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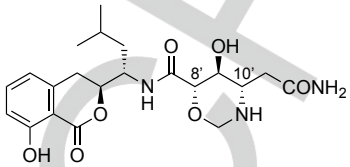
# Unified Total Synthesis of Hetiamacins A–D

Shogo Tsukaguchi,[a] Masaru Enomoto,*[a] Ryo Towada,[a] Yusuke Ogura,[a] and Shigefumi Kuwahara*[a]

**Abstract:** A concise enantioselective total synthesis of hetiamacin A has been accomplished from a known L-aspartic acid derivative by an eight-step sequence that features ammonolytic opening of the γ-lactone moiety of amicoumacin C followed by 1,3-oxazinane ring formation in one pot. Hetiamacins B–D with putatively assigned stereochemistries have also been synthesized from amicoumacin C, each in three steps involving tetrahydro-4(1*H*)-pyrimidinone ring formation. The excellent NMR spectroscopic agreement of the synthetic materials with the corresponding natural products, coupled with biosynthetic considerations, has enabled the full stereochemical assignments of hetiamacins B–D.

## Introduction

Hetiamacins A (also called PJS) (**1**), an antibacterial and cytotoxic substance isolated by Sun and co-workers from the endophytic bacterium *Bacillus subtilis* subsp. *inaquosorum*,[1] belongs to the amicoumacin family of natural products (Figure 1). Many members of this family are known to exhibit various biological properties such as antiulcer, antimicrobial, anticancer, and herbicidal activities.[2] This class of secondary metabolites produced mainly by bacteria of the genus *Bacillus* structurally features a dihydroisocoumarin unit composed of an aromatic tetraketide and a leucin molecule (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,[2a,3] xenocoumacins 1 and 2,[4] and bacilosarcins A–C.[2b,5] In their first report on the structure of hetiamacin A, Sun et al. proposed another structure for hetiamacin A on the basis of spectroscopic analysis,[1] but later they revised the structure to **1** through total synthesis of the initially proposed structure as well as the newly assigned one **1**.[6] They also isolated three additional amicoumacin-type natural products from the same species of bacterium and named them hetiamacins B, C, and D, among which hetiamacin B was found to exhibit significant antibacterial activity against Gram-positive bacteria.[7,8] Extensive spectroscopic analysis including HMBC experiments enabled them to propose the planar structures of the three hetiamacins as depicted in Figure 1. Additionally, analysis of their coupling constants and ROESY experiments indicated that the 3-H and 10'-H of hetiamacin B and the 3-H, 10'-H, and 14'-H of hetiamacins C and D should all be axially oriented.[9]



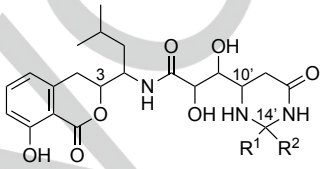




**Figure 1.** Hetiamacin A (**1**) and structures of hetiamacins B–D proposed by Sun et al.

Although full stereochemical assignments for hetiamacins B, C, and D were not shown in the paper by Sun et al.,[7] we presumed that their absolute stereostructures would most likely be represented by structures **2**, **3**, and **4**, respectively (Figure 2). This presumption is based on the following considerations: (1) the absolute configurations of all amicoumacins reported so far are, without exception, 3*S*, 5'*S*, 8'*S*, 9'*S*, and 10'*S* as shown in **2**–**4**; and (2) the putatively assigned stereochemistries of **3** and **4** are consistent with the assignments by Sun et al. that the protons at the C10' and C14' positions are both axially oriented. As part of our ongoing efforts toward the total synthesis of amicoumacin-type natural products,[10] we describe herein a unified total synthesis of hetiamacins A (**1**) and the candidate structures for hetiamacins B–D (**2**–**4**), which led to the complete stereochemical assignments of hetiamacins B–D.

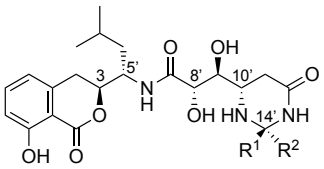



**Figure 2.** Putative stereochemistries (**2**–**4**) assigned to hetiamacins B–D.

## Results and Discussion

Scheme 1 outlines our retrosynthetic analysis of **1**–**4** via amicoumacin C (**6**) as a common synthetic intermediate. Hetiamacin A (**1**) which features a 1,3-oxazinane structural unit

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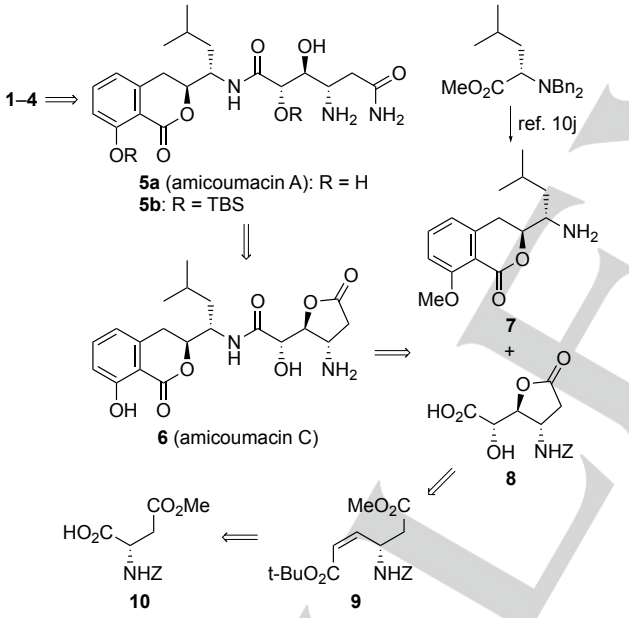
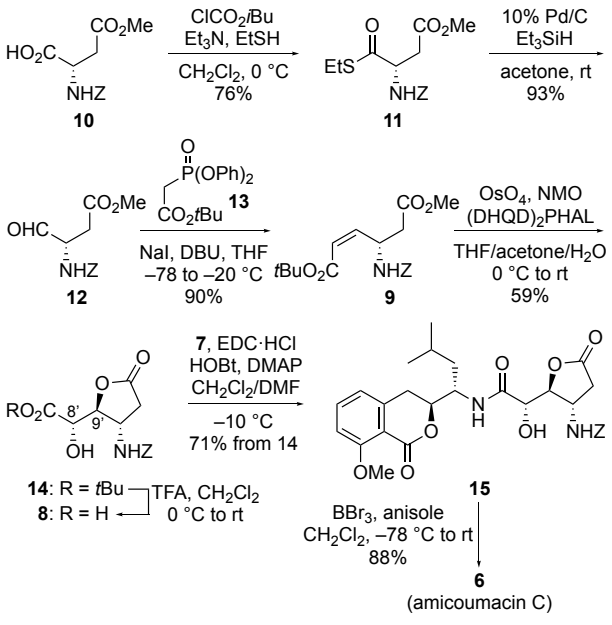
would be obtained from amicoumacin A (**5a**) by cyclic N,O-acetalization with formaldehyde at the 1,3-amino alcohol moiety. The amide **5a** is known to be preparable by selective ammonolysis of the γ-lactone of amicoumacin C (**6**), as described in our previous study.[10g] Synthesis of **2**–**4**, on the other hand, would be possible by the following sequence of reactions: (1) prior TBS-protection of the two hydroxy groups of **6** to prevent the formation of the 1,3-oxazinane ring as found in **1**; (2) ammonolytic opening of the γ-lactone ring to afford **5b**; (3) N,N-acetal ring formation between the β-amino amide moiety of **5b** and acetone, acetaldehyde, or propanal; and (4) removal of the protecting groups of the resulting N,N-acetalization products to furnish **2**, **3**, and **4**, respectively. The amide **6** was then dissected into amine segment **7** and acid segment **8**. The enantioselective preparation of **7** from methyl *N*,*N*-dibenzyl-L-leucinate in 43% overall yield through 5 steps had already been established in our total synthesis of amicoumacin C (**6**).[10j] To obtain the lactonic intermediate **8**, we planned to utilize the Sharpless asymmetric dihydroxylation on (*Z*)-α,β-unsaturated ester **9**, which in turn would be easily prepared from known aspartic acid derivative **10**.[11]



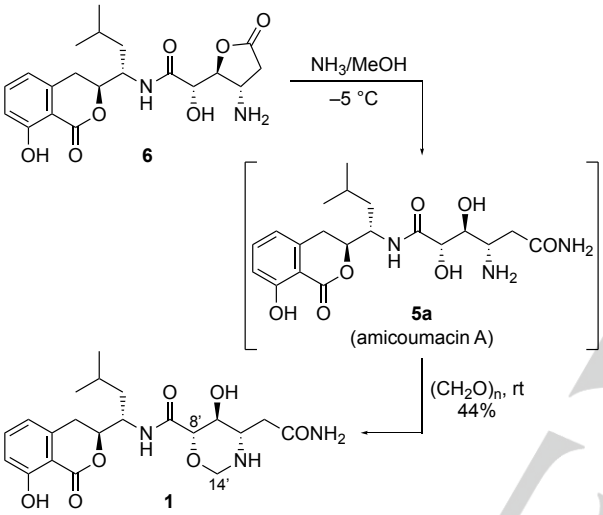

**Scheme 1.** Retrosynthetic analysis of **1**–**4**.

Our synthesis of the key intermediate **6** via the condensation of the amine segment **7** with the lactonic acid segment **8** is shown in Scheme 2. We previously reported the preparation of the N-Boc version of **8** from benzyl 4-oxo-2-butenoate by a six-step sequence beginning with the Córdova asymmetric epoxidation of the α,β-unsaturated aldehyde.[10g] The synthetic route, however, required careful ozonolytic cleavage of a diene ester (benzyl sorbate) to obtain the starting unsaturated aldehyde, and, unfortunately, gave the N-Boc protected lactonic acid in a modest overall yield of 20% as an inseparable 5:1 diastereomeric mixture. We, therefore, sought a more efficient approach to the acid segment **8**, which commenced with a two-step conversion of the protected L-aspartic acid **10** into the corresponding aldehyde **12** in 71% yield via thioester **11** (Scheme 2).[12,13] The Horner–Wadsworth–Emmons olefination of **12** with phosphonate **13** under Ando's conditions gave *Z*-olefin **9** in 90% isolated yield along with its *E*-isomer (9%),[14] the former of which was then subjected to the Sharpless asymmetric dihydroxylation using $(DHQD)_2PHAL$ as a chiral ligand.[15] This dihydroxylation reaction was accompanied by concomitant lactonization to directly afford a ca. 2:1 mixture of **14** [(8'*S*,9'*S*)-isomer] and its diastereomer [(8'*R*,9'*R*)-isomer], from which the desired product **14** was readily isolated in an acceptable yield of 59% by $SiO_2$ column chromatography. It is worth mentioning that the dihydroxylation of **9**, when conducted in the absence of the chiral ligand or in the presence of $(DHQ)_2PHAL$ [instead of $(DHQD)_2PHAL$], gave **14** and the (8'*R*,9'*R*)-isomer in a ratio of 1:1.2 or 1:4.6, respectively, favoring the undesired isomer.[16] Removal of the *t*-butyl protecting group of **14** with TFA in $CH_2Cl_2$ completed the preparation of the lactonic acid **8**. This new approach to **8**, which was realized in nearly 38% overall yield from the commercially available aspartic acid derivative **10** through 5 steps, is considered to be superior to our above-mentioned approach to the N-Boc version of **8** in overall yield as well as in conciseness, although the diastereoselectivity of the dihydroxylation step (**9** → **14**) was modest (ca. 2:1).[17] The acid segment **8** thus obtained was condensed with the amine segment **7** which was prepared according to our previously reported protocol,[10j] giving rise to amide **15**. Finally, the protected phenol and amine moieties were unmasked by treating with $BBr_3$ in $CH_2Cl_2$ in the presence of anisole to furnish amicoumacin C (**6**) ($[\alpha]_D^{20}$ = –120 (*c* = 0.070, MeOH); lit.[10g] $[\alpha]_D^{22}$ = –123 (*c* = 0.045, MeOH), lit. [10j] $[\alpha]_D^{25}$ = –120 (*c* = 0.070, MeOH)) in 23% overall yield from **10** through 7 steps.[10g,18]



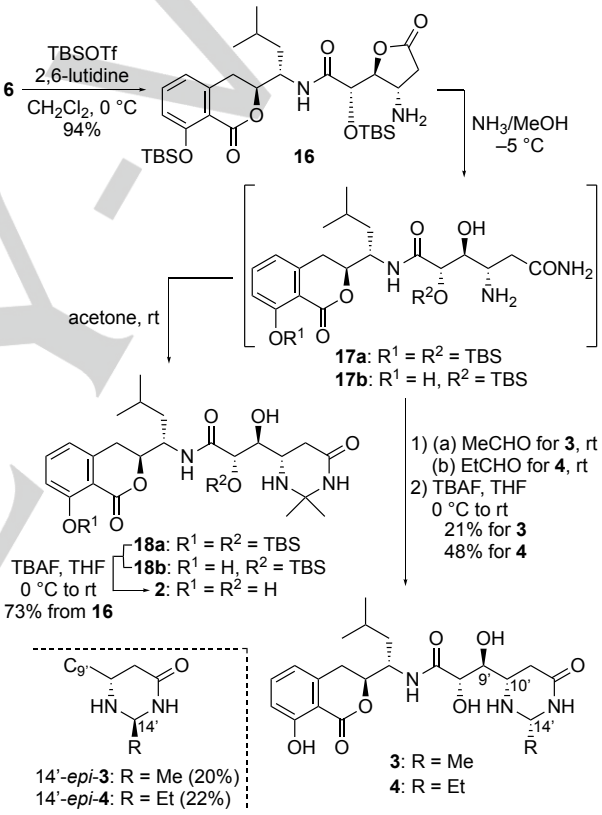
**Scheme 2.** Synthesis of amicoumacin C (**6**).

With the pivotal intermediate **6** in hand, we first undertook its conversion into hetiamacin A (**1**) (Scheme 3). Ammonolysis of **6** in methanol gave amicoumacin A (**5a**) as a labile intermediate,[10g] which was, without isolation, allowed to react with paraformaldehyde to form the N,O-acetal ring, providing hetiamacin A (**1**) ($[\alpha]_D^{20}$ = –106 (*c* = 0.260, MeOH); lit.[6] $[\alpha]_D^{22}$ = –140.0 (*c* = 0.01, MeOH)) in 44% yield. The $^1$H and $^{13}$C NMR spectra of **1** were identical with those of natural and synthetic hetiamicin A.[1,6] Formation of the 1,3-oxazinane ring was ensured by HMBC correlations from the 14'-$H_2$ to 8'-C.




**Scheme 3.** Conversion of amicoumacin C (**6**) into hetiamacin A (**1**).

The synthesis of **2**–**4**, in which the cyclic N,N-acetal unit is embedded instead of the N,O-acetal ring in hetiamacin A (**1**), was performed as shown in Scheme 4. Exposure of amicoumacin C (**6**) to TBSOTf (3 equiv) and 2,6-lutidine (6 equiv) in $CH_2Cl_2$ gave bis-TBS ether **16**. Ammonolytic opening of the γ-lactone moiety of **16** afforded a mixture of amide **17a** and its partially deprotected derivative **17b**,[19] the in-situ treatment of which with acetone then provided a mixture of N,N-acetals **18a** and **18b**. Finally, removal of their TBS protecting groups with TBAF furnished hetiamacin B (**2**) in 73% yield from **16**. The $^1$H and $^{13}$C NMR spectra of **2** were identical with those of natural hetiamacin B.[6] On the other hand, treatment of a mixture of **17a** and **17b** with acetaldehyde and subsequent TBS-deprotection delivered a mixture of **3** and its epimer (14'-*epi*-**3**), from which the former was isolated in 21% yield and the latter in 20% yield by repeated silica gel column chromatography. Application of the same two-step sequence (N,N-acetal ring formation and TBS-deprotection) to **17a**/**17b** using propanal instead of acetaldehyde afforded **4** and its epimer (14'-*epi*-**4**) in isolated yields of 48% and 22%, respectively. The $^1$H and $^{13}$C NMR spectra of **3** and **4** were also in good agreement with those of natural hetiamacins C and D, respectively.[6] The stereochemical assignments for **3**, 14'-*epi*-**3**, **4**, and 14'-*epi*-**4** were corroborated by some diagnostic NOE correlations and coupling constants shown in Figure 3. Based on the excellent agreement of the $^1$H and $^{13}$C NMR spectra of **2**–**4** with those of hetiamacins B–D of microbial origin, respectively, we concluded that the relative stereostructures of hetiamacins B, C, and D should be represented by **2**, **3**, and **4**, respectively (see Supporting Information for comparison of their $^{13}$C NMR data with authentic data). At present, non-availability of chiroptical information on natural hetiamacins B–D precludes decisive determination of their absolute configuration. However, considering the stereochemical commonality of amicoumacin-type natural products produced by bacteria of the genus *Bacillus*, the absolute configurations of hetiamacins B, C, and D would also surely be shown by **2**, **3**, and **4**, respectively.




**Scheme 4.** Conversion of amicoumacin C (**6**) into **2**–**4**.

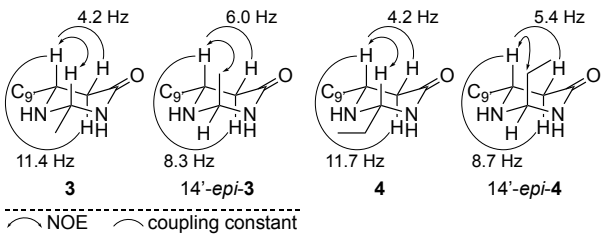



**Figure 3.** Diagnostic NOE correlations and coupling constants for **3**, 14'-*epi*-**3**, **4**, and 14'-*epi*-**4**.

## Conclusions

In conclusion, an eight-step enantioselective total synthesis of hetiamacin A (**1**) was accomplished in 12% overall yield from the protected aspartic acid **10** via ammonolytic opening of the γ-lactone moiety of amicoumacin C (**6**) followed by in-situ 1,3-oxazinane ring formation. Transformation of **6** to the putative structures (**2**–**4**) of hetiamacins B–D was also performed each in 3 steps consisting of protection, N,N-acetal ring formation, and deprotection. Base on the excellent agreement of the NMR spectra of the synthetic materials with those of respective authentic samples as well as biosynthetic considerations of the hetiamacins, the absolute configurations of hetiamacins B–D were concluded to be represented by structures **2**, **3**, and **4**, respectively.

## Experimental Section

**General Information.** IR spectra were recorded by a Jasco FT/IR-4100 spectrometer using an ATR (ZnSe) attachment. $^1$H NMR spectra were recorded with TMS as an internal standard in $CDCl_3$, while $^{13}$C NMR were obtained using residual solvent peaks as internal standards ($CHCl_3$, $\delta$ 77.0; $CHD_2OD$, $\delta$ 49.0) by a Varian 400-MRTT spectrometer (400 MHz for $^1$H and 100 MHz for $^{13}$C) or a Varian 600TT spectrometer (600 MHz for $^1$H and 150 MHz for $^{13}$C). Optical rotation values were measured with a Jasco P-2200 polarimeter. Mass spectra were obtained with Jeol JMS-700 spectrometer operated in the FAB mode. Melting points were determined with a Yanaco MP-J3 apparatus and are uncorrected. Kanto Chemical silica gel 60N (spherical neutral, 40–50 μm or 63–210 μm) was used for column chromatography. Analytical thin-layer chromatography was performed using Merck silica gel 60 $F_{254}$ plates (0.25 mm thick). Solvents for reactions were distilled prior to use: THF from Na and benzophenone; $CH_2Cl_2$ and DMF from $CaH_2$; acetone from $CaCl_2$. All air- or moisture-sensitive reactions were conducted under an argon atmosphere.

**Methyl (*S*)-3-{[(Benzyloxy)carbonyl]amino}-4-(ethylthio)-4-oxobutanoate (11)**. To a stirred solution of **10** (2.00 g, 7.11 mmol) in $CH_2Cl_2$ (24 mL) were successively added $ClCO_2$*i*Bu (1.03 mL, 7.94 mmol) and $Et_3N$ (1.09 mL, 7.82 mmol) at 0 °C. After 15 min of stirring, EtSH (0.682 mL, 9.21 mmol) and $Et_3N$ (0.995 mL, 7.14 mmol) were successively added at 0 °C and the resulting mixture was stirred for 15 min at the same temperature. The reaction mixture was quenched with $H_2O$ and extracted with $CH_2Cl_2$. The extract was washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 7:1–4:1) to give **11** (1.76 g, 76%) as a white solid. M.p. 81–82 °C; $[\alpha]_D^{20}$ = +2.7 (*c* = 0.74, $CHCl_3$); IR (ATR): $\nu$ = 3341 (m), 2954 (m), 1729 (s), 1683 (m), 1506 (m), 1225 (m), 1052 (w); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.25 (t, *J* = 7.6 Hz, 3H), 2.75 (dd, *J* = 4.5, 17.4 Hz, 1H), 2.89 (dq, *J* = 1.1, 7.6 Hz, 2H), 3.15 (dd, *J* = 4.5, 17.4 Hz, 1H), 3.68 (s, 3H), 4.70 (ddd, *J* = 4.5, 4.5, 9.8 Hz, 1H), 5.18 (s, 2H), 5.94 (br d, *J* = 9.8 Hz, 1H), 7.30–7.41 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 14.3, 23.6, 36.1, 52.1, 57.0, 67.4, 128.1, 128.3, 128.6, 136.0, 155.9, 171.4, 200.2; HRMS (FAB): *m*/*z* calcd. for $C_{15}H_{20}O_5NS$ ($[M+H]^+$) 326.1057, found 326.1065.

**Methyl (*S*)-3-{[(Benzyloxy)carbonyl]amino}-4-oxobutanoate (12)**. To a stirred mixture of **11** (1.00 g, 3.07 mmol) and 10% Pd/C (0.171g) in acetone (3.1 mL) was added dropwise $Et_3SiH$ (0.734 mL, 4.61 mmol) at room temperature. After 20 min, the mixture was diluted with $CH_2Cl_2$. The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1–1:1) to give **12** (0.758 g, 93%) as a white solid. M.p. 68–70 °C; $[\alpha]_D^{24}$ = −10 (*c* = 0.15, $CHCl_3$); IR (ATR): $\nu$ = 3353 (s), 3034 (w), 2954 (w), 1732 (s), 1523 (s), 1455 (w), 1438 (w), 1365 (w), 1261 (s), 1058 (w); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.86 (dd, *J* = 4.6, 17.4 Hz, 1H), 3.04 (dd, *J* = 4.6, 17.4 Hz, 1H), 3.69 (s, 3H), 4.44 (ddd, *J* = 4.6, 4.6, 9.2 Hz, 1H), 5.14 (s, 2H), 5.90 (br d, *J* = 9.2 Hz, 1H), 7.32–7.38 (m, 5H), 9.66 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 34.2, 52.2, 56.3, 67.4, 128.2, 128.4, 128.6, 135.8, 156.1, 171.4, 198.6; HRMS (FAB): *m*/*z* calcd. for $C_{13}H_{16}O_5N$ ($[M+H]^+$) 266.1023, found 266.1025.

**1-(*tert*-Butyl) 6-Methyl (*S*,*Z*)-4-{[(benzyloxy)carbonyl]amino}hex-2-enedioate (9)**. To a stirred solution of **13** (0.946 g, 2.72 mmol) in THF (27 mL) were successively added NaI (0.487 g, 3.25 mmol) and DBU (0.445 mL, 2.98 mmol) at 0 °C. The mixture was stirred at the same temperature for 15 min and then cooled to –78 °C. To the mixture was added a solution of **12** (0.720 g, 2.71 mmol) in THF (6.8 mL) and the stirring was continued for 1.5 h. The mixture was warmed to –20 °C, quenched with saturated aqueous $NH_4Cl$, and extracted with EtOAc. The extract was successively washed with saturated aqueous $NaHCO_3$ and brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (toluene/EtOAc = 10:1) to give **9** (0.891 g, 90%) as a white solid. M.p. 43–46 °C; $[\alpha]_D^{24}$ = +37 (*c* = 0.45, $CHCl_3$); IR (ATR): $\nu$ = 3350 (s), 2979 (m), 1714 (s), 1527 (m), 1411 (w), 1369 (w), 1244 (m), 1159 (m), 1048 (m), 827 (w), 749 (w); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.49 (9H, s), 2.79 (dd, *J* = 4.8, 16.6 Hz, 1H), 2.91 (dd, *J* = 4.4, 16.6 Hz, 1H), 3.68 (s, 3H), 5.09 (s, 2H), 5.40-5.51 (m, 1H), 5.73 (d, *J* = 11.6 Hz, 1H), 5.82 (br d, *J* = 7.6 Hz, 1H), 6.24 (dd, *J* = 8.2, 11.6 Hz, 1H), 7.29–7.36 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 28.1, 38.8, 46.2, 51.8, 66.7, 81.1, 122.5, 128.1, 128.5 (2C), 136.4, 146.5, 155.6, 164.9, 172.0; HRMS (FAB): *m*/*z* calcd. for $C_{19}H_{26}O_6N$ ($[M+H]^+$) 364.1755, found 364.1758.

***tert*-Butyl (*S*)-2-((2*S*,3*S*)-3-{[(Benzyloxy)carbonyl]amino}-5-oxotetrahydrofuran-2-yl)-2-hydroxyacetate (14)**. To a stirred suspension of $(DHQD)_2PHAL$ (45.0 mg, 0.0578 mmol) and $OsO_4$ (2.2 mg, 0.0087 mmol) in acetone/$H_2O$ (1:1, 4.4 mL) was added a solution of **9** (0.199 g, 0.548 mmol) in THF (2.2 mL) at 0 °C. After 25 min, NMO (0.129 g, 1.10 mmol) was added, and the resulting mixture was stirred at 0 °C for 24 h. The mixture was warmed to room temperature and the stirring was continued for another 15 h. $Na_2SO_3$ (0.139 g, 1.10 mmol) was then added, and the resulting mixture was stirred for 24 h. The mixture was diluted with brine and extracted with EtOAc. The extract was successively washed with saturated aqueous $NH_4Cl$, saturated aqueous $NaHCO_3$, and brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was passed through a short pad of silica gel (hexane/EtOAc = 2:1), and the eluate was concentrated in vacuo. The residue was purified by repeated silica gel column chromatography (hexane/$Et_2O$ = 1:1) to give **14** (0.119 g, 59%) as a white solid. M.p. 136–138 °C; $[\alpha]_D^{25}$ = –12 (*c* = 0.45, $CHCl_3$); IR (ATR): $\nu$ = 3345 (s), 2980 (m), 1786 (s), 1728 (s), 1536 (s), 1456 (w), 1396 (w), 1371 (w), 1259 (s), 1157 (s), 1048 (w); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.48 (s, 9H), 2.49 (dd, *J* = 4.6, 18.2 Hz, 1H), 3.05 (dd, *J* = 9.0, 18.2 Hz, 1H), 3.18 (d, *J* = 3.6 Hz, 1H), 4.35–4.43 (m, 2H), 4.71 (br s, 1H), 5.01 (br s, 1H), 5.10 (s, 2H), 7.26–7.40 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 27.9, 35.6, 48.1, 67.2, 71.1, 84.8, 85.6, 128.3, 128.4, 128.6, 135.8, 155.1, 169.7, 174.2; HRMS (FAB): *m*/*z* calcd. for $C_{18}H_{23}O_7NNa$ ($[M+Na]^+$) 388.1367, found 388.1368.

**Benzyl {(2*S*,3*S*)-2-[(*S*)-1-Hydroxy-2-({(*S*)-1-[(*S*)-8-methoxy-1-oxoisochroman-3-yl]-3-methylbutyl}amino)-2-oxoethyl]-5-oxotetrahydrofuran-3-yl}carbamate (15)**. To a stirred suspension of **14** (0.119 g, 0.326 mmol) in $CH_2Cl_2$ (3.4 mL) was added dropwise $CF_3CO_2H$ (1.0 mL) at 0 °C. After 15 h of stirring at room temperature, the resulting solution was concentrated in vacuo and the residue (**8**) (0.101 g) was

taken up in a mixture of $CH_2Cl_2$ (3.8 mL) and DMF (2.0 mL). To the solution were successively added EDC·HCl (75.0 mg, 0.391 mmol), HOBt (59.6 mg, 0.389 mmol), DMAP (7.8 mg, 0.064 mmol) and a solution of **7** (97.4 mg, 0.370 mmol) in $CH_2Cl_2$ (4.0 mL) at –10 °C. The resulting mixture was stirred at the same temperature for 20 h, quenched with saturated aqueous $NH_4Cl$, and then extracted with $Et_2O$. The extract was washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 40:1) to give **15** (0.128 g, 71% from **14**) as a white solid. M.p. 125–130 °C (dec.); $[\alpha]_D^{28}$ = –100 (*c* = 1.78, $CHCl_3$); IR (ATR): $\nu$ = 3394 (s), 3329 (s), 2957 (m), 1784 (s), 1720 (s), 1666 (s), 1600 (w), 1585 (w), 1531 (s), 1477 (m), 1247 (s), 1173 (w), 1073 (w), 913 (w), 733 (m), 698 (w); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.85 (d, *J* = 4.4 Hz, 3H), 0.91 (d, *J* = 4.0 Hz, 3H), 1.32–1.37 (m, 1H), 1.55–1.65 (m, 1H), 1.77–1.84 (m, 1H), 2.50 (d, *J* = 18.4 Hz, 1H), 2.68 (d, *J* = 15.9 Hz, 1H), 2.95 (dd, *J* = 12.6, 15.9 Hz, 1H), 3.04 (dd, *J* = 8.7, 18.4 Hz, 1H), 3.86 (s, 3H), 4.21–4.26 (m, 1H), 4.27 (d, *J* = 12.6 Hz, 1H), 4.31–4.36 (m, 1H), 4.61 (dd, *J* = 2.4, 5.4 Hz, 1H), 4.88–4.99 (m, 3H), 5.06 (d, *J* = 12.0 Hz, 1H), 5.89 (br s, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 7.24–7.34 (m, 5H), 7.36 (d, *J* = 9.6 Hz, 1H), 7.39 (dd, *J* = 7.8, 8.4 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 21.6, 23.0, 24.7, 31.5, 36.7, 40.0, 48.0, 49.1, 56.1, 67.0, 71.7, 79.3, 85.4, 110.7, 112.8, 119.4, 128.2 (2C), 128.5, 134.9, 135.9, 141.9, 155.7, 160.9, 162.9, 170.0, 176.0; HRMS (FAB): *m*/*z* calcd. for $C_{29}H_{35}O_9N_2$ ([M+H]$^+$) 555.2337, found 555.2339.

**(*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 (amicoumacin C) (6)**. To a stirred solution of **15** (0.109 g, 0.197 mmol) and anisole (85 μL, 0.78 mmol) in $CH_2Cl_2$ (11 mL) was added dropwise $BBr_3$ (1.0 M in $CH_2Cl_2$, 0.79 mL, 0.79 mmol) at –78 °C. The mixture was gradually warmed to 0 °C over a period of 3 h and stirred at 0 °C for 18 h and then at room temperature for another 20 min. The reaction mixture was quenched by successive addition of solid $NaHCO_3$ (1.1 g) and saturated aqueous $NaHCO_3$ (0.79 mL) at 0 °C, stirred for 15 min, warmed to room temperature, and then mixed with anhydrous $Na_2SO_4$. After 30 min of stirring, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 1:0–20:1) to give **6** (70.4 mg, 88%) as a white amorphous solid. $[\alpha]_D^{20}$ = –120 (*c* = 0.070, MeOH); IR (ATR): $\nu$ = 3401 (s), 2957 (m), 1789 (m), 1733 (m), 1670 (s), 1618 (m), 1465 (w), 1232 (w), 1165 (w), 1113 (w), 1046 (w); $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ = 0.93 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 1.43 (ddd, *J* = 4.0, 10.0, 14.5 Hz, 1H), 1.61–1.74 (m, 1H), 1.82 (ddd, *J* = 4.0, 11.0, 14.5 Hz, 1H), 2.24 (dd, *J* = 3.1, 18.0 Hz, 1H), 2.94 (dd, *J* = 7.9, 18.0 Hz, 1H), 2.96–3.06 (m, 2H), 3.74 (ddd, *J* = 3.1, 3.1, 7.9 Hz, 1H), 4.32 (ddd, *J* = 4.0, 8.4, 11.0 Hz, 1H), 4.39 (d, *J* = 3.1 Hz, 1H), 4.55 (dd, *J* = 3.1, 3.1 Hz, 1H), 4.65 (ddd, *J* = 4.4, 4.4, 8.4 Hz, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 8.4, 7.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ = 21.8, 23.8, 26.0, 30.9, 38.8, 40.5, 40.9, 50.5, 73.1, 82.7, 90.0, 109.4, 116.8, 119.5, 137.6, 141.3, 163.2, 171.0, 173.2, 178.5; HRMS (FAB): *m*/*z* calcd. for $C_{20}H_{27}O_7N_2$ ([M+H]$^+$) 407.1813, found 407.1823.

**(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)**. Compound **6** (20.0 mg, 49.2 μmol) was mixed with a solution of $NH_3$ in MeOH (7 M, 1.0 mL) at –5 °C. After 18 h of stirring at –5 °C, an additional 0.20 mL of the ammonia solution was added and the resulting mixture was stirred for 17 h at –5 °C. The mixture was warmed to room temperature and paraformaldehyde (15.7 mg, 0.523 mmol) was added. The mixture was stirred for 70 min and then additional paraformaldehyde (15.3 mg, 0.509 mmol) was added. After 5 h of stirring, paraformaldehyde (7.8 mg, 0.26 mmol) was added again and the mixture was stirred for 5 min. The mixture was concentrated in vacuo and the residue was purified by repeated silica gel column chromatography ($CHCl_3$/MeOH = 40:1) to give **1** (9.4 mg, 44%) as a white solid. M.p. 100–102 °C; $[\alpha]_D^{28}$ –106 (*c* = 0.260, MeOH); IR (ATR): $\nu$ = 3341 (s), 2957 (m), 1674 (s), 1533 (m), 1464 (w), 1408 (w), 1232 (m), 1112 (w), 756 (w); $^1$H NMR (600 MHz, $CD_3OD$): $\delta$ = 0.94 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 1.44 (ddd, *J* = 4.2, 9.6, 13.8 Hz, 1H), 1.65–1.72 (m, 1H), 1.83 (ddd, *J* = 4.5, 11.1, 13.8 Hz, 1H), 2.28 (dd, *J* = 9.0, 15.0 Hz, 1H), 2.68 (dd, *J* = 3.0, 15.0 Hz, 1H), 2.89 (dd, *J* = 2.4, 16.4 Hz, 1H), 2.96 (ddd, *J* = 3.0, 9.0, 9.0 Hz, 1H), 3.08 (dd, *J* = 12.9, 16.4 Hz, 1H), 3.29 (dd, *J* = 9.0, 9.0 Hz, 1H), 3.82 (d, *J* = 9.0 Hz, 1H), 4.21 (d, *J* = 10.2 Hz, 1H), 4.34–4.37 (m, 1H), 4.56 (d, *J* = 10.2 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 7.8, 7.8 Hz, 1H); $^{13}$C NMR (150 MHz, $CD_3OD$): $\delta$ = 22.0, 23.8, 25.9, 30.9, 38.2, 40.7, 50.2, 58.8, 70.4, 79.4, 81.4, 82.8, 109.4, 116.7, 119.5, 137.5, 141.7, 163.2, 171.1, 173.0, 176.8; HRMS (FAB): *m*/*z* calcd. for $C_{21}H_{30}O_7N_3$ ([M+H]$^+$) 436.2078, found 436.2081.

**(*S*)-2-[(2*S*,3*S*)-3-Amino-5-oxotetrahydrofuran-2-yl]-2-[(*tert*-butyldimethylsilyl)oxy]-*N*-((*S*)-1-{(*S*)-8-[(*tert*-butyldimethylsilyl)oxy]-1-oxoisochroman-3-yl}-3-methylbutyl)acetamide (16)**. To a stirred solution of **6** (41.9 mg, 0.103 mmol) in $CH_2Cl_2$ (2.0 mL) were successively added 2,6-lutidine (72 μL, 0.62 mmol) and TBSOTf (71 μL, 0.31 mmol) at 0 °C and the mixture was stirred at 0 °C for 25 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$. The extract was washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 1:0–100:1) to give **16** (61.5 mg, 94%) as a white amorphous solid. $[\alpha]_D^{26}$ –88 (*c* = 0.84, $CHCl_3$); IR (ATR): $\nu$ = 3414 (w), 2956 (s), 2931 (s), 2859 (m), 1785 (s), 1737 (s), 1676 (m), 1519 (w), 1470 (s), 1255 (m), 1228 (m), 1058 (w), 844 (m); $^1$H NMR (400 MHz, $CDCl_3$) : $\delta$ = 0.06 (s, 3H), 0.13 (s, 3H), 0.23 (s, 3H), 0.25 (s, 3H), 0.92 (s, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.03 (s, 9H), 1.46–1.54 (m, 1H), 1.54–1.66 (m, 1H), 1.81 (ddd, *J* = 5.4, 10.0, 13.8 Hz, 1H), 2.28 (dd, *J* = 4.2, 18.0 Hz, 1H), 2.77 (dd, *J* = 2.5, 16.0 Hz, 1H), 2.86 (dd, *J* = 8.1, 18.0 Hz, 1H), 2.93 (dd, *J* = 12.5, 16.0 Hz, 1H), 3.75 (ddd, *J* = 3.6, 4.2, 8.1 Hz, 1H), 4.26–4.34 (m, 1H), 4.45 (ddd, *J* = 2.4, 2.5, 12.5 Hz, 1H), 4.55 (d, *J* = 2.4 Hz, 1H), 4.66 (dd, *J* = 2.4, 3.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 9.6 Hz, 1H), 7.36 (dd, *J* = 8.0, 7.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = –5.3, –5.0, –4.4, –4.3, 17.9, 18.5, 21.9, 23.0, 24.9, 25.6, 25.8, 31.9, 38.8, 40.6, 47.7, 49.0, 73.2, 78.6, 88.4, 115.9, 120.1, 120.8, 134.3, 140.9, 157.9, 161.4, 169.7, 175.2; HRMS (FAB): *m*/*z* calcd. for $C_{32}H_{55}O_7N_2Si_2$ ([M+H]$^+$) 635.3542, found 635.3542.

**(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 **16** (10.2 mg, 16.1 μmol) in 7 M $NH_3$/MeOH (1.1 mL) was stirred at –5 °C for 24 h. The mixture was warmed to room temperature and acetone (12 μL, 0.16 mmol) was added. The mixture was stirred for 24 h, and then additional acetone (6 μL, 0.08 mmol) was added. After another 19 h of stirring, acetone (6 μL, 0.08 mmol) was added again and the mixture was stirred for 5 h. Additional acetone (6 μL, 0.08 mmol) was added once more, and the resulting mixture was stirred for 3 h. The reaction mixture was concentrated in vacuo and the resulting residue (**18a**/**18b**) was mixed with a solution of TBAF (0.1 M in THF, 0.320 mL, 32.0 μmol) at 0 °C and stirred at room temperature for 5 min. To the mixture were successively added THF (1.4 mL) and silica gel [Kanto Chemical silica gel 60N (40–50 μm), 0.55 g] at 0 °C, and the resulting slurry was stirred at room temperature for 1 h. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by repeated silica gel column chromatography ($CHCl_3$/MeOH = 20:1) to give **2** (5.4 mg, 73% from **16**) as a white solid. M.p. 103–105 °C; $[\alpha]_D^{27}$ = –115 (*c* = 0.080, $CHCl_3$); IR: $\nu$ = 3288 (s), 2956 (m), 1659 (s), 1528 (w), 1462 (m), 1231 (m), 1111 (m), 754 (w); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.95 (d, *J* = 6.6

Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.42 (s, 3H), 1.44 (s, 3H), 1.44–1.50 (m, 1H), 1.60−1.68 (m, 1H), 1.87 (ddd, *J* = 5.1, 10.2, 14.1 Hz, 1H), 2.22 (dd, *J* = 11.3, 17.4 Hz, 1H), 2.61 (dd, *J* = 3.6, 17.4 Hz, 1H), 2.82 (dd, *J* = 3.0, 16.2 Hz, 1H), 3.07 (dd, *J* = 12.6, 16.2 Hz, 1H), 3.45 (ddd, *J* = 3.6, 6.6, 11.3 Hz, 1H), 3.59 (dd, *J* = 6.6, 9.6 Hz, 1H), 4.02 (d, *J* = 9.6 Hz, 1H), 4.32–4.38 (m, 1H), 4.62 (ddd, *J* = 3.0, 3.0, 12.6 Hz, 1H), 4.90 (br s, 1H), 6.25 (s, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 12.0 Hz, 1H), 7.42 (dd, *J* = 7.8, 7.8 Hz, 1H), 10.79 (s, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 21.8, 23.1, 24.8, 28.5, 30.3, 31.4, 32.6, 40.5, 48.7, 51.2, 68.1, 72.4, 73.2, 81.1, 108.0, 116.2, 118.3, 136.6, 139.3, 162.1, 169.5, 170.1, 174.6; HRMS (FAB): *m*/*z* calcd. for $C_{23}H_{34}O_7N_3$ ($[M+H]^+$) 464.2391, found 464.2401.

**(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) and 14'-*epi*-3**. A solution of **16** (10.8 mg, 17.0 μmol) in 7 M $NH_3$/MeOH (1.1 mL) was stirred at –5 °C for 24 h. The mixture was warmed to room temperature and acetaldehyde (19 μL, 0.34 mmol) was added. The mixture was stirred for 24 h, and then additional acetaldehyde (19 μL, 0.34 mmol) was added. After another 2 h of stirring, the mixture was concentrated in vacuo, and the residue was mixed with a solution of TBAF (0.1 M in THF, 0.340 mL, 34.0 μmol) at 0 °C and stirred at room temperature for 1 h. To the mixture were successively added THF (0.85 mL) and silica gel [Kanto Chemical silica gel 60N (40–50 μm), 0.54 g] at 0 °C, and the resulting slurry was stirred at room temperature for 1 h. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by repeated silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to give **3** (1.6 mg, 21%) as a white solid and 14'-*epi*-**3** (1.5 mg, 20%) as a white solid. **3**: M.p. 104–106 °C; $[\alpha]_D^{26}$ = –99 (*c* = 0.115, $CHCl_3$); IR: $\nu$ = 3295 (s), 2957 (m), 1666 (s), 1529 (w), 1464 (m), 1232 (m), 1111 (m), 756 (w); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.95 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 3H), 1.34 (d, *J* = 6.0 Hz, 3H), 1.44–1.49 (m, 1H), 1.59–1.67 (m, 1H), 1.83–1.89 (m, 1H), 2.28 (dd, *J* = 11.4, 17.6 Hz, 1H), 2.60 (dd, *J* = 4.2, 17.6 Hz, 1H), 2.83 (dd, *J* = 3.0, 16.4 Hz, 1H), 3.08 (dd, *J* = 12.9, 16.4 Hz, 1H), 3.28 (ddd, *J* = 4.2, 6.6, 11.4 Hz, 1H), 3.61 (dd, *J* = 6.6, 9.0 Hz, 1H), 4.02 (d, *J* = 9.0 Hz, 1H), 4.33–4.38 (m, 1H), 4.46 (q, *J* = 6.0 Hz, 1H), 4.62 (ddd, *J* = 1.5, 3.0, 12.9 Hz, 1H), 4.86 (br s, 1H), 6.33 (br s, 1H), 6.70 (d, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 9.6 Hz, 1H), 7.42 (dd, *J* = 7.2, 8.4 Hz, 1H), 10.78 (s, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 21.8, 22.5, 23.1, 24.8, 30.3, 32.6, 40.5, 48.7, 55.3, 63.9, 72.2, 73.3, 81.1, 108.0, 116.2, 118.3, 136.6, 139.3, 162.1, 169.6, 170.9, 174.5; HRMS (FAB): *m*/*z* calcd. for $C_{22}H_{31}O_7N_3$ ($[M+H]^+$) 450.2235, found 450.2242. 14'-*epi*-**3**: M.p. 106–108 °C; $[\alpha]_D^{26}$ = –122 (*c* = 0.075, $CHCl_3$); IR: $\nu$ = 3289 (s), 2956 (m), 1665 (s), 1528 (w), 1462 (m), 1231 (m), 1111 (m), 758 (w); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.95 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.38 (d, *J* = 5.7 Hz, 3H), 1.46–1.52 (m, 1H), 1.60–1.69 (m, 1H), 1.82–1.88 (m, 1H), 2.44 (dd, *J* = 8.3, 17.7 Hz, 1H), 2.62–2.70 (m, 1H), 2.83 (dd, *J* = 3.0, 16.5 Hz, 1H), 3.07 (dd, *J* = 13.2, 16.5 Hz, 1H), 3.45 (ddd, *J* = 6.0, 8.3, 13.8 Hz, 1H), 3.55–3.60 (m, 1H), 4.06 (d, *J* = 9.0 Hz, 1H), 4.33–4.34 (m, 1H), 4.53 (q, *J* = 5.7 Hz, 1H), 4.63 (d, *J* = 13.2 Hz, 1H), 4.97 (s, 1H), 6.52 (br s, 1H), 6.71 (d, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 9.6 Hz, 1H), 7.42 (dd, *J* = 7.8, 7.8 Hz, 1H), 10.79 (s, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 21.9, 22.1, 23.0, 24.8, 30.3, 33.2, 40.5, 48.7, 52.6, 61.1, 72.2, 73.3, 81.0, 108.0, 116.2, 118.3, 136.6, 139.3, 162.1, 169.5, 170.5, 174.3; HRMS (FAB): *m*/*z* calcd. for $C_{22}H_{31}O_7N_3$ ($[M+H]^+$) 450.2235, found 450.2238.

**(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) and 14'-*epi*-4**. A solution of **16** (12.2 mg, 19.2 μmol) in 7 M $NH_3$/MeOH (1.3 mL) was stirred at –5 °C for 36 h. The mixture was warmed to room temperature and propionaldehyde (14 μL, 0.19 mmol) was added. The mixture was stirred for 24 h, and then additional propionaldehyde (14 μL, 0.19 mmol) was added. After another 24 h of stirring, the mixture was concentrated in vacuo, and the residue was mixed with a solution of TBAF (0.1 M in THF, 0.576 mL, 57.6 μmol) at 0 °C and stirred at room temperature for 25 min. To the mixture were successively added THF (2.5 mL) and silica gel [Kanto Chemical silica gel 60N (40–50 μm), 0.98 g] at 0 °C, and the resulting slurry was stirred at room temperature for 1 h. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by repeated silica gel column chromatography ($CHCl_3$/MeOH = 20:1) to give **4** (4.3 mg, 48%) as a white solid and 14'-*epi*-**4** (2.0 mg, 22%) as a white solid. **4**: M.p. 97–101 °C; $[\alpha]_D^{27}$ = –97 (*c* = 0.155, $CHCl_3$); IR: $\nu$ = 3297 (s), 2960 (m), 1665 (s), 1530 (w), 1463 (m), 1232 (m), 1111 (m), 755 (w); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.95 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H), 1.45–1.51 (m, 1H), 1.58–1.70 (m, 2H), 1.83–1.89 (m, 1H), 2.27 (dd, *J* = 11.7, 17.6 Hz, 1H), 2.73 (dd, *J* = 4.2, 17.6 Hz, 1H), 2.83 (dd, *J* = 2.7, 16.4 Hz, 1H), 3.07 (dd, *J* = 13.2, 16.4 Hz, 1H), 3.25 (ddd, *J* = 4.2, 7.4, 11.7 Hz, 1H), 3.54 (dd, *J* = 7.4, 8.7 Hz, 1H), 4.06 (d, *J* = 8.7 Hz, 1H), 4.27 (t, *J* = 6.0 Hz, 1H), 4.36 (ddd, *J* = 3.9, 6.3, 14.1 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.91 (br s, 1H), 6.33 (br s, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 7.26 (br d, *J* = 7.2 Hz, 1H), 7.42 (dd, *J* = 8.4, 7.8 Hz, 1H), 10.79 (s, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 8.7, 21.8, 23.1, 24.8, 29.4, 30.3, 34.0, 40.5, 48.7, 56.3, 68.8, 73.0, 73.2, 81.0, 108.0, 116.2, 118.3, 136.6, 139.3, 162.1, 169.5, 170.5, 174.4; HRMS (FAB): *m*/*z* calcd. for $C_{23}H_{34}O_7N_3$ ($[M+H]^+$) 464.2391, found 464.2397. 14'-*epi*-**4**: M.p. 104–107 °C; $[\alpha]_D^{27}$ = –91 (*c* = 0.085, $CHCl_3$); IR: $\nu$ = 3296 (s), 2959 (m), 1668 (s), 1527 (w), 1463 (m), 1232 (m), 1111 (m), 756 (w); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.96 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H), 1.47–1.53 (m, 1H), 1.59–1.72 (m, 2H), 1.83–1.89 (m, 1H), 2.44 (dd, *J* = 8.7, 17.9 Hz, 1H), 2.71 (dd, *J* = 5.4, 17.9 Hz, 1H), 2.83 (dd, *J* = 3.0, 16.4 Hz, 1H), 3.07 (dd, *J* = 13.2, 16.4 Hz, 1H), 3.41 (ddd, *J* = 5.4, 8.7, 8.7 Hz, 1H), 3.54 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.07 (d, *J* = 8.7 Hz, 1H), 4.25 (t, *J* = 6.0 Hz, 1H), 4.33–4.39 (m, 1H), 4.63 (ddd, *J* = 1.8, 3.0, 13.2 Hz, 1H), 5.00 (br s, 1H), 6.37 (br s, 1H), 6.71 (d, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 9.6 Hz, 1H), 7.42 (dd, *J* = 7.2, 8.4 Hz, 1H), 10.80 (s, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 9.5, 21.9, 23.0, 24.8, 28.8, 30.3, 33.9, 40.5, 48.7, 52.9, 66.4, 72.1, 73.6, 81.0, 108.0, 116.2, 118.3, 136.6, 139.3, 162.1, 169.5, 170.2, 174.3; HRMS (FAB): *m*/*z* calcd. for $C_{23}H_{34}O_7N_3$ ($[M+H]^+$) 464.2391, found 464.2394.

## Acknowledgments

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**Keywords:** Alkaloids • Hetiamacin • Natural products • Nitrogen heterocycles • Total synthesis

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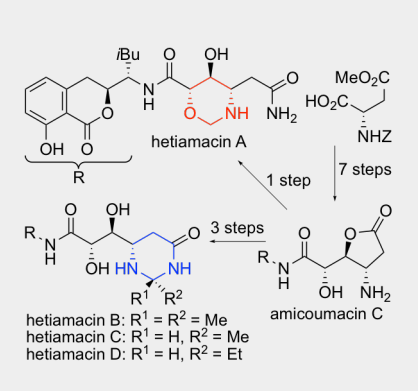
Layout 1:

# FULL PAPER

A concise total synthesis of hetiamacins A–D, members of the amicoumacin family of natural products that feature naturally rare heterocyclic ring systems, has been achieved using amicoumacin C as a common intermediate. This work is the first synthesis of hetiamacins B–D which has enabled their full stereochemical assignments.




**Natural Product Synthesis**

*Shogo Tsukaguchi, Masaru Enomoto,* Ryo Towada, Yusuke Ogura, Shigefumi Kuwahara**

***Page No. – Page No.***

**Unified Total Synthesis of Hetiamacins A–D**

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