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Enantioselective Synthesis of the *R*-Enantiomer of the Feeding Deterrent (*S*)-Ypaoamide

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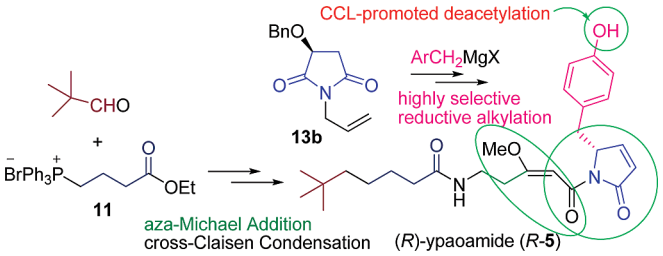

The enantioselective synthesis of the *R*-enantiomer of the marine natural product (*S*)-ypaoamide (**5**) is reported. The synthesis features both a flexible racemization-free approach to the 5-substituted 3-pyrrolin-2-one segment, and a lipase (CCL)-promoted deacetylation reaction to reach the orthogonal deprotection. Through this work the absolute configuration of the natural ypaoamide was determined as *S*.

Introduction

Many marine natural products possess diverse and important bioactivities[1,2] and/or have ecological significance.[3] The marine cyanobacteria (blue-green algae) have been proven to be a prolific source of novel bioactive natural products. Over 300 nitrogen-containing natural products have been identified from marine cyanobacteria.[2] For example, microcolins A (**1**) and B (**2**) were lipopeptides isolated from a Venezuelan sample of the blue-green alga *Lyngbya majuscula*,[4] which exhibited very potent immunosuppressive and antiproliferative properties (Figure 1).[5] Jamaicamides A−C (e.g., **3** and **4**) are a series of potent neurotoxins isolated from a chemically rich Jamaican strain of *L. majuscula*.[6] Given that immunosuppressive agents are indispensable for the success of transplantation, and microcolins A (**1**) and B (**2**) are more potent inhibitors of the human two-way mixed lymphocyte response (MLR) than FK506 and cyclosporin A, two drugs currently in clinical use in transplantation, they have attracted multidisciplinary attention.[4,5,7−9] It has been

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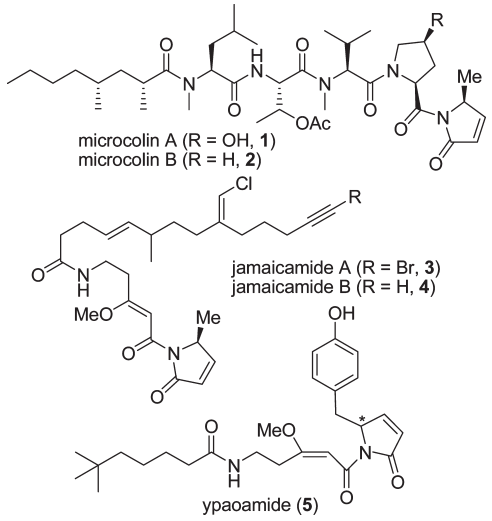

FIGURE 1. Structures of some 5-alkyl-3-pyrrolin-2-one substructure-containing marine natural products.

revealed that the 3-pyrrolin-2-one moiety is mandatory for the immunosuppressive activity.[7]

In May 1994 at Ypao Beach on Guam (a Micronesia island), a simultaneous blue-green algal bloom and a massive die off of pelagic larval rabbitfish occurred, which led to a temporary closure of the beach. From the extract of a mixed cyanobacteria assemblage, which was composed of *Schizothrix calcicola* and *Lyngbya majuscule*, ypaoamide (**5**) was isolated. It was shown that this compound can also be produced from the isolated cells of the *L. majuscula* in laboratory culture.[10] Ypaoamide was shown to be a new broadly acting feeding deterrent, and its ecological significance has been studied.[11] The structure of ypaoamide (**5**) was determined by 2D NMR and high-resolution FAB mass spectroscopy; however, its absolute configuration was not established. While ypaoamide (**5**) presents partial structural similarity with microcolins A and B (**1** and **2**),[4] jamaicamides A and B (**3** and **4**),[6] majusculamide D,[12] and malyngamides,[13] its unusual *tert*-butyl lipid side chain has little biosynthetic precedent. As a continuation of a program aimed at the development of the malimide-based synthetic methodology for the asymmetric synthesis of bioactive nitrogen-containing natural products,[14] we now report the first total synthesis of (*R*)-ypaoamide (**5**).

Results and Discussion

The enantioselective synthesis of ypaoamide (**5**) presents several challenges. The most difficult one is the incorporation of two acid and/or base sensitive functional groups (the 5-alkyl-3-pyrrolin-2-one subgroup and the *E*-β-methoxy-α,β-unsaturated imide moiety) together with a phenolic moiety. Our retrosynthetic analysis of (*R*)-ypaoamide (**5**) is outlined in Scheme 1, which suggested a convergent synthesis involving the coupling of the lipid moiety with the 5-alkyl-3-pyrrolin-2-one portion. The *tert*-butyl-containing lipid side chain was envisioned to be synthesized from glutarimide or pivaldehyde (Scheme 1). As regarding the 5-alkyl-3-pyrrolin-2-one moiety, although there are several reports on their synthesis,[9,15,16] most of them use α-amino acids as the starting materials,[9,15] which may suffer from partial racemization,[15b,d] and lack generality. In view of the presence of 5-alkyl-3-pyrrolin-2-one subunits in several marine cyanobacteria-origin natural products and the possibility to use them as leads for drug development, a nonamino acid-based approach would offer a greater flexibility for the synthesis of synthetic analogues bearing different C-5 substituents. On the basis of these considerations, we envisioned the use of lactams such as **12** and **6** as latent forms of the 5-alkyl-3-pyrrolin-2-one portion, which, according to our previous results, can be derived from (*S*)-malimide **13** by Grignard addition.[17] There are two advantages in this approach. First, as we have demonstrated earlier,[14] the installation of different C-5 alkyl groups is easy by just changing the Grignard reagent, and second, the coupling of lactams (e.g., **12**) with the lipid chain **7** can be performed under racemization-free conditions.

The synthesis started with *N*-(*p*-methoxybenzyl)glutarimide **10**, which was derived from glutaric anhydride **14** (Scheme 2). Disappointingly, addition of *tert*-butyl lithium led to the desired keto-ester **15** in only 17% yield, along with 38% of the recovered starting material. A similar low yield (16%) was reported in the reaction of *tert*-butyl lithium with a glutarimide derivative.[18] The low yield may be attributed to the strong basicity of *tert*-butyllithium, which abstracts an acidic α-proton. The deoxygenation of **15** was achieved by Maryanoff's method,[19] namely, reduction of the *p*-tosylhydrazone derivative with $NaBH_3CN$, which gave the desired side chain **9** in 55% yield.

Although amide **9** can be obtained in only three steps from glutaric anhydride **14**, the low yield in the formation of keto amide **15** led us to consider an alternative approach starting from ethyl 4-bromobutyrate (**16**) as shown in Scheme 3. The Wittig reaction of the ylide, generated by deprotonation of the phosphonium bromide salt **11** with sodium hexamethyldisilylamide (NHMDS), with pivaldehyde gave volatile olefin *Z*-**17** as a single product in 74% yield.[20] The ester **17** was

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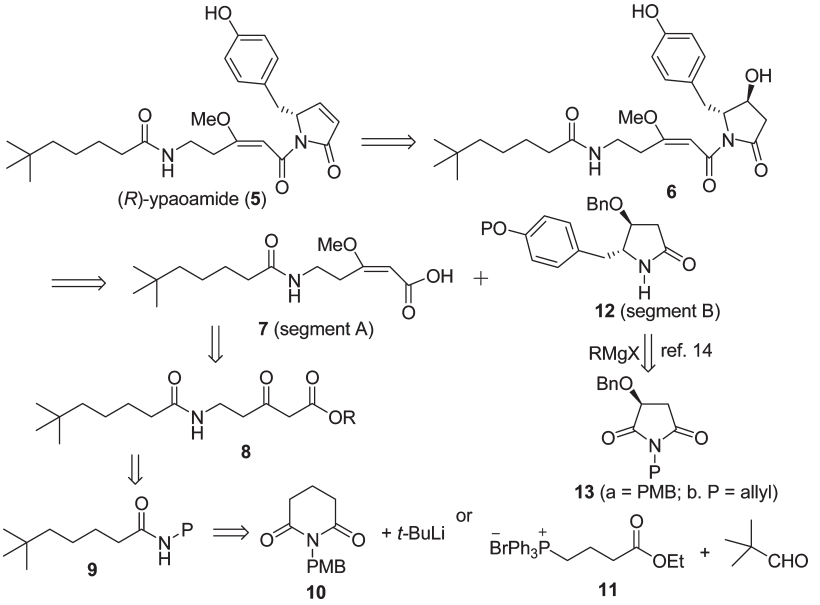
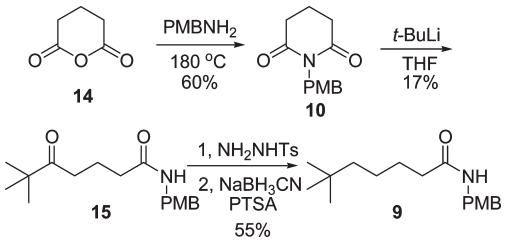
SCHEME 1



SCHEME 2



converted to amide **18** in 94% yield by the method previously developed in these laboratories.[21] Catalytic hydrogenation of olefin **18** gave amide **9** in 95% yield. For the aza-Michael addition of the secondary amide **9** with ethyl acrylate, a number of conditions were tested. When 0.2 mol equiv of potassium *tert*-butoxide was used, the desired product **19** was formed in 55% yield, along with 43% of the recovered starting material. A better result was obtained (**19**: 68%; **9**: 30%) when the TBSOTf/ NEt_3 reagent system[22] was used as the promoter. To undertake the chain elongation of **19** by a base-mediated cross-Claisen reaction, a prior *N*-deprotection was necessary to avoid the possible retro-Michael reaction of **19** under basic conditions. Attempts to cleave the *N*-PMB group under oxidative conditions (CAN−MeCN−H_2O)[14b] produced **20** in only 20% yield. An alternative method by heating **19** in trifluoroacetic acid[23] at reflux for 5 h was tried. However, due to both the poor visibility of the desired product on TLC detection and the formation of a large number of colored side products, isolation of the desired product was difficult even by following the Brooke's workup procedure,[23] which led to amide **20** in only 26% yield. This difficulty was overcome by modifying the Brooke's workup procedure: after the reaction, most of the TFA was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2, neutralized with sodium bicarbonate at −20 °C, extracted with CH_2Cl_2, and chromatographed on SiO_2 to give **20** in 86% yield.

The cross-Claisen condensation reaction was carried out by deprotonation of EtOAc with LDA, allowing the resulting enolate to react with ester **20**, which gave keto ester **8a** in 50% yield (Scheme 4). To convert **8a** into **22a**, Pinnick method[24] was adopted. Thus, in the presence of a catalytic amount of concentrated H_2SO_4, a mixture of **8a** and trimethyl orthoester was heated at reflux to yield a mixture of **21a** and **22a**, which was heated at 80 °C under reduced pressure for 5 h. In such a manner, **21a** was further converted to **22a**, and the latter was isolated in 71% yield. The final step for the synthesis of the fragment **A** was the saponification of **22a**. Disappointingly, attempted saponification under a number of conditions (e.g., LiOH−MeOH−H_2O; 1, 4, or 6 N aq NaOH) failed, and keto ester **8a** was obtained after acidic workup. At this point, we decided to synthesize benzyl ester **22b** in the hope that it would be cleavable under hydrogenolytic debenzylation conditions. The cross-condensation of benzyl acetate with **20** gave **8b** in 62% yield. The latter was converted to **22b** in 75% yield by following the procedure described for **8a**. The *E*-stereochemistry of **22b** was assigned on the basis of the observed NOEs between the methoxyl (δ 3.62) and olefinic (δ 5.14) protons. Under the catalytic transfer hydrogenolytic conditions (10% Pd/C, HCO_2H/EtOH = 1:9, *v*/*v*, rt, 3 h), **22b** was smoothly transformed into the desired acid **7** in 92% yield.

After achieving the synthesis of **7**, we turned to the synthesis of the 5-(*p*-hydroxyphenylmethyl)-3-pyrrolin-2-one subunit (**12**). Stepwise reductive *p*-methoxybenzylation of (*S*)-malimide **13a** afforded **23a** as the only observable regio- and diastereomer in 83% overall yield (Scheme 5). For the cleavage of the *p*-methoxybenzyl (PMB) group in **23a**, the CAN-mediated oxidative deprotection[14] gave a complex mixture, from which the desired product could not be isolated. This failure may be due to both over reduction

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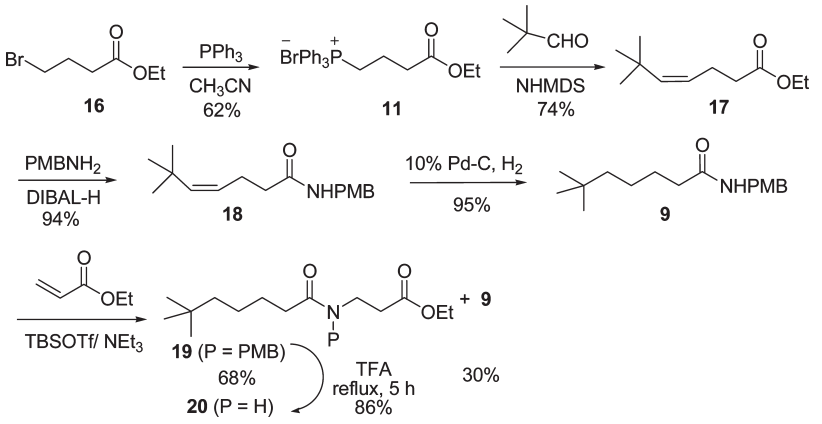
SCHEME 3



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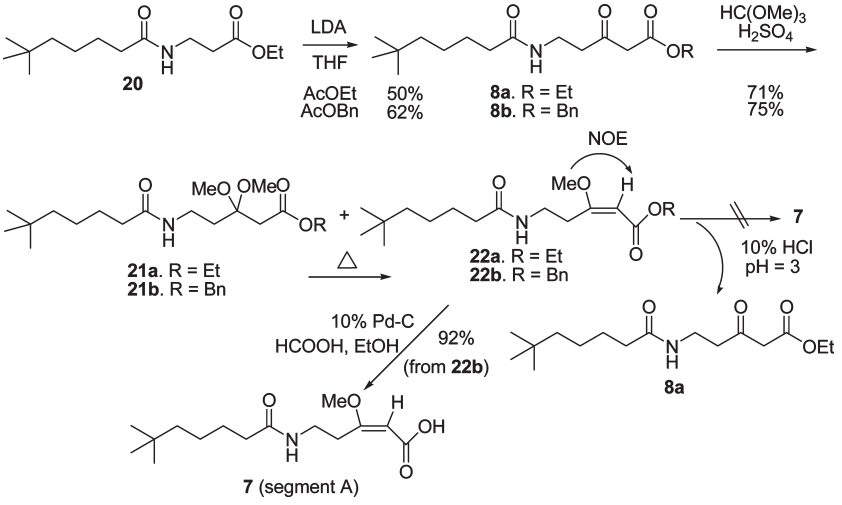

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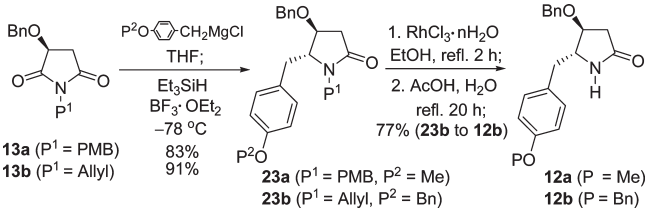

and concomitant oxidation of the methoxybenzyl group at C-5. At this point, the protecting group strategy was taken into consideration, and we decided to synthesize *N*-allyl protected[25] lactam **23b** as the precursor of the pyrrolinone segment. Thus, the known *N*-allyl malimide **13b**[26] was used as the starting material, which has been converted to lactam **12b** in our recent synthesis of melleumin A.

Now the stage was set for the coupling of segment **A** (**7**) with segment **B** (**12b**). Although several methods have been reported,[27,28] we elected to use the Andrus's pentafluorophenyl ester method.[9b,28] Thus, using DCC as a coupling agent, the reaction of the acid **7** with pentafluorophenol afforded the activated ester **24** in 94% yield. Reaction of ester **24** (−78 °C; then warm up to −5 °C) with the anion, generated by deprotonation of the lactam **12b** with 1.0 mol equiv of *n*-butyllithium at −78 °C, furnished the coupling product **25** in 63% yield (Scheme 6). To form the pyrrolinone moiety in a racemization-free manner, a switch of protecting groups for the C-4 hydroxyl group was necessary. Compound **25** was subjected to catalytic hydrogenolysis (10% Pd/C, HCO_2H, EtOH), which produced the bis-debenzylated product **6** in 86% yield. In light of Mattern's report,[15b] the 4-*O*-Boc-derivative of **6** was envisioned as a ready precursor of **5**. Treatment of compound **6** with 2.0 mol equiv of di-*tert*-butyl dicarbonate (Boc_2O, DMAP, THF) at room temperature for 5 h led to the desired elimination in the pyrrolidinone subunit and concomitant protection of the phenol group, yielding compound **26**, the Boc-protected analogue of

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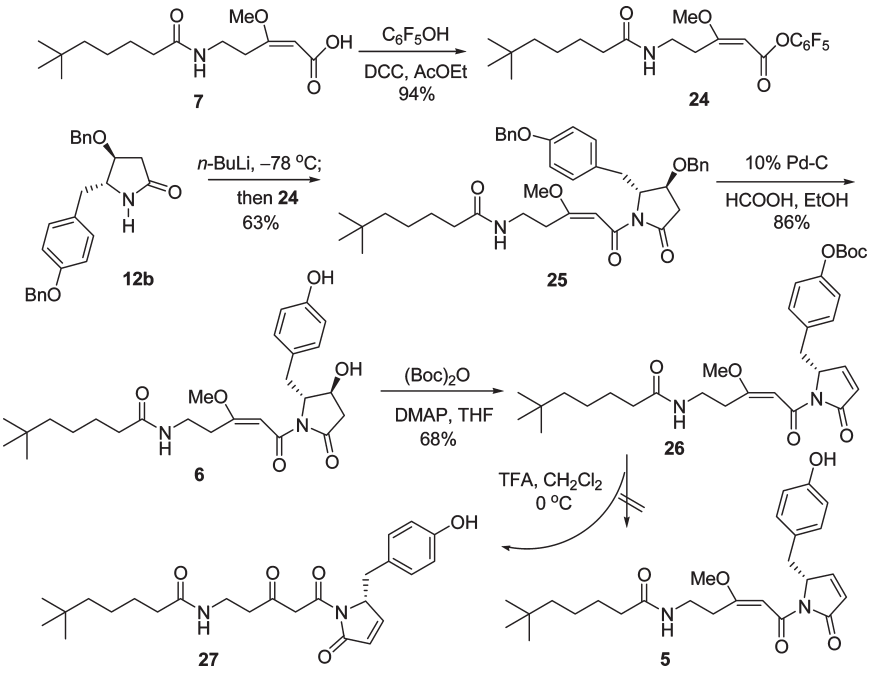
SCHEME 6



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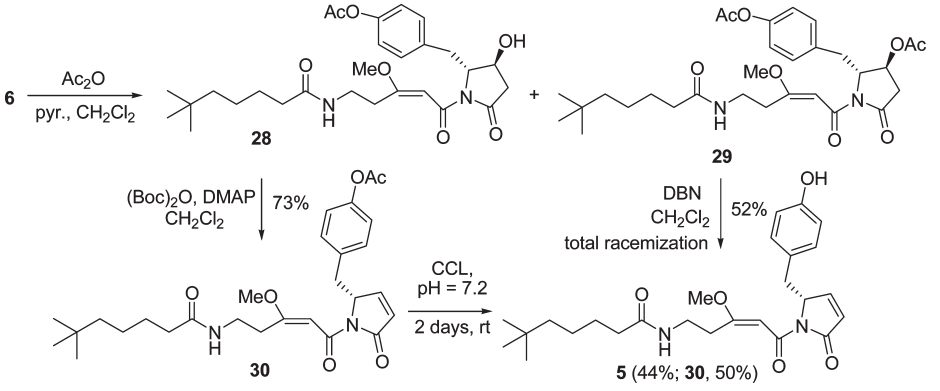

TABLE 1. Acetylation of Compound 6

entry	Ac_2O (equiv)	pyridine (equiv)	temp (°C)	time (h)	ratio **28**:**29**	yield (%)
1	1.5	1.5	0	2	100:0	92
2	2.0	2.0	20	0.5	52:48	90
3	2.0	2.0	20	8	0:100	94

ypoamide (**5**). However, due to the fragility of both molecules **26** and **5**, the last deprotection step (TFA, CH_2Cl_2) appeared problematic, due to a concomitant hydrolysis of the enol ether function (at either 0 or −20 °C), leading to compound **27**.

At this stage, an acetyl protecting group was selected to replace the Boc group. As can be seen from Scheme 7 and Table 1, no desired C-4 *O*-monoacetylated product could be obtained. Instead, either phenol monoacetylated product **28** or bis-acetylated product **29** was obtained in high yield. In an attempt to eliminate the acetic acid, bis-acetate **29** was treated with DBN in CH_2Cl_2. After reaction at rt for 1.5 h, the desired product **5** was obtained in 52% yield, whose spectral data were in agreement with those reported for the natural product.[10] Unfortunately, no optical rotation was observed, which implied that a complete racemization occurred.

We next turned our attention to the monoacetylated product **28**. Compound **28** was converted to the known compound **30**[10] by reacting with Boc_2O in the presence of 0.1 mol equiv of DMAP. Treatment of a methanolic solution of compound **30** with 1.0 mol equiv of K_2CO_3 at room temperature for 1.5 h produced ypaoamide (**5**) in 55% yield. The enantiomeric excess of the product **5** was 10%, indicating that substantial racemization occurred.

At this stage, enzymatic deacetylation[29] of compound **30** was envisioned. Initial attempts with use of porcine pancreatic lipase (PPL) were unsuccessful. To our satisfaction, when compound **30** was treated with CCL (*Candida cylindracea* lipase) in a buffer solution[30] at pH 7.2, and at rt for 2 days, the desired

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ypaoamide (**5**) was obtained in 88% yield based on the recovered starting material **30** (50%). The physical and spectroscopic data of the synthetic compound were in agreement with those reported for the natural product.[10] Comparing the optical rotations {synthetic **5**: $[\alpha]^{20}_{D}$ −194 (*c* 0.8, $CHCl_3$); natural product: $[\alpha]^{20}_{D}$ +197 (*c* 1.0, $CHCl_3$)} allowed the conclusion that the absolute configuration of the natural ypaoamide (**5**) is *S*, and our synthetic product is the enantiomer of the natural product. The recovered starting material showed the same optical rotation as that of the starting material **30**, implying that the high enantioselectivity of compound **5** was a result of the mild racemization-free conditions of the enzyme-catalyzed reaction, not of a kinetic resolution.

Conclusion

In summary, the first enantioselective synthesis of the unnatural enantiomer of ypaoamide (**5**) was achieved in a convergent manner in 19 steps with 1.0% overall yield starting from (*S*)-*N*-allylmalimide **13b** and ethyl 4-bromobutyrate (**16**). This work established the absolute configuration of the natural ypaoamide (**5**) as *S*. In this synthesis, we were able to demonstrate that the difficult problem associated with the need for an orthogonal deprotection can be tackled by mild enzymatic deacetylation. Our approach to the 5-substituted 3-pyrrolin-2-one segment is both racemization-free and flexible. By using other Grignard reagents, this method should allow access to other 5-substituted 3-pyrrolin-2-ones, which are found as key structural features in many bioactive natural products. This work is currently in progress in these laboratories, and will be reported in due course.

Experimental Section

Ethyl 3-(6,6-Dimethylheptanamido)propanoate (20). A mixture of compound **19** (1.35 g, 3.57 mmol) and TFA (17.8 mL) was refluxed for 6 h and then cooled to room temperature. The mixture was concentrated under reduced pressure, then dissolved in CH_2Cl_2 (10 mL). The solution was neutralized with a saturated aqueous solution of $NaHCO_3$ at −20 °C and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc−PE (1: 3) to give compound **20** (763 mg, 2.98 mmol, 83%) as a pale yellow oil. IR (film) ν_{max} 3419, 2953, 1736, 1650, 1548, 1364, 1184 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 0.85 (s, 9H), 1.09−1.16 (m, 2H), 1.17−1.26 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.49−1.58 (m, 2H), 2.12 (t, *J* = 7.6 Hz, 2H), 2.48 (t, *J* = 6.0 Hz, 2H), 3.43−3.50 (dd, *J* = 12.0, 6.0 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 6.15 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 24.1, 26.4, 29.2 (3C), 30.1, 33.9, 34.6, 36.7, 43.7, 60.5, 172.6, 173.1; MS (ESI) *m*/*z* 280 (M + Na^+, 100); ESI-HRMS calcd for [$C_{14}H_{27}NO_3$ + H^+] 257.1991, found 257.1994.

Benzyl 5-(6,6-Dimethylheptanamido)-3-oxopentanoate (8b). To a solution of LDA (0.65 M solution in THF, 9.5 mL, 6.2 mmol) was added dropwise benzyl acetate (0.9 mL, 6.2 mmol) at −78 °C under a nitrogen atmosphere over 15 min. After 15 min a solution of compound **20** (355 mg, 1.39 mmol) in THF (8.0 mL) was added over 15 min. The reaction mixture was stirred overnight while the temperature was allowed to warm to room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10.0 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc−PE (1:3) to give compound **8b** (309 mg, 0.85 mmol, 62%) as a pale yellow oil. IR (film) ν_{max} 3303, 2952, 1743, 1716, 1545, 1262, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 9H), 1.12−1.19 (m, 2H), 1.20−1.30 (m, 2H), 1.50−1.60 (m, 2H), 2.11 (t, *J* = 7.7 Hz, 2H), 2.77 (t, *J* = 5.6 Hz, 2H), 3.44−3.50 (m, 2H), 3.49 (s, 2H), 5.18 (s, 2H), 5.90 (br s, 1H), 7.30−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 26.5, 29.3 (3C), 30.2, 33.7, 36.7, 42.6, 43.8, 49.1, 67.2, 128.3 (2C), 128.5 (2C), 128.6, 135.0, 166.6, 173.1, 202.5; MS (ESI) *m*/*z* 362 (M + H^+, 100); ESI-HRMS calcd for [$C_{21}H_{31}NO_4$ + Na^+] 384.2151, found 384.2148.

Benzyl (*E*)-5-(6,6-Dimethylheptanamido)-3-methoxypent-2-enoate (22b). To a mixture of compound **8b** (892 mg, 2.47 mmol) and $HC(OMe)_3$ (1.0 mL, 9.1 mmol) was added 5 drops of concentrated H_2SO_4. The mixture was stirred at 40 °C for 4 days then concentrated under reduced pressure. The oily residue was purified by chromatographic purification on silica gel eluting with EtOAc−PE (1:3) to give an oily residue, along with the recovered starting material (110 mg). The oily residue was heated at 80 °C under reduced pressure for 3 h. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1/2) to give compound **22b** (680 mg, 1.81 mmol, 75%) as a colorless oil. IR (film) ν_{max} 3302, 2951, 1712, 1632, 1620, 1133 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 9H), 1.12−1.18 (m, 2H), 1.18−1.29 (m, 2H), 1.49−1.58 (m, 2H), 2.08 (t, *J* = 7.6 Hz, 2H), 2.93 (t, *J* = 6.3 Hz, 2H), 3.46−3.52 (m, 2H), 3.62 (s, 3H), 5.14 (s, 2H), 5.16 (s, 1H), 6.22 (br s, 1H), 7.28−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 26.5, 29.3 (3C), 30.2, 31.4, 36.8, 37.9, 43.9, 55.8, 65.8, 92.0, 128.1 (3C), 128.5 (2C), 136.2, 168.3, 173.2, 174.2; MS (ESI) *m*/*z* 398 (M + Na^+, 100); ESI-HRMS calcd for [$C_{22}H_{33}NO_4$ + H^+] 376.2476, found 376.2478.

***N*-[(*E*)-5-((2*R*,3*S*)-2-(4-(Benzyloxy)benzyl)-3-(benzyloxy)-5-oxopyrrolidin-1-yl)-3-methoxy-5-oxopent-3-enyl]-6,6-dimethylheptanamide (25).** To a solution of (4*S*,5*R*)-5-(4-(benzyloxy)-benzyl)-4-(benzyloxy)pyrrolidin-2-one **12b** (70 mg, 0.18 mmol) in THF (1.0 mL) was added dropwise *n*-BuLi (2.5 M in hexane) (0.9 mL, 0.18 mmol) at −80 °C. The mixture was stirred for 15 min. To the resulting mixture was added a THF solution (2.0 mL) of ester **24** (96 mg, 0.21 mmol). After the solution was stirred for 3 h at −80 °C, the reaction temperature was allowed to rise to −5 °C. The mixture was quenched with a saturated aqueous solution of NH_4Cl (2.0 mL). The resulting mixture was extracted with EtOAc (3 × 4 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc−PE (1:2) to give compound **25** (74 mg, 0.11 mmol, 63%) as a pale yellow oil. $[\alpha]^{20}_{D}$ −28 (*c* 0.6, $CHCl_3$); IR (film) ν_{max} 3318, 2937, 1731, 1664, 1599, 1510, 1196, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 9H), 1.10−1.17 (m, 2H), 1.18−1.28 (m, 2H), 1.57 (p, *J* = 7.6 Hz, 2H), 2.16 (t, *J* = 7.7 Hz, 2H), 2.53 (dd, *J* = 13.6, 4.5 Hz, 1H), 2.53−2.64 (m, 2H), 2.87−2.97 (m, 1H), 2.93−3.03 (m, 1H), 3.16 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.50−3.55 (m, 1H), 3.55−3.59 (m, 1H), 3.74 (s, 3H), 3.80−3.83 (m, 1H), 4.14 (d, *J* = 12.1 Hz, 1H), 4.34 (d, *J* = 12.1 Hz, 1H), 4.66−4.72 (dm, *J* = 9.1 Hz, 1H), 5.05 (s, 2H), 6.69 (br s, 1H), 6.74 (s, 1H), 6.90−7.50 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 26.5, 29.2 (3C), 30.1, 32.3, 36.5, 36.8, 38.1, 39.5, 41.9, 43.7, 56.0, 64.2, 70.0, 71.9, 94.9, 115.1 (2C), 127.3 (2C), 127.6 (2C), 127.7, 127.9, 128.3 (2C), 128.5 (2C), 128.7, 130.2 (2C), 136.8, 136.9, 157.8, 166.9, 173.2, 173.6, 175.5; MS (ESI) *m*/*z* 677 (M + Na^+, 100); ESI-HRMS calcd for [$C_{40}H_{50}N_2O_6$ + H^+] 655.3747, found 655.3737.

***N*-[(*E*)-5-((2*R*,3*S*)-2-(4-Hydroxybenzyl)-3-hydroxy-5-oxopyrrolidin-1-yl)-3-methoxy-5-oxopent-3-enyl]-6,6-dimethylheptanamide (6).** To 10% Pd/C (50 mg) was added a solution of

compound **25** (64 mg, 0.10 mmol) in anhydrous EtOH (1.6 mL) and formic acid (0.2 mL). The mixture was stirred for 5 h at room temperature under a nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure. The oily residue was purified by flash column chromatography on silica gel eluting with EtOAc−PE (2:1) to give compound **6** (40 mg, 0.08 mmol, 86%) as a white solid. Mp 140−141 °C (EtOAc−PE); $[\alpha]^{20}_D$ −36 (*c* 0.8, $CHCl_3$); IR (film) ν_{max} 3325, 2951, 1731, 1722, 1650, 1595, 1197, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 9H), 1.10−1.17 (m, 2H), 1.18−1.28 (m, 2H), 1.57 (p, J = 7.6 Hz, 2H), 2.16 (t, J = 7.6 Hz, 2H), 2.32−2.36 (m, 1H), 2.50−2.61 (m, 2H), 2.84−2.96 (m, 2H), 2.99−3.07 (m, 1H), 3.40−3.50 (m, 2H), 3.59 (s, 3H), 3.90 (s, 1H), 4.14−4.24 (m, 1H), 4.47−4.54 (m, 1H), 6.70 (s, 1H), 6.77 (d, J = 8.4 Hz, 2H), 6.85 (br s, 1H), 6.99 (d, J = 8.4 Hz, 2H), 8.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 26.5, 29.3 (3C), 30.1, 32.4, 36.3, 36.7, 38.1, 41.9, 43.7, 56.1, 66.0, 67.6, 94.9, 115.8 (2C), 127.5, 130.3 (2C), 155.6, 166.9, 174.3, 174.4, 175.4; MS (ESI) m/z 497 ($M + Na^+$, 100). Anal. Calcd for $C_{26}H_{38}N_2O_6$: C, 65.80; H, 8.07; N, 5.90; O, 20.23. Found: C, 65.84; H, 8.10; N, 5.91; O, 20.26.

4-[((2*R*,3*S*)-1-((*E*)-5-(6,6-dimethylheptanamido)-3-methoxypent-2-enoyl)-3-hydroxy-5-oxopyrrolidin-2-yl)methyl]phenyl Acetate (28). To a solution of compound **6** (132 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (1.8 mL) was added Ac_2O (0.04 mL, 0.42 mmol) and pyridine (0.03 mL, 0.42 mmol) at 0 °C. The mixture was stirred for 2 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (2 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 1.0 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc−PE (1:1) to give compound **28** (132 mg, 0.25 mmol, 92%) as a pale yellow oil. $[\alpha]^{20}_D$ −21 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3322, 2951, 1731, 1649, 1599, 1195, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 9H), 1.10−1.19 (m, 2H), 1.19−1.30 (m, 2H), 1.57 (p, J = 7.7 Hz, 2H), 2.12 (t, J = 7.7 Hz, 2H), 2.30 (s, 3H), 2.42−2.46 (m, 1H), 2.54−2.70 (m, 2H), 2.78−2.95 (m, 2H), 3.20 (dd, J = 14.0, 3.5 Hz, 1H), 3.42−3.58 (m, 2H), 3.72 (s, 3H), 3.90 (s, 1H), 4.12−4.20 (m, 1H), 4.50−4.60 (dm, J = 9.1 Hz, 1H), 6.70 (br s, 1H), 6.71 (s, 1H), 7.05 (dt, J = 8.6, 2.0 Hz, 2H), 7.23 (dt, J = 8.6, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 24.2, 26.5, 29.3 (3C), 30.1, 32.3, 36.6, 36.8, 38.0, 41.8, 43.8, 56.1, 65.8, 67.4, 94.9, 121.9 (2C), 130.2 (2C), 134.4, 149.6, 166.9, 169.5, 173.5, 173.8, 175.5; MS (ESI) m/z 539 ($M + Na^+$, 100); ESI-HRMS calcd for $[C_{28}H_{40}N_2O_7 + H^+]$ 517.2913, found 517.2903.

(*R*,*E*)-4-[(1-(5-(6,6-Dimethylheptanamido)-3-methoxypent-2-enoyl)-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)methyl]phenyl Acetate (30). To a solution of compound **28** (50 mg, 0.10 mmol) and DMAP (1.5 mg, 0.01 mmol) in anhydrous CH_2Cl_2 (1.0 mL) was added $(Boc)_2O$ (0.05 mL, 0.19 mmol) at 0 °C. The mixture was allowed to rise to room temperature and stirred for 4 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (1.0 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 1.0 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc−PE (1:1) to give the known compound[10] **30** (35 mg, 0.07 mmol, 73%) as a pale yellow oil. $[\alpha]^{20}_D$ −110 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3310, 2938, 1720, 1664, 1598, 1196, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 9H), 1.10−1.18 (m, 2H), 1.19−1.30 (m, 2H), 1.57 (p, J = 7.7 Hz, 2H), 2.18 (t, J = 7.7 Hz, 2H), 2.28 (s, 3H), 2.75 (dd, J = 13.4, 9.1 Hz, 1H), 2.94 (ddd, J = 13.3, 7.1, 4.9 Hz, 1H), 3.04 (ddd, J = 13.3, 8.3, 4.9 Hz 1H), 3.50−3.60 (m, 2H), 3.60 (dd, J = 13.4, 3.7 Hz, 1H), 3.75 (s, 3H), 4.96−5.08 (dm, J = 9.1 Hz, 1H), 6.05 (dd, J = 6.0, 1.6 Hz, 1H), 6.71 (s, 1H), 6.74 (br s, 1H), 7.05 (dt, J = 8.6, 2.0 Hz, 2H), 7.15−7.17 (m, 1H), 7.18 (dt, J = 8.6, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 24.3, 26.6, 29.3 (3C), 30.2, 32.4, 36.9, 37.4, 38.2, 43.8, 56.2, 62.8, 94.8, 121.7 (2C), 126.7, 130.3 (2C), 133.3, 149.7, 151.0, 166.2, 169.3, 170.0, 173.2, 175.7; MS (ESI) m/z 521 ($M + Na^+$, 100); ESI-HRMS calcd for $[C_{28}H_{38}N_2O_6 + H^+]$ 499.2808, found 499.2823.

(*R*)-Ypaoamide (*R*-5). To a solution of compound **30** {20 mg, 0.04 mmol, $[\alpha]^{20}_D$ −110 (*c* 1.0, $CHCl_3$)} in MeCN (2 mL) and pH 7.2 phosphate buffer (2 mL) was added CCL (25 mg) at room temperature. The mixture was stirred for 2 days. The enzyme was filtered off and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc−PE (1:1) to give (*R*)-ypaoamide (*R*-**5**) (8.0 mg, 0.02 mmol, 44%) as a pale yellow oil, and the recovered starting material {**30**, 10 mg, 0.02 mmol, $[\alpha]^{20}_D$ −106 (*c* 0.7, $CHCl_3$)}. (*R*)-**5**: $[\alpha]^{20}_D$ −194 (*c* 0.8, $CHCl_3$) {lit.[10] $[\alpha]^{20}_D$ +197 (*c* 1.0, $CHCl_3$)}; IR (film) ν_{max} 3310, 2952, 1720, 1712, 1648, 1596, 1199, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (s, 9H), 1.04−1.16 (m, 2H), 1.18−1.28 (m, 2H), 1.57 (p, J = 7.7 Hz, 2H), 2.18 (t, J = 7.7 Hz, 2H), 2.72 (dd, J = 13.4, 9.1 Hz, 1H), 2.88 (ddd, J = 13.3, 7.1, 5.0 Hz, 1H), 3.04 (ddd, J = 13.3, 8.3, 5.0 Hz, 1H), 3.47 (dd, J = 13.4, 3.7 Hz, 1H), 3.50−3.58 (m, 1H), 3.54−3.64 (m, 1H), 3.74 (s, 3H), 4.92−5.02 (dm, J = 9.1 Hz, 1H), 6.02 (dd, J = 6.0, 1.6 Hz, 1H), 6.15 (br s, 1H), 6.71 (s, 1H), 6.78 (dt, J = 8.6, 2.0 Hz, 2H), 6.92 (br s, 1H), 6.98 (dt, J = 8.6, 2.0 Hz, 2H), 7.16 (dd, J = 6.0, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 26.6, 29.3 (3C), 30.2, 32.3, 37.0, 37.1, 38.3, 43.8, 56.2, 63.2, 95.1, 115.5 (2C), 126.4, 126.9, 130.5 (2C), 151.6, 155.5, 166.3, 170.3, 173.9, 175.5; MS (ESI) m/z 479 ($M + Na^+$, 100); ESI-HRMS calcd for $[C_{26}H_{36}N_2O_5 + H^+]$ 457.2702, found 457.2707.

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Supporting Information Available: Experimental procedures and spectral data for compounds **10**, **15**, **9**, **17**, **18**, **19**, **8a**, **22a**, **7**, **24**, **27**, and **29**, ^1H NMR and ^{13}C NMR spectra for the intermediates and final products, and chiral HPLC chromatograms of ypaoamide (**5**). This material is available free of charge via the Internet at http://pubs.acs.org.