atmosphere before use. Unless otherwise noted, reactions were magnetically stirred and monitored by thin-layer chromatography with Sorbent Technologies 0.20 mm silica gel 60 plates. Column chromatography was performed with silica gel 300−400 supplied by Sorbent Technologies. The preparative HPLC separations were performed on a prominence system (LC−20AT, Shimadzu) instrument equipped with a binary pump and a UV−visible diode array detector (190−800 nm) using a ZORBAX SB−C18 column (9.4 × 250 mm, i.d. of 5 μm; Agilent). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded using an internal deuterium lock on Bruker 500 spectrometers or Bruker 600 spectrometers. All signals were reported in ppm with the internal references of 7.26 ppm or 77.0 ppm for chloroform, 2.50 ppm or 39.5 ppm for dimethyl sulfoxide, and 3.30 ppm or 49.1 ppm for methanol as standards. Data is presented as follows: multiplicity (s = singlet, d = doublet, t = triplet, m = mutiplet, br = broad, ABq = AB quartet, dd = doublet of doublet, and dt = doublet of triplet), coupling constant (J/Hz), and integration. Optical rotations were recorded on an Autopol IV digital polarimeter at 589 nm and reported as follows: $[\alpha]_D^T$ concentration (g/100 mL) and solvent. High-resolution mass spectra were obtained on a Waters Xevo G2-XS QTof with an ESI-QTof high-resolution mass spectrometer.

***tert*-Butyl (*S*)-2-(2-(*tert*-Butoxy)-2-oxoethyl)-3,5-dioxopyrrolidine-1-carboxylate (12).** A solution of ester **11** (5 g, 17.28 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (3.74 g, 25.92 mmol, 1.5 equiv), and DMAP (3.17 g, 25.92 mmol, 1.5 equiv) in CH_2Cl_2 (150 mL) was treated with EDCI (4.97 g, 25.92 mmol, 1.5 equiv) at 0 °C, then warmed to room temperature, and stirred for 2 h. The reaction mixture was cooled to 0 °C, diluted with EtOAc (300 mL), quenched with brine (10 mL), and then washed with 5% $KHSO_4$ (100 mL × 3) and brine (100 mL × 3). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was added to EtOAc (200 mL), refluxed for 0.5 h, and concentrated to give compound **12** as a yellow oil for the next step without being purified. $[\alpha]_D^{26}$ = −42.9 (c = 0.212, $CHCl_3$); ^{1}H NMR (500 MHz, methanol-d_4) δ 4.93 (s, 2H), 4.68 (dd, J = 6.7, 2.7 Hz, 1H), 2.97 (dd, J = 14.4, 6.7 Hz, 1H), 2.87 (dd, J = 14.4, 2.7 Hz, 1H), 1.57 (s, 9H), 1.42 (s, 9H). ^{13}C NMR (125 MHz, methanol-d_4) δ 178.31, 173.21, 169.83, 150.45, 83.87, 82.45, 58.85, 37.24, 28.39, 28.21. HRMS (ESI-TOF): m/z calcd. for $C_{15}H_{23}NO_6Na$ ($[M + Na]^+$) 336.1423, found 336.1441.

***tert*-Butyl (*S*)-2-(2-(*tert*-Butoxy)-2-oxoethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (10).** To a solution of tetramic acid **12** (5 g) in CH_2Cl_2:CH_3COOH (10:1, 99 mL) was added portionwise $NaBH_4$ (1.21 g, 31.91 mmol) over 1 h at 0 °C. The reaction was quenched with water after 10 h and then extracted with CH_2Cl_2 (100 mL × 3). The combined organic layer was washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude residue was then finally purified by flash chromatography on a silica gel (hexane:EtOAc = 1:1) to afford alcohol **13** (3 g, 60%). To a solution of alcohol **13** (2 g, 6.34 mmol) and Et_3N (1.76 mL, 12.68 mmol) in CH_2Cl_2 (50 mL) was added methanesulfonyl chloride (1.21 g, 31.91 mmol) at 0 °C. The solution was warmed to room temperature, stirred for 2 h, then added with DBU, quenched with NH_4Cl after 30 min, and extracted with EtOAc (100 mL × 3). The combined organic layer was washed with water (100 mL × 3) and brine (100 mL × 3), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude residue was then finally purified by flash chromatography on a silica gel (hexane:EtOAc = 85:15) to afford compound **10** (1.7 g, 90%) as a white solid. $[\alpha]_D^{24}$ = +158.5 (c = 0.26, $CHCl_3$); ^{1}H NMR (500 MHz, chloroform-d) δ 7.30 (dd, J = 6.1, 2.0 Hz, 1H), 6.10 (dd, J = 6.1, 1.7 Hz, 1H), 4.81 (ddt, J = 9.7, 3.7, 1.8 Hz, 1H), 3.13 (dd, J = 15.6, 3.7 Hz, 1H), 2.41 (dd, J = 15.6, 9.7 Hz, 1H), 1.55 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, chloroform-d) δ 169.08, 168.80, 150.17, 149.38, 126.95, 83.45, 81.87, 59.06, 37.85, 28.23, 28.15. HRMS (ESI-TOF): m/z calcd. for $C_{15}H_{23}NO_5Na$ ($[M + Na]^+$) 320.1474, found 320.1471.

***tert*-Butyl (2*S*,3*S*,4*S*)-2-(2-(*tert*-Butoxy)-2-oxoethyl)-3,4-dihydroxy-5-oxopyrrolidine-1-carboxylate (14).** To a solution of compound **10** (1 g, 3.36 mmol) in acetone:acetonitrile:H_2O (1:1:1, 90 mL) were added OsO_4 (13.6 mg, 0.054 mmol) and NMO (473 mg, 4.04 mmol). After

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stirring at room temperature for 48 h, the reaction was quenched by adding saturated Na_2SO_3 (100 mL) and the resultant mixture was stirred for 1 h at room temperature. The mixture was then diluted with EtOAc (300 mL). The organic layer was separated, and the aqueous phase was further extracted with EtOAc (300 mL). The combined organic layer was washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude residue was then finally purified by flash chromatography on a silica gel (hexane:EtOAc = 1:1) to afford diol **14** (0.7 g, 63.1%) as a white solid. $[\alpha]_D^{26}$ = +2.7 (*c* = 0.26, $CHCl_3$); ^{1}H NMR (500 MHz, chloroform-*d*) δ 4.43 (d, *J* = 4.8 Hz, 1H), 4.38 (dd, *J* = 10.6, 3.3 Hz, 1H), 4.31 (d, *J* = 4.8 Hz, 1H), 3.30−3.04 (m, 1H), 2.89 (s, 1H), 2.80 (dd, *J* = 15.7, 3.3 Hz, 1H), 2.42 (dd, *J* = 15.4, 10.4 Hz, 1H), 1.54 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, chloroform-*d*) δ 172.82, 169.16, 149.37, 84.30, 82.12, 70.87, 69.16, 59.79, 36.82, 28.16, 28.10. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{15}H_{25}NO_7Na$ ([M + Na]$^+$) 354.1529, found 354.1542.

***tert*-Butyl (3*aS*,4*S*,6*aS*)-4-(2-(*tert*-Butoxy)-2-oxoethyl)-2,2-dimethyl-6-oxotetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]-pyrrole-5-carboxylate (9).** To a solution of the diol **14** (200 mg, 0.6 mmol) in 2,2-dimethoxypropane (5 mL) was added P-toluene sulfonic acid and stirred at room temperature for 30 min. The solution mixture was poured into saturated $NaHCO_3$ (100 mL) and extracted with EtOAc (100 mL × 2). The organic layer was washed with water (100 mL × 2) and brine (100 mL × 2), dried over Na_2SO_4, and concentrated in vacuum to give the crude compound, and the residue was purified by flash column chromatography on a silica gel (hexane:EtOAc =85:15) to give compound **9** as a colorless oil (220 mg, 97.9%). $[\alpha]_D^{26}$ = +6.5 (*c* = 0.184, $CHCl_3$); ^{1}H NMR (500 MHz, chloroform-*d*) δ 4.81 (d, *J* = 5.7 Hz, 1H), 4.58 (d, *J* = 5.7 Hz, 1H), 4.34 (dd, *J* = 7.3, 2.8 Hz, 1H), 2.79 (dd, *J* = 16.1, 7.3 Hz, 1H), 2.71 (dd, *J* = 16.1, 2.9 Hz, 1H), 1.54 (s, 9H), 1.45 (s, 3H), 1.43 (s, 9H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, chloroform-*d*) δ 170.95, 169.57, 149.72, 112.63, 84.00, 82.23, 77.75, 76.47, 58.17, 37.38, 28.14, 28.12, 27.10, 25.61. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{18}H_{29}NO_7Na$ ([M + Na]$^+$) 394.1842, found 394.1841.

***tert*-Butyl (*S*)-3-((*tert*-Butoxycarbonyl)amino)-3-((4*S*,5*S*)-5-(((*S*)-1-((*S*)-8-hydroxy-1-oxoisochroman-3-yl)-3-methylbutyl)carbamoyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (16).** To a solution of the compound **9** (120 mg, 0.32 mmol) in THF:H_2O (1:1, 5 mL) was added LiOH·H_2O (15 mg, 0.35 mmol) and stirred at 0 °C for 1 h. The solution was acidified and extracted with EtOAc (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, and then concentrated in vacuum to give the compound **15** as a yellow oil for the next step without being further purified. To a solution of compound **15** (120 mg, 0.31 mmol), dihydroisocoumarin **8** (87 mg, 0.31 mmol), and DIEA (0.06 mL, 0.34 mmol) in CH_2Cl_2 (20 mL) was added HATU (117 mg, 0.31 mmol) at 0 °C. The solution was warmed to room temperature and stirred for 2 h. Then, the solution was added to CH_2Cl_2 (50 mL), washed with HCl (1 mol/L, 50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated in vacuum. The crude residue was purified by flash column chromatography on a silica gel (hexane:EtOAc = 85:15) to give compound **16** as a white solid (150 mg, 78.4%). $[\alpha]_D^{20}$ = −28.6 (*c* = 0.184, $CHCl_3$); ^{1}H NMR (500 MHz, chloroform-*d*) δ 10.84 (s, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 6.89 (dd, *J* = 14.2, 9.2 Hz, 2H), 6.72 (d, *J* = 7.4 Hz, 1H), 5.55 (s, 1H), 5.32 (s, 1H), 4.72−4.60 (m, 2H), 4.56 (d, *J* = 7.4 Hz, 1H), 4.43−4.35 (m, 1H), 4.25−4.16 (m, 1H), 3.05 (dd, *J* = 16.5, 13.0 Hz, 1H), 2.85 (dd, *J* = 16.6, 2.9 Hz, 1H), 2.63−2.53 (m, 1H), 1.80 (ddd, *J* = 13.5, 9.3, 5.9 Hz, 1H), 1.74−1.65 (m, 1H), 1.56 (s, 4H), 1.45 (d, *J* = 6.7 Hz, 18H), 1.38 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, chloroform-*d*) δ 170.94, 170.03, 169.82, 155.31, 139.63, 136.73, 118.46, 116.41, 110.02, 108.26, 80.92, 80.78, 76.16, 48.86, 40.55, 30.64, 28.60, 28.24, 27.05, 24.91, 24.74, 23.03, 22.36. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{32}H_{49}N_2O_{10}$ ([M + H]$^+$) 621.3382, found 621.3376.

(*S*)-2-((2*S*,3*S*)-3-Amino-5-oxotetrahydrofuran-2-yl)-2-hydroxy-*N*-((*S*)-1-((*S*)-8-hydroxy-1-oxoisochroman-3-yl)-3-methylbutyl)acetamide hydrochloride (Amicoumacin C·HCl) (7). The amide **16** (100 mg, 0.161 mmol) was added to a solution of HCl in dioxane (4 M, 2 mL) at room temperature. After stirring for 4 h, the mixture was concentrated in vacuo to give the crude compound **7** as a yellow oil. The crude compound was purified by flash column chromatography on a silica gel (CH_2Cl_2:MeOH = 40:1) to give **7** as a white solid (65 mg, 91.1%). $[\alpha]_D^{26}$ = −62.5 (*c* = 0.024, MeOH); ^{1}H NMR (600 MHz, methanol-d_4) δ 7.46−7.41 (m, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 7.4 Hz, 1H), 4.68 (ddt, *J* = 9.9, 6.2, 3.6 Hz, 1H), 4.42 (q, *J* = 2.1, 1.6 Hz, 1H), 4.19−4.12 (m, 2H), 3.17 (dd, *J* = 18.7, 8.8 Hz, 1H), 3.00 (qd, *J* = 16.5, 7.3 Hz, 2H), 2.52 (dq, *J* = 18.8, 2.6 Hz, 1H), 1.76 (dddd, *J* = 13.2, 11.0, 4.3, 1.6 Hz, 1H), 1.69−1.60 (m, 1H), 1.38 (ddd, *J* = 13.7, 9.8, 4.0 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, methanol-d_4) δ 174.95, 172.46, 171.08, 163.19, 141.03, 137.75, 119.65, 116.89, 109.38, 84.43, 82.19, 73.01, 51.27, 49.35, 40.00, 34.69, 30.92, 25.92, 23.80, 21.81. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{20}H_{27}O_7N_2$ ([M + H]$^+$) 407.1813, found 407.1841.

(4*S*,5*S*,6*S*)-4-(2-Amino-2-oxoethyl)-5-hydroxy-*N*-((*S*)-1-((*S*)-8-hydroxy-1-oxoisochroman-3-yl)-3-methylbutyl)-1,3-oxazinane-6-carboxamide (Hetiamacin A) (1). To a solution of the compound **7** (10 mg, 25 μmol) in THF:H_2O (1:1, 5 mL) was added LiOH·H_2O (2.1 mg, 25 μmol) and stirred at 0 °C for 1 h. The solution was acidified and extracted with EtOAc (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, and concentrated in vacuum to give the oil compound **18**. Then, the crude residue **18** was dissolved in methanol (5 mL) before the formaldehyde (4 mg, 50 μmol, 37%) was added. After stirring for 12 h, the solution was concentrated in vacuo to give the crude compound. To a solution of the crude compound in DMF (2 mL) were added NH_4Cl (1.9 mg, 35 μmol), DIEA (10.5 μL, 59 μmol), and HATU (12.5 mg, 35 μmol). After stirring at rt for 2 h, the solution was filtered and the filtrate was purified by prepared HPLC (MeOH:H_2O = 60:40) to give **1** (7 mg, 65.4%) as a white solid. $[\alpha]_D^{26}$ = −113.3 (*c* = 0.03, MeOH); ^{1}H NMR (600 MHz, methanol-d_4) δ 7.38 (dd, *J* = 8.4, 7.2 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 7.2 Hz, 1H), 4.60 (dt, *J* = 12.5, 3.0 Hz, 1H), 4.50 (d, *J* = 10.4 Hz, 1H), 4.29 (dt, *J* = 10.9, 4.0, 2.8 Hz, 1H), 4.15 (d, *J* = 10.5 Hz, 1H), 3.75 (d, *J* = 9.3 Hz, 1H), 3.22 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.02 (dd, *J* = 16.5, 12.5 Hz, 1H), 2.89 (dd, *J* = 9.3, 3.6 Hz, 1H), 2.84 (dd, *J* = 16.6, 3.1 Hz, 1H), 2.62 (dd, *J* = 15.3, 3.6 Hz, 1H), 2.22 (dd, *J* = 15.3, 8.8 Hz, 1H), 1.80−1.73 (m, 1H), 1.67−1.59 (m, 1H), 1.42−1.36 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, methanol-d_4) δ 176.8, 173.0, 171.0, 163.2, 141.6, 137.5, 119.5,

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116.7, 109.4, 82.9, 81.4, 79.4, 70.4, 58.8, 50.3, 40.8, 38.2, 30.9, 25.9, 23.7, 22.0; HRMS (ESI-TOF): m/z calcd. for $C_{21}H_{30}O_7N_3$ ($[M + H]^+$) 436.2078, found 436.2088.

(2*S*,3*S*,4*S*)-4-Amino-2,3-dihydroxy-*N*1-((*S*)-1-((*S*)-8-hydroxy-1-oxoisochroman-3-yl)-3-methylbutyl)-hexanediamide (Amicoumacin A) (17). The compound **7** (10 mg, 25 μmol) was dissolved in a solution of NH_3 in methanol (7 M, 3 mL). After stirring for 12 h, the mixture was concentrated in vacuo to give the crude compound **17** as a yellow oil for the next step without being further purified. $[\alpha]_D^{23}$ = −104 (c = 0.022, $CHCl_3$); ^{1}H NMR (600 MHz, chloroform-d) δ 7.39 (dd, J = 17.5, 9.6 Hz, 2H), 6.87 (d, J = 8.4 Hz, 1H), 6.69 (t, J = 6.8 Hz, 1H), 6.08 (s, 1H), 5.58 (s, 1H), 5.30 (s, 1H), 4.62 (dd, J = 11.4, 7.5 Hz, 1H), 4.32 (q, J = 9.6, 9.1 Hz, 1H), 4.04 (d, J = 8.7 Hz, 1H), 3.77−3.70 (m, 1H), 3.69−3.63 (m, 1H), 3.60 (dt, J = 8.5, 4.2 Hz, 1H), 3.43 (s, 1H), 3.30 (s, 1H), 3.05 (t, J = 14.7 Hz, 1H), 2.86−2.77 (m, 1H), 2.59 (dd, J = 24.7, 11.4 Hz, 2H), 1.84 (d, J = 13.5 Hz, 1H), 1.64 (dd, J = 14.5, 7.5 Hz, 1H), 1.54−1.43 (m, 1H), 0.96 (t, J = 7.0 Hz, 3H), 0.93 (d, J = 6.3 Hz, 3H); ^{13}C NMR (150 MHz, chloroform-d) δ 175.30, 174.06, 169.62, 162.26, 139.46, 136.59, 118.35, 116.36, 108.24, 81.00, 74.05, 72.56, 71.49, 53.80, 48.83, 40.42, 30.39, 24.93, 23.19, 22.01. HRMS (ESI-TOF): m/z calcd. for $C_{20}H_{30}O_7N_3$ ($[M + H]^+$) 424.2078, found 424.2098.

(2*S*,3*S*)-3-((*S*)-2,2-Dimethyl-6-oxohexahydropyrimidin-4-yl)-2,3-dihydroxy-*N*-((*S*)-1-((*S*)-8-hydroxy-1-oxoisochroman-3-yl)-3-methylbutyl)propanamide (Hetiamacin B) (2). A solution of compound **17** (8 mg, 19 μmol) in MeOH (5 mL) was added 2,2-dimethoxypropane (5.2 μL, 38 μmol) at room temperature. After stirring for 4 h, the mixture was concentrated in vacuo to give the crude product as a yellow oil. The crude product was purified by prepared HPLC (MeOH:H_2O = 60:40) to give **2** (5 mg, 57.1%) as a white solid. $[\alpha]_D^{25}$ = −120 (c = 0.01, $CHCl_3$); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.74 (s, 1H), 7.64 (d, J = 9.6 Hz, 1H), 7.48 (t, J = 7.9 Hz, 1H), 6.84 (dd, J = 16.1, 7.9 Hz, 2H), 5.59 (d, J = 6.0 Hz, 1H), 4.97 (d, J = 5.4 Hz, 1H), 4.70 (dt, J = 12.7, 3.0 Hz, 1H), 4.20 (ddd, J = 13.7, 10.0, 3.5 Hz, 1H), 3.91 (t, J = 6.4 Hz, 1H), 3.68−3.61 (m, 1H), 3.25−3.17 (m, 1H), 3.04 (dd, J = 16.6, 12.6 Hz, 1H), 2.86 (dd, J = 16.7, 3.0 Hz, 1H), 2.06−1.97 (m, 2H), 1.92 (d, J = 13.0 Hz, 1H), 1.67 (tdd, J = 15.9, 8.8, 4.5 Hz, 2H), 1.33 (ddd, J = 13.0, 9.0, 3.8 Hz, 2H), 1.24 (s, 3H), 1.19 (s, 3H), 0.89 (d, J = 6.5 Hz, 4H), 0.85 (d, J = 6.5 Hz, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 172.70, 169.03, 160.80, 140.65, 136.24, 118.49, 115.16, 108.29, 81.09, 73.46, 72.43, 66.80, 48.18, 47.86, 40.02, 31.71, 30.60, 29.09, 28.44, 23.96, 23.28, 21.53. HRMS (ESI-TOF): m/z calcd. for $C_{23}H_{34}O_7N_3$ ($[M + H]^+$) 464.2391, found 464.2403.

(2*S*,3*S*)-2,3-Dihydroxy-*N*-((*S*)-1-((*S*)-8-hydroxy-1-oxoisochroman-3-yl)-3-methylbutyl)-3-((2*R*,4*S*)-2-methyl-6-oxohexahydropyrimidin-4-yl)propanamide (Hetiamacin C) (3). A solution of compound **17** (8 mg, 19 μmol) in MeOH:CH_3CN:H_2O (1:1:1 3 mL) were added acetaldehyde (2.1 μL, 38 μmol) and NH_4Cl (5 mg) at room temperature. After stirring for 30 h, the mixture was filtered and the filtrate was concentrated in vacuo to give the crude product as a yellow oil. The crude product was purified by prepared HPLC (MeOH:H_2O = 60:40) to give **3** (6 mg, 71%) as a white solid. $[\alpha]_D^{24}$ = −100 (c = 0.02, $CHCl_3$); ^{1}H NMR (600 MHz, chloroform-d) δ 10.77 (s, 1H), 7.40 (t, J = 7.9 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 7.4 Hz, 1H), 6.32 (s, 1H), 6.19 (s, 1H), 4.84 (s, 1H), 4.61 (d, J = 12.9 Hz, 1H), 4.45 (q, J = 6.1 Hz, 1H), 4.34 (td, J = 10.1, 4.4 Hz, 1H), 4.02 (d, J = 9.5 Hz, 1H), 3.56 (m, J = 8.1, 6.9 Hz, 1H), 3.25 (p, J = 5.1 Hz, 1H), 3.06 (dd, J = 16.4, 13.0 Hz, 1H), 2.82 (dd, J = 16.7, 2.9 Hz, 1H), 2.64 (dd, J = 17.9, 4.2 Hz, 1H), 2.25 (dd, J = 17.8, 11.6 Hz, 1H), 1.83 (m, 2H), 1.62 (m, J = 6.4 Hz, 2H), 1.47 (m, 1H), 1.33 (d, J = 6.0 Hz, 2H), 0.94 (dd, J = 11.8, 6.5 Hz, 7H); ^{13}C NMR (150 MHz, chloroform-d) δ 174.42, 170.54, 169.50, 162.09, 139.28, 136.54, 118.25, 116.22, 108.02, 81.04, 73.25, 72.62, 63.88, 55.86, 48.75, 40.54, 33.14, 30.32, 24.81, 23.07, 22.59, 21.78. HRMS (ESI-TOF): m/z calcd. for $C_{22}H_{32}O_7N_3$ ($[M + H]^+$) 450.2235, found 450.2243.

(2*S*,3*S*)-3-((2*R*,4*S*)-2-Ethyl-6-oxohexahydropyrimidin-4-yl)-2,3-dihydroxy-*N*-((*S*)-1-((*S*)-8-hydroxy-1-oxoisochroman-3-yl)-3-methylbutyl)propanamide (Hetiamacin D) (4). A solution of compound **17** (8 mg, 19 μmol) in MeOH:CH_3CN:H_2O (1:1:1, 3 mL) were added propionaldehyde (2.7 μL, 38 μmol) and NH_4Cl (5 mg) at room temperature. After stirring for 30 h, the mixture was filtered and the filtrate was concentrated in vacuo to give the crude product as a yellow oil. The crude product was purified by prepared HPLC (MeOH:H_2O = 60:40) to give **4** (6 mg, 68.5%) as a white solid. $[\alpha]_D^{27}$ = −90 (c = 0.02, $CHCl_3$); ^{1}H NMR (600 MHz, chloroform-d) δ 10.78 (s, 1H), 7.46−7.38 (m, 1H), 7.22 (d, J = 10.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 7.4 Hz, 1H), 6.15 (s, 1H), 4.88 (s, 1H), 4.61 (ddd, J = 12.9, 2.9, 1.7 Hz, 1H), 4.34 (tdd, J = 10.1, 4.9, 1.7 Hz, 1H), 4.25 (t, J = 6.1 Hz, 1H), 4.06 (d, J = 9.0 Hz, 1H), 3.53 (m, 1H), 3.22 (ddd, J = 11.9, 8.2, 4.3 Hz, 1H), 3.05 (dd, J = 16.4, 13.0 Hz, 1H), 2.82 (dd, J = 16.5, 3.0 Hz, 1H), 2.76 (dd, J = 18.0, 4.2 Hz, 1H), 2.24 (dd, J = 17.9, 11.6 Hz, 1H), 1.84 (ddd, J = 13.9, 10.3, 5.2 Hz, 1H), 1.61 (ddd, J = 16.4, 13.2, 7.2 Hz, 4H), 1.48 (ddd, J = 13.9, 9.0, 4.8 Hz, 1H), 1.00 (t, J = 7.4 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, chloroform-d) δ 174.39, 169.50, 162.10, 139.27, 136.54, 118.26, 116.23, 108.00, 81.01, 68.77, 48.69, 40.54, 30.32, 29.33, 24.80, 23.06, 21.80, 8.65. HRMS (ESI-TOF): m/z calcd. for $C_{23}H_{34}O_7N_3$ ($[M + H]^+$) 464.2391, found 464.2384.

(2*S*,3*S*)-2,3-Dihydroxy-*N*-((*S*)-1-((*S*)-8-hydroxy-1-oxoisochroman-3-yl)-3-methylbutyl)-3-((*S*)-6-oxohexahydropyrimidin-4-yl)propanamide (Hetiamacin E) (5). A solution of compound **17** (8 mg, 0.19 μmol) in MeOH (5 mL) was added formaldehyde (1.5 μL, 0.19 μmol) at room temperature. After stirring for 4 h, the mixture was concentrated in vacuo to give the crude product as a yellow oil. The crude product was purified by prepared HPLC (MeOH:H_2O = 60:40) to give **5** (6 mg, 72.9%) as a white solid. $[\alpha]_D^{26}$ = −153.7 (c = 0.08, $CHCl_3$); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.84 (s, 1H), 7.64 (d, J = 9.5 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 7.50 (dd, J = 8.4, 7.4 Hz, 1H), 6.85 (dd, J = 14.9, 7.9 Hz, 2H), 5.57 (s, 1H), 4.98 (d, J = 5.6 Hz, 1H), 4.71 (dt, J = 12.7, 3.0 Hz, 1H), 4.24−4.17 (m, 1H), 4.05−3.97 (m, 2H), 3.92 (dd, J = 6.5, 2.9 Hz, 1H), 3.69 (dt, J = 6.6, 5.0 Hz, 1H), 3.08−2.98 (m, 2H), 2.87 (dd, J = 16.7, 3.0 Hz, 1H), 2.14−2.09 (m, 2H), 1.76 (s, 1H), 1.68 (dddd, J = 25.6, 13.1, 10.9, 5.6 Hz, 2H), 1.34 (td, J = 9.2, 4.4 Hz, 1H), 0.91 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 172.65, 169.36, 169.03, 160.79, 140.64, 136.24, 118.49, 115.16, 108.28, 81.12, 73.66, 72.28, 56.71, 52.56, 47.87, 40.02, 32.77, 29.10, 23.90, 23.31, 21.50. HRMS (ESI-TOF): m/z calcd. for $C_{21}H_{30}O_7N_3$ ($[M + H]^+$) 436.2078, found 436.2087.

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(3*S*,4*S*,4*aS*)-4-Hydroxy-*N*-((*S*)-1-((*S*)-8-hydroxy-1-oxoisochroman-3-yl)-3-methylbutyl)-6-oxohexahydro-1*H*,3*H*-pyrimido[1,6-*c*][1,3]oxazine-3-carboxamide (Hetiamacin F) (6). A solution of compound **17** (10 mg, 0.24 μmol) in MeOH (5 mL) was added formaldehyde (3.8 μL, 0.48 μmol) at room temperature. After stirring for 4 h, the mixture was concentrated in vacuo to give the crude product as a yellow oil. The crude product was purified by prepared HPLC (MeOH:H_2O = 60:40) to give **6** (8 mg, 78.1%) as a white solid. $[\alpha]_D^{24.5} = -105$ (c = 0.02, $CHCl_3$); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.10 (d, J = 9.2 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.46 (t, J = 7.9 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 5.28 (d, J = 6.2 Hz, 1H), 4.66 (dt, J = 12.7, 2.8 Hz, 1H), 4.48 (d, J = 9.2 Hz, 1H), 4.18 (tt, J = 11.2, 3.5 Hz, 1H), 4.14 (dd, J = 9.1, 2.7 Hz, 1H), 3.92 (d, J = 9.2 Hz, 1H), 3.69 (d, J = 9.3 Hz, 1H), 3.63 (dd, J = 9.0, 2.2 Hz, 1H), 3.44 (td, J = 9.4, 6.2 Hz, 1H), 3.14 (d, J = 4.9 Hz, 1H), 2.97 (dd, J = 16.6, 12.8 Hz, 1H), 2.79 (dd, J = 16.7, 2.9 Hz, 1H), 2.57 (dt, J = 9.5, 6.3 Hz, 1H), 2.40 (dd, J = 17.7, 6.3 Hz, 1H), 2.18 (dd, J = 17.6, 6.3 Hz, 1H), 1.68 (ddd, J = 13.5, 10.8, 4.6 Hz, 1H), 1.62−1.55 (m, 1H), 1.31 (ddd, J = 13.5, 9.4, 4.0 Hz, 1H), 0.88 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.14, 168.87, 167.68, 160.88, 140.71, 136.35, 118.59, 115.26, 108.28, 81.49, 81.03, 65.89, 59.17, 57.61, 48.18, 40.04, 32.94, 29.23, 24.13, 23.31, 21.54. HRMS (ESI-TOF): m/z calcd. for $C_{22}H_{30}O_7N_3$ ($[M + H]^+$) 448.2078, found 448.2077.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c06267.

NMR spectra of all new compounds and comparative ^{13}C NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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