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A Convergent Route for the Total Synthesis of Malyngamides O, P, Q, and R

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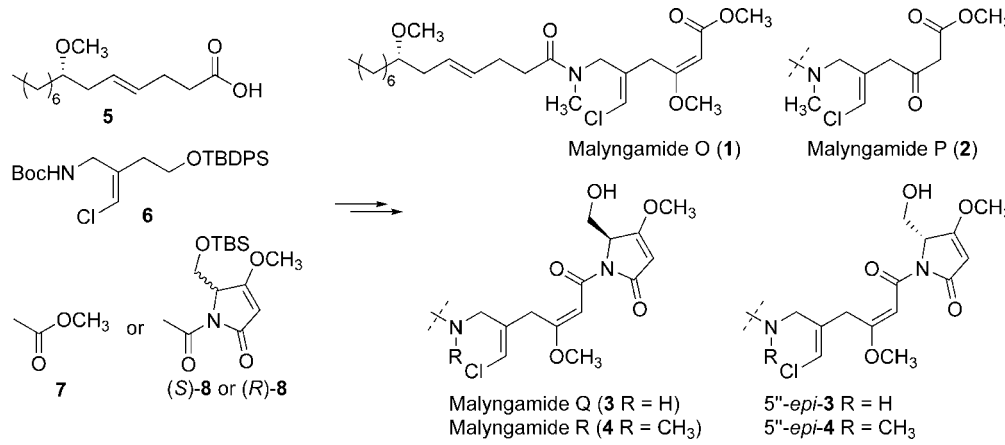

A convergent, enantioselective and general synthetic route to a class of marine natural products—malyngamides O (**1**), P (**2**), Q (**3**), R (**4**), 5″-*epi*-**3** and 5″-*epi*-**4**—bearing a novel vinyl chloride structural motif was developed. The key steps involved construction of the vinyl chloride functionality by Wittig reaction, a DCC/HOBt-promoted amidation, an aldol reaction in the construction of the basic backbone of **1**, **2**, **3**, **4**, 5″-*epi*-**3**, and 5″-*epi*-**4**, and methylation of an enol moiety via either base/acid conditions or a Mitsunobu reaction. Moreover, the absolute configuration of the stereogenic center at C-5″ in **3** was further confirmed by synthesis of the natural product and its C-5″ epimer.

Introduction

The malyngamides are a class of secondary metabolites isolated from the marine cyanophyte *Lyngbya majuscule*. To date, 30 different malyngamides have been isolated including malyngamides A−X, serinol-derived malyngamides, toxic-type malyngamides (hermitamides A and B), and isomalyngamides.[1] Interestingly, 18 of the malyngamide family members are a class of amide compounds containing a fatty acid chain bonded to an amine moiety carrying a communal, but an interesting terminal vinylic chloride functionality. These natural products have been found to possess a wide range of biological properties. Malyngamides O and P were isolated from the sea hare *Stylocheilus longicauda*, which was known to feed on *L. majuscula* by Scheuer's group in 2000.[1c] Bioassay assessment with mouse lymphoma (P-388), human lung carcinoma (A-549), and human colon carcinoma (HT-29) cell lines indicated that malyngamide O possessed moderate activity (IC_{50} 2 μg/mL), but the biological activity of malyngamide P was still unknown due to an inadequate quantity of the sample. Malyngamides Q and R were isolated from a shallow-water Madagascan *L. majuscula* by Gerwick's group in 2000.[1d] While the biological properties of the former compound could not be evaluated due to its instability, and its absolute configuration of the C-5″ center was not secured, the latter compound displayed brine-shrimp toxicity (LD_{50} 18 ppm). The total synthesis of malyngamide X was first reported by Isobe's group,[2] while the first total synthesis and the structural revision of the correct absolute

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(2) Suntornchashwej, S.; Suwanborirux, K.; Isobe, M. *Tetrahedron* **2007**, *63*, 3217.

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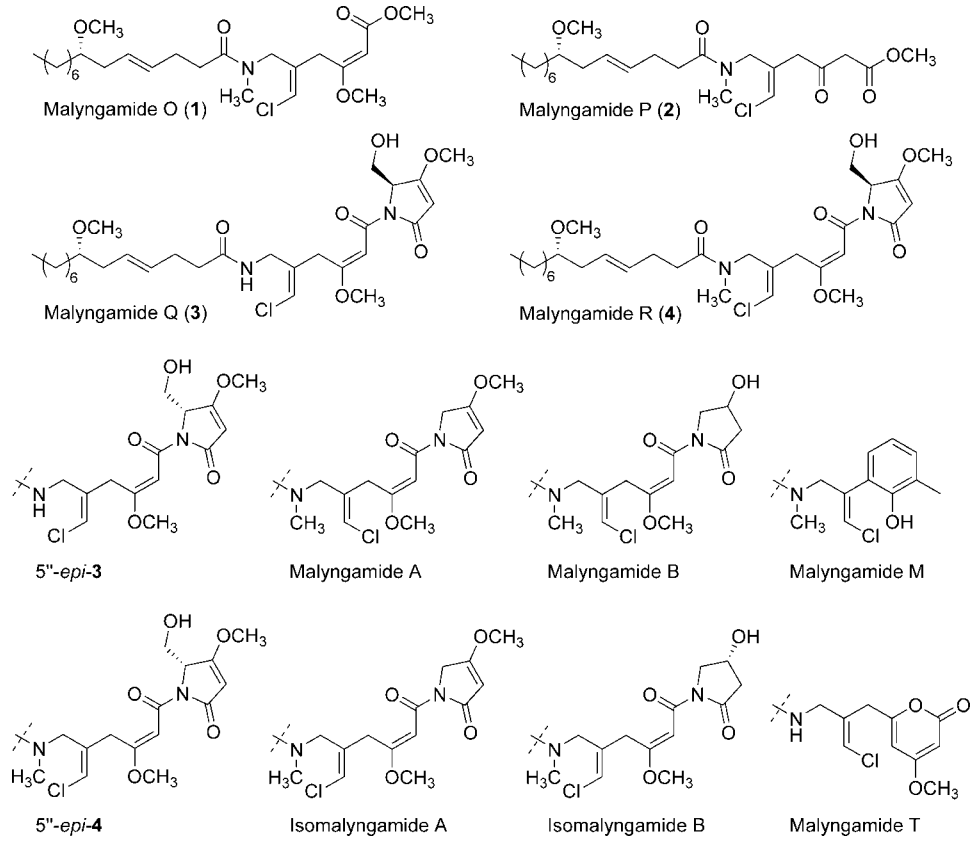

FIGURE 1. Structure of malyngamides O, P, Q, R, A, B, iso-A, iso-B, M, T, 5″-*epi*-**3**, and 5″-*epi*-**4**.

configuration of malyngamide U,[1e,3] and its 2′-epimer,[3] as well as several serinol-derived malyngamides were accomplished by us.[4]However, there are no reports on the total synthesis of malyngamides containing the terminal vinylic chloride moiety. The scarcity of malyngamides in natural sources has hampered biological evaluation of these fascinating molecules. To provide materials for more extensive biological evaluation and confirm the absolute configuration of their stereogenic centers, we are interested in the synthesis of these malyngamides with such a structurally interesting vinyl chloride functionality.

A survey of the literature revealed several methods for the construction of terminal vinyl chlorides such as Wittig reaction,[5a−c] Takai-type reaction,[5d,e] transition metal-catalyzed cross-coupling reactions of deliberately functionalized precursors,[5f,g] Mg/$TiCl_4$/$CHCl_3$,[5h] Julia olefination,[5i] and other methods.[5j−n] The Wittig reaction, Takai-type reaction, and metal-mediated coupling reaction have been used widely in the synthesis of natural products. In the present study, we chose the Wittig reaction to construct the vinyl chloride motif in this work, and a highly general synthetic route to these malyngamides O (**1**), P (**2**), Q (**3**), R (**4**), 5″-*epi*-**3**, and 5″-*epi*-**4** was reported. This newly developed procedure should allow the synthesis of other structurally related malyngamides containing the same vinyl chloride structure, such as malyngamides A, B, iso-A, iso-B, M, and T (Figure 1).

Results and Discussion

As outlined in Scheme 1, malyngamides O (**1**), P (**2**), Q (**3**), R (**4**), 5″-*epi*-**3**, and 5″-*epi*-**4** could be retrosynthetically divided into three parts: a carboxylic acid component **5**, a Boc-protected amine component **6** that bears the vinyl chloride part, and an acetate **7** or an acetamide **8** that contains a pyrrolidone moiety. Amidation of **5** and **6** and aldol reaction of **6** and **7** (or **8**) would furnish the skeleton of the target malyngamides. The chiral fatty acid **5**, *E*,(7*S*)-7-methoxytetradec-4-enoic acid, had been synthesized earlier by us in six steps using a Johnson−Claisen rearrangement as a key step starting from octanal in 50% overall yield.[3] Other key intermediates, such as the vinyl chloride in **6**, could be introduced via Wittig reaction of the oxidized derivative of **9**, and alcohol **9** in turn could be derived from **10** via functional transformations. Pyrrolidone derivative **8** could be generated from L- or D-serine **11**, and hence the sense of chirality at C-5″ in malyngamides Q and R could be derived from the chirality of the serine.

The preparation of compound **6** began with ethyl 4-chloro-3-oxobutanoate (**10**) (Scheme 2). Thus, reaction of **10** with sodium azide provided a 78% yield of the azide **12** in acetone/

(3) Feng, J. P.; Shi, Z. F.; Li, Y.; Zhang, J. T.; Qi, X. L.; Chen, J.; Cao, X. P. *J. Org. Chem.* **2008**, *73*, 6873.
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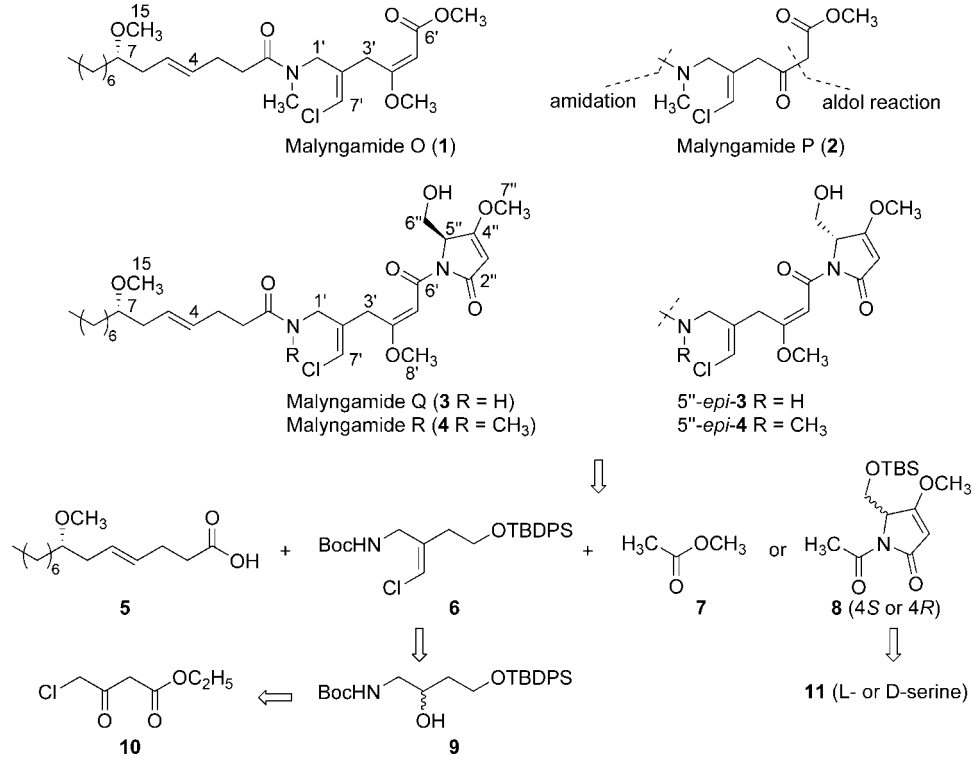
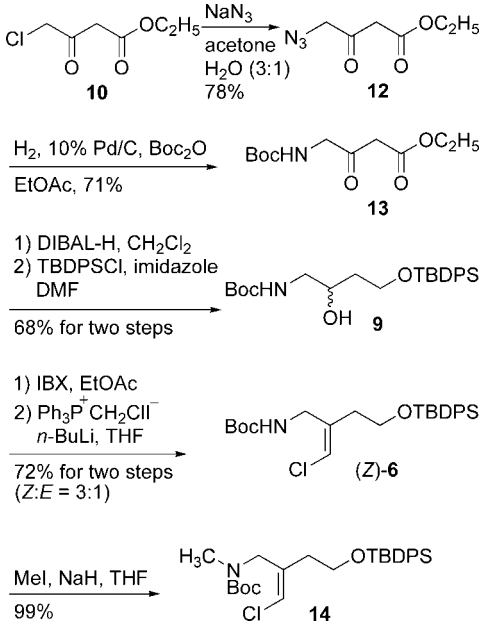
SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Preparation of Key Intermediates 6 and 14



water (3:1) under reflux.[6] Subsequent hydrogenation of **12** under H_2 atmosphere with 10% Pd/C in the presence of di-*tert*-butyl dicarbonate (Boc_2O) in EtOAc gave the Boc-protected amine **13** in 71% yield.[7] Reduction of both keto and ester carbonyl groups in ester **13** with diisobutylaluminum hydride (DIBAL-H) afforded the intermediate diol,[8] followed by monoprotection of the primary hydroxy group with *tert*-butyldiphenylsilyl chloride (TBDPSCl) to give the corresponding silyl ether **9** in 68% yield for two steps. As expected, oxidation of secondary alcohol **9** with 2-iodoxybenzoic acid (IBX) in EtOAc provided the corresponding ketone, which was subjected directly to Wittig olefination with chloromethyltriphenylphosphonium iodide ($Ph_3P^+CH_2ClI^-$) in the presence of *n*-BuLi in THF to give the vinyl chloride **6** in a 72% yield as a mixture of *Z*- and *E*-isomers (*Z*:*E*, 3:1).[9] The mixture could be separated by careful flash chromatography over silica gel. Fortunately, the major product **6** with the *Z*-configuration was the desired one which was obtained in 54% yield. The *Z*-configuration of the vinyl chloride was consistent with that in natural malyngamides O and P, which provided a foundation for the preparation of these malyngamides. Finally, *N*-methylation of (*Z*)-**6** provided the key vinyl chloride **14** in 99% yield.

With fatty acid **5** and vinyl chloride **14** in hand, we focused our efforts on the formation of the skeleton of malyngamides O and P via aldol and amidation reactions (Scheme 3). Thus, deprotection of the TBDPS group of compound **14** with TBAF in THF generated alcohol **15** in 94% yield, followed by oxidation of alcohol **15** with IBX to afford aldehyde **16**, which was used directly in the next step without further purification. Subsequently, the aldehyde **16** underwent successfully low-temperature condensation with the enolate derived from methyl acetate in THF to give alcohol **17** in 57% (brsm 87%) yield.[10] Racemic **17** was immediately submitted to deprotection of the Boc group with trifluoroacetic acid (TFA) to generate the corresponding amine, which was directly condensed with the carboxylic acid **5** in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole (HOBt), and *N*-methylmorpholine (NMM) in CH_2Cl_2 to afford amide **18** in 85% yield.[1e] Finally, oxidation of **18** with Dess−Martin periodinane

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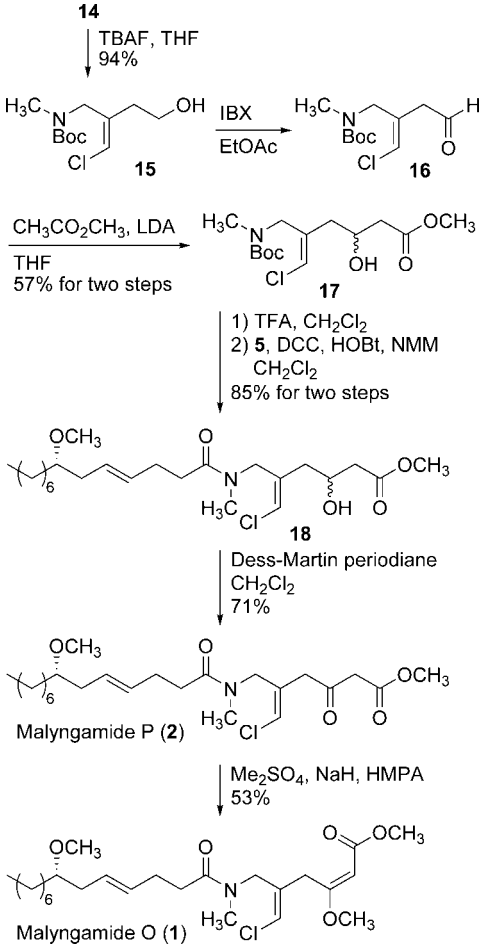
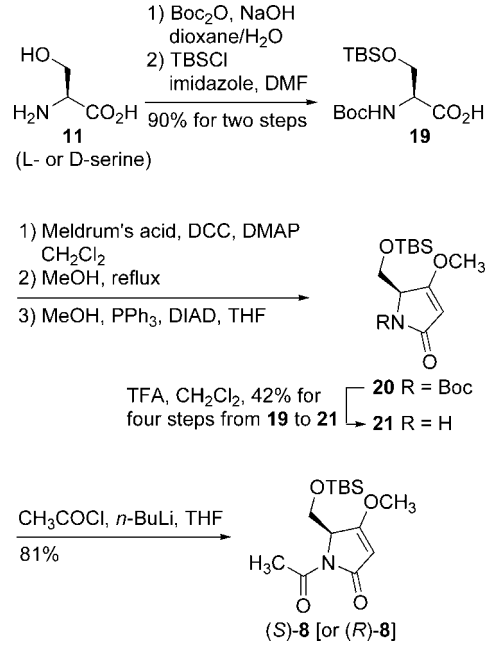
SCHEME 3. Preparation of Malyngamides O and P



in CH_2Cl_2 gave malyngamide P (**2**) in 71% yield.[10] As expected, malyngamide O (**1**) could be prepared from **2** via deprotionation with NaH in hexamethylphosphoramide (HMPA) followed by methylation with freshly distilled dimethyl sulfate in 53% yield.[10] The spectral data of synthetic malyngamides O (**1**) and P (**2**) were in good agreement with those reported in the literature.[1c]

On the basis of the preparation of malyngamides O and P, we continued to synthesize malyngamides Q and R bearing the more challenging structure. Hence, using a similar reaction sequence, construction of the amine portion via aldol reaction and then amidation with acid **5** would form the carbon framework of malyngamides Q and R. The acetamide **8** bearing the pyrrolidone ring was prepared as described in Scheme 4. Thus, protection of the amino group in L-serine (**11**) with Boc_2O followed by silylation of the hydroxy group provided acid **19** in 90% yield.[11] Then the reaction of **19** with Meldrum's acid using DCC and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2, followed by removal of the solvent and then heating in MeOH furnished the pyrrodidone intermediate,[12] which was subjected to a Mitsunobu reaction by treatment with PPh_3 and diisopropyl azodicarboxylate (DIAD) in MeOH to give *O*-methyl pyrrolidone derivative **20**.[2] Compound **20** happened to have a similar R_f value as the reduced byproduct of DIAD, and separation was carried out in the next step. Hence, removal of the Boc group

SCHEME 4. Preparation of Pyrrolidone 8



with TFA provided pure amine **21** in 42% yield from **19** via flash chromatography over silica gel. Several other procedures were attempted to synthesize the enol ether **20**, including NaH/Me_2SO_4/HMPA (no product),[10] K_2CO_3/Me_2SO_4/acetone (19% yield),[13] and K_2CO_3/Me_2SO_4/DMSO (11% yield),[14] but the product yields were all unsatisfactory in this case. Finally, *N*-acetylation of **21** with *n*-BuLi and acetyl chloride provided *N*-acetyl pyrrolidone (*S*)-**8** in 81% yield.[15] Using DMAP/MeMgBr/AcCl conditions developed by Isobe's group met with limited success in our hands,[2] and with Et_3N/AcCl, **21** was obtained only in 16% yield.[16] In a similar manner, (*R*)-**8** was also prepared from D-serine in 29% total yield.

With the key intermediates **8** and **16** in hand, we sought to construct the C(1)−C(6) framework of **22** via aldol reaction of aldehyde **16** and ketone (*S*)-**8** (Scheme 5). Thus, various conditions were tried as shown in Table 1. No desired product resulted when aldehyde **16** was subjected to the enolate of (*S*)-**8** in the presence of LDA at −78 or −40 °C; however, as the reaction temperature was raised to 0 °C, (*S*)-**8** was found to decompose. Aldol reaction of oxazolidinone (*S*)-**8** with aldehyde **16** under Evans condition (Bu_2BOTf) provided a complex mixture.[17] Fortunately, compound **22** was achieved by the aldol reaction of the chlorotitanium enolate of ketone (*S*)-**8** (enolization with 1.1 equiv of $TiCl_4$ and excess *i*-Pr_2NEt) and aldehyde **16** in 53% yield.[18] Subsequent deprotection of the Boc group of **22** followed by amidation with acid **5** resulted in little of the desired compound **23** after several experiments. Therefore we

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(18) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473.

SCHEME 5. Aldol Reaction

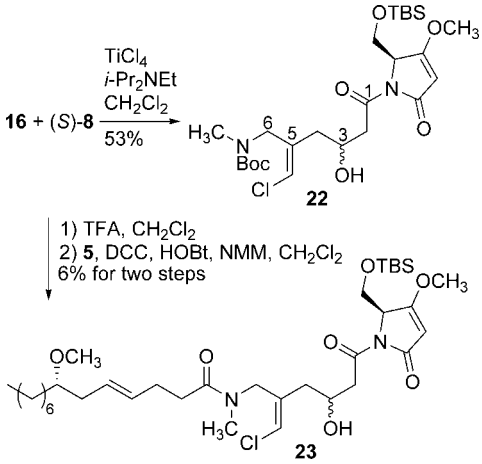

TABLE 1. Optimization for the Aldol Reaction of 16 and (*S*)-8

entry	condition	% yield of **23**
1	LDA, THF, −78 °C, 1 h, then **16**, −78 °C (2 h)[a]	no reaction
2	LDA, THF, −78 °C, 1 h, then **16**, −78 to −40 °C (2 h)[b]	no reaction
3	LDA, THF, −78 °C, 1 h, then **16**, −78 to 0 °C (1 h)[c]	complex
4	Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, 1 h, then −78 °C, **16**, −78 to 0 °C (1 h)[c]	complex
5	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 2.5 h, then **16**, −78 to 0 °C (2 h)[c]	53

[a] Reaction was performed at −78 °C and maintained at this temperature throughout the procedure. [b] After the addition of **16**, the reaction was allowed to warm to −40 °C, and kept there for 2 h. [c] After the addition of **16**, the reaction was allowed to warm to 0 °C, and kept there for 1 or 2 h.

decided to carry out the amidation of **5** and (*Z*)-**6** first, and then conduct the aldol reaction with (*S*)-**8** in the second step.

Thus, starting from the key intermediates (*Z*)-**6** and **14**, removal of the Boc groups in both compounds was carried out first (Scheme 6), followed by amidation with acid **5** in the presence of DCC, HOBt, and NMM in CH_2Cl_2 to produce amides **24** and **25** in 86% and 87% yields, respectively. Subsequent deprotection of the TBDPS groups in **24** and **25** with TBAF in THF gave the corresponding alcohols **26** and **27** (97% and 98% yields, respectively). Oxidation of alcohol **26** with IBX followed by aldol reaction with (*S*)-**8** gave no desired product, presumably due to the interference of the amide NH bond.[19] So the acidic hydrogen of amide **24** was protected as the Boc protected silyl ether **28** in 93% yield.[19b,c] However, deprotection of the TBDPS group by TBAF gave only the Boc transferred side-product **29** in 95% yield.[20] Several other conditions were tried (Table 2). Finally we found that conducting the desilylation in the presence of TBAF/AcOH 1:1 resulted in good selectivity for **30** (**30**:**29**, 20:1) with satisfactory yield. Thus, the primary alcohol **30** was obtained in 85% yield.

With alcohols **27** and **30** in hand, the remaining task was to complete the aldol reaction to construct the skeleton of malyngamides Q and R. As shown in Scheme 7, oxidation of alcohol **27** with IBX provided condensation precursor amido aldehyde **31**,

(19) (a) Toumi, M.; Couty, F.; Evano, G. *Tetrahedron Lett.* **2008**, *49*, 1175. (b) Haug, B. E.; Rich, D. H. *Org. Lett.* **2004**, *6*, 4783. (c) Burk, M. J.; Allen, J. G. *J. Org. Chem.* **1997**, *62*, 7054.

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SCHEME 6. Preparation of Primary Alcohols 27 and 30

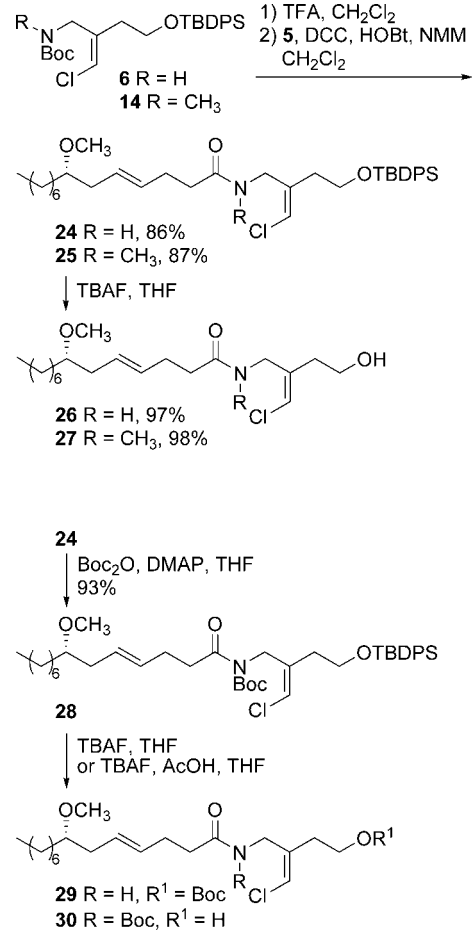

TABLE 2. Deprotection of Silyl Ether 28

entry	condition	product	% conversion
1	TBAF	only **29**	95
2	TBAF:AcOH (3:1)	**30**:**29** (1:1)	92
3	TBAF:AcOH (1:1)	**30**:**29** (20:1)	89

which was used in the next step without purification. Condensation of **31** with the enolate of pyrrolidone (*S*)-**8** in the presence of $TiCl_4$/*i*-Pr_2NEt afforded a diastereomeric mixture of alcohols **23** in 56% (brsm 91%) yield for two steps. The diastereomeric mixture of alcohols **33** was also prepared by using the similar procedure described above in 57% (brsm 92%) yield for two steps. Both alcohols **23** and **33** were immediately submitted for oxidation to give the β-keto esters **34** and **35** with Dess−Martin periodinane in CH_2Cl_2 in 75% and 73% yields, respectively. At this stage, we are faced with the task of forming the methyl enol ethers of β-keto esters **34** and **35**. Several conditions including NaH/Me_2SO_4/HMPA, K_2CO_3/Me_2SO_4/DMSO, and K_2CO_3/Me_2SO_4/acetone tested on compound **34** were all unsuccessful due to decomposition under basic conditions. So acidic conditions were attempted, and the desired methyl enol ether was achieved as expected. Thus, treatment of **34** with trimethyl orthoformate in the presence of a catalytic amount of sulfuric acid in MeOH gave the desired malyngamide R (**4**) in 52% yield with the TBS group removed simultaneously.[21] On the other hand, intermediate **36** with only the TBS group

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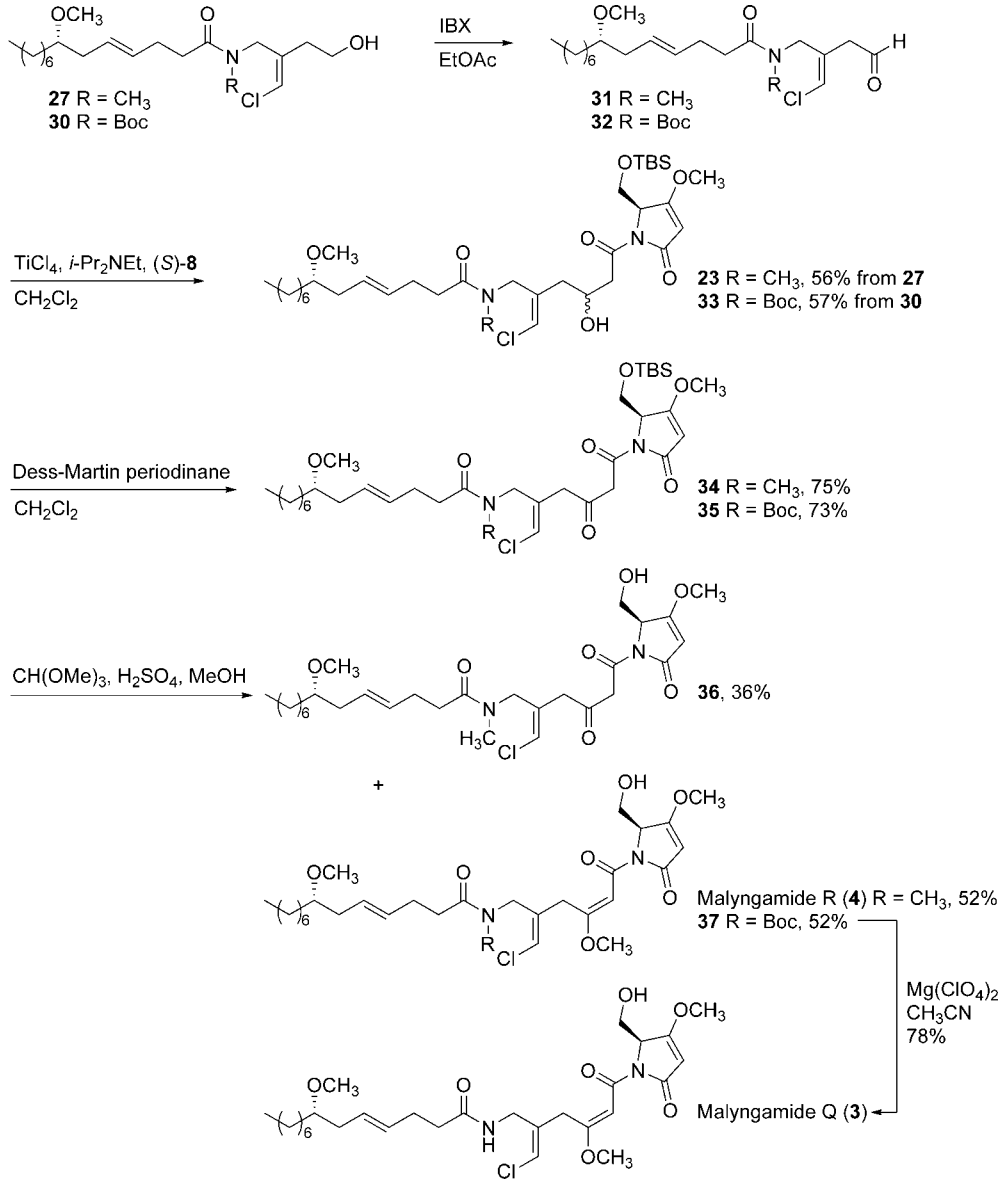
SCHEME 7. Preparation of Malyngamides Q and R



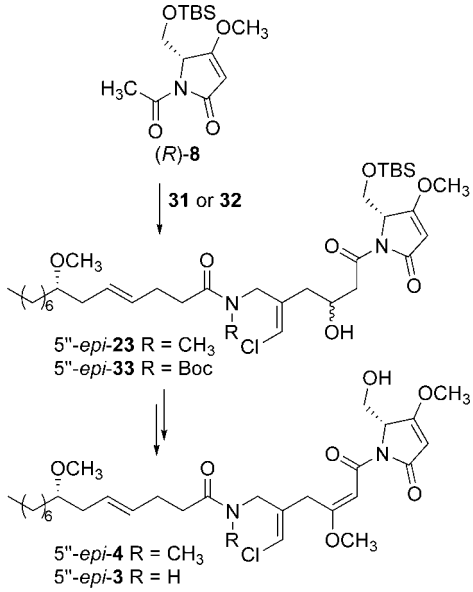
removed was also obtained in 36% yield, which could be transformed to **4** in 50% yield when repeated under the same conditions. The 4′*E*- and 2′*Z*-configuration double bonds in the amine moiety of **4** were confirmed by NOE experiments. Hence, selective irradiation of H-5′ of **4** resulted in signal enhancement of H-8′, while selective irradiation of H-7′ resulted in enhancement of H-3′a (see the Supporting Information). The spectral data and optical rotation value of synthetic **4** were in good agreement with isolated **4**.[1d] Using the similar route for the preparation of malyngamide R, enol methylation of **35** gave *N*-Boc protected **37** in 52% yield. Removal of the Boc group by various concentrations of TFA gave either starting material or decomposed mixture.[22] Finally, according to the literature,[23] the preparation of malyngamide Q (**3**) was accomplished under the mild Lewis acid $Mg(ClO_4)_2$ in CH_3CN in 78% (brsm 87%) yield. The NMR spectral data and optical rotation value of synthetic **3** were all consistent with those reported in the literature.[1d] In the accumulation of ^{13}C NMR spectrum, compound **3** was found to decompose in $CDCl_3$ for 1.5 h, but was stable in the pretreated $CDCl_3$ bypass through a short column of neutral Al_2O_3.

The chirality of the stereocenter C-5″ in the amine portion was determinated as the *S* configuration by chiral GCMS analysis of the amino acid fragment produced from the isolated malyngamide R (**4**) by degradative methods. However, the chirality of the stereocenter C-5″ in the amine portion of malyngamide Q (**3**) was not determined directly, and it was assigned with the same absolute configuration as that of C-5″ in malyngamide R (the structures of isolated malyngamides Q and R were drawn incorrectly as having the *R* configuration at the C-5″ position in the literature).[1d] To further confirm the structures of malyngamides Q and R, the other two diastereoisomers were then synthesized (Scheme 8). Thus,

(22) (a) Connell, R. D.; Rein, T.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845. (b) Papageorgiou, G.; Ogden, D.; Corrie, J. E. T. *J. Org. Chem.* **2004**, *69*, 7228. (c) Farran, D.; Toupet, L.; Martinez, J.; Dewynter, G. *Org. Lett.* **2007**, *9*, 4833. (d) Ferreira, P. M. T.; Monteiro, L. S.; Pereira, G.; Ribeiro, L.; Sacramento, J.; Silva, L. *Eur. J. Org. Chem.* **2007**, 5934.

(23) (a) Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. *Tetrahedron Lett.* **1993**, *34*, 7873. (b) Padwa, A.; Zhang, H. J. *J. Org. Chem.* **2007**, *72*, 2570. (c) Burkhart, F.; Hoffmann, M.; Kessler, H. *Angew. Chem., Int. Ed.* **1997**, *36*, 1191.

SCHEME 8. Preparation of 5″-*epi*-3 and 5″-*epi*-4



beginning with (*R*)-**8**, after aldol reaction with compound **31** or **32**, followed by Dess−Martin oxidation, enol methylation, and deprotection of the Boc group, 5″-*epi*-**4** and 5″-*epi*-**3** were accomplished in 21% and 17% yields, respectively, from (*R*)-**8**. The NMR data of 5″-*epi*-**3** and 5″-*epi*-**4** were identical to the data reported for isolated **3** and **4**, presumably because the chiral centers between the fatty acid and amine moieties were too remote from each other. This deduction was also confirmed by our similar observations of the spectral data from the total synthesis and correct absolute configuration of malyngamide U, and the synthesis of serinol-derived malyngamides and their 1′-*epi* isomers.[1e,4] The specific rotation values of 5″-*epi*-**3** and 5″-*epi*-**4** were found to be $[\alpha]^{20}_D$ −37 (*c* 0.4, MeOH) and $[\alpha]^{20}_D$ −46 (*c* 1.0, MeOH), which were different from the reported values of $[\alpha]^{20}_D$ +2.1 (*c* 0.8, MeOH) and $[\alpha]^{20}_D$ +2 (*c* 0.9, MeOH) for isolated **3** and **4**.[1d] The specific rotation values of the synthetic **3** and **4** were found to be $[\alpha]^{20}_D$ +4.5 (*c* 1.0, MeOH) and $[\alpha]^{20}_D$ +4 (*c* 1.0, MeOH), which were consistent with those in isolated **3** and **4**. These results further prove that the absolute configuration of the 5″ position is *S* in malyngamide R, and also confirm the same configuration of malyngamide Q at the C-5″ position. It is very interesting to note that 5″-*epi*-**3** was more stable than synthetic **3** in $CDCl_3$, as it was not changed in $CDCl_3$ over a period of 2 h.

Conclusion

In summary, we have achieved the first total synthesis of novel chlorinated malyngamides O, P, Q, and R via a highly convergent strategy. The determination of the absolute configuration of C-5″ in the amine portion of malyngamides Q and R was accomplished by total synthesis and the synthesis of their diastereomers 5″-*epi*-**3** and 5″-*epi*-**4**. The key steps involved a Wittig reaction employed in the preparation of terminal vinyl chlorides with a *Z*-configuration, an amidation, and an aldol reaction. Further application of this strategy toward the synthesis of the structurally related malyngamides with a vinylic chloride functionality such as A, B, iso-A, iso-B, F, G, I, K, M, and T is currently in progress and will be presented in due course.

Experimental Section

(2*Z*)-*N*-(*tert*-Butoxycarbonyl)-4-(*tert*-butyldiphenylsilyloxy)-2-(chloromethylene)-1-butylamine [(*Z*)-6]. To a solution of amide alcohol **9** (840 mg, 1.89 mmol) in dry EtOAc (15 mL) was added IBX (1.59 g, 5.67 mmol) under an argon atmosphere. The resulting suspension was refluxed for 8 h. The reaction was cooled to rt and filtered through a short column with EtOAc as an eluent to give the crude ketone. To a suspension of $Ph_3P^+CH_2ClI^-$ (2.90 g, 6.62 mmol) in dry THF (50 mL) was added *n*-BuLi (1.89 mL, 2.5 M in hexane, 4.73 mmol) at −78 °C. The mixture was stirred at this temperature for 1 h and allowed to warm to −30 °C slowly. The resulting red solution was recooled to −78 °C, and the above ketone was added in dry THF (5 mL) dropwise. After an additional 2 h, the reaction mixture was warmed to −30 °C and stirred for 1 h, and then quenched by the addition of saturated NH_4Cl solution (40 mL) and extracted with Et_2O (4 × 35 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 30:1) afforded compound (*Z*)-**6** (483 mg, 54% yield) as a colorless oil. IR (KBr) 2933, 1714, 1504, 1169, 1109, 739, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.11 (s, 9H, 3 × CH_3), 1.48 (s, 9H, 3 × CH_3), 2.38 (t, J = 6.2 Hz, 2H, H-3), 3.80 (t, J = 6.2 Hz, 2H, H-4), 3.93 (d, J = 5.7 Hz, 2H, H-1), 4.95 (br, 1H, NH), 5.98 (s, 1H, H-5), 7.39−7.48 (m, 6H, 6 × ArH), 7.69−7.72 (m, 4H, 4 × ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0 (C), 26.7 (CH_3), 28.2 (CH_3), 36.1 (CH_2, C-3), 39.5 (CH_2, C-1), 62.1 (CH_2, C-4), 79.1 (C), 116.2 (CH, C-5), 127.6 (CH), 129.6 (CH), 133.2 (C), 135.4 (CH), 136.9 (C, C-2), 155.8 (C); HRMS (ESI) *m*/*z* $C_{26}H_{37}ClNO_3Si$ $[M + H]^+$ calcd 474.2226, found 474.2224.

(5*Z*)-Methyl 6-(*tert*-Butoxycarbonylmethylamino)-5-(chloromethylene)-3-hydroxyhexanoate (17). To a solution of alcohol **15** (230 mg, 0.92 mmol) in dry EtOAc (8 mL) was added IBX (773 mg, 2.76 mmol) under an argon atmosphere. The resulting suspension was refluxed for 6 h. The reaction was then cooled to rt and filtered through a short column with EtOAc as an eluent to give the crude aldehyde **16**. To a solution of LDA (0.46 mL, 2 M in THF/pentane, 0.92 mmol) in dry THF (1.5 mL) was added a solution of methyl acetate (**7**) (68 mg, 0.92 mmol) in THF (1 mL) dropwise over 6 min under an argon atmosphere at −78 °C. The mixture was stirred for 40 min at this temperature, followed by the addition of the crude aldehyde **16** in THF (1 mL) via syringe. After being stirred for 1 h at −78 °C, the reaction mixture was quenched by the addition of saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 15 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 2:1) afforded ester **17** (169 mg, 57% yield) as a colorless oil. IR (KBr) 3429, 2976, 1737, 1694, 1394, 1252, 1158, 874, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H, 3 × CH_3), 2.19−2.21 (m, 2H, H-4), 2.44−2.46 (m, 2H, H-2), 2.78 (s, 3H, NCH_3), 3.71 (s, 3H, OCH_3), 4.11−4.26 (m, 3H, H-3 and H-6), 6.13 (s, 1H, H-7); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.1 (CH_3), 33.5 (NCH_3), 39.0 (CH_2, C-4), 41.1 (CH_2, C-2), 46.4 (CH_2, C-6), 51.6 (OCH_3), 65.4/66.4 (CH, C-3), 79.9 (C), 117.7 (CH, C-7), 135.0 (C, C-5), 156.3 (C), 172.3 (C, C-1); HRMS (ESI) *m*/*z* $C_{14}H_{24}ClNO_5Na$ $[M + Na]^+$ calcd 344.1235, found 344.1241.

***E*,(7*S*)-*N*-[(2*Z*)-(Chloromethylene)-4-oxo-5-(methoxycarbonyl)-pentanyl]-7-methoxy-*N*′-methyltetradec-4-enamide [Malyngamide P (2)].**[1c] To a stirred solution of compound **18** (57 mg, 0.12 mmol) in CH_2Cl_2 (4 mL) was added Dess−Martin periodinane (140 mg, 0.30 mmol) at 0 °C. The reaction mixture was stirred for 2.5 h at this temperature, and the solution was then concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 3:1 to 2:1) afforded malyngamide P (**2**) (39 mg, 71% yield) as a colorless oil. $[\alpha]^{20}_D$ −72 (*c* 0.05, MeOH) [lit.[1c] $[\alpha]^{20}_D$ −75 (*c* 0.02, MeOH)]; IR (KBr) 2928, 2855, 1742, 1723, 1644, 1406, 1098, 972, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.6 Hz, 3H, H-14), 1.27−1.36 (m, 10H, 5 × CH_2, H-9, H-10, H-11, H-12, and H-13), 1.42−1.45 (m, 2H, H-8), 2.19 (t, J = 5.4 Hz, 2H, H-6), 2.34−2.36 (m, 4H, H-2 and H-3), 2.90/2.92 (s, 3H, NCH_3), 3.15 (t, J = 6.0 Hz, 1H, H-7), 3.29 (s, 2H, H-3′), 3.33 (s, 3H, OCH_3, H-15), 3.46/3.50 (s, 2H, H-5′), 3.73/

3.74 (s, 3H, OCH_3), 4.22/4.25 (s, 2H, H-1′), 5.46−5.55 (m, 2H, H-4 and H-5), 6.10/6.17 (s, 1H, H-7′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0 (CH_3, C-14), 22.5 (CH_2, C-13), 25.2 (CH_2, C-9), 27.9 (CH_2, C-3), 29.2 (CH_2, C-11), 29.6 (CH_2, C-10), 31.7 (CH_2, C-12), 33.0 (CH_2, C-2), 33.2 (CH_2, C-8), 35.1 (NCH_3), 36.2 (CH_2, C-6), 46.1 (CH_2, C-3′), 46.2 (CH_2, C-1′), 48.8 (CH_2, C-5′), 52.2 (OCH_3), 56.4 (OCH_3, C-15), 80.6 (CH, C-7), 120.3 (CH, C-7′), 127.0 (CH, C-4), 131.1 (CH, C-5), 131.4 (C, C-2′), 167.4 (C, C-6′), 173.2 (C, C-1), 199.3 (C, C-4′); MS (ESI) *m*/*z* 458.4 ([M + H]$^+$).

***E*,(7*S*)-*N*-[(2*Z*,4*E*)-2-(Chloromethylene)-4-methoxy-5-(methoxycarbonyl)-4-pentenyl]-7-methoxy-*N*′-methyltetradec-4-enamide [Malyngamide O (1)].**[1c] To a suspension of NaH (3 mg, 55% in mineral oil, 0.08 mmol) in HMPA (1.2 mL) was added a solution of compound **2** (19 mg, 0.04 mmol) in HMPA (0.2 mL) via syringe at 0 °C, then the mixture was stirred until gas evolution ceased. Dimethyl sulfate (11 mg, 0.09 mmol) was then added. The reaction was stirred for 30 h at rt, followed by the addition of saturated NH_4Cl solution (8 mL), and extracted with Et_2O (3 × 10 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 4:1 to 3:1) afforded malyngamide O (**1**) (10 mg, 53% yield) as a colorless oil. $[\alpha]^{20}_D$ −53 (*c* 0.05, MeOH) [lit.[1c] $[\alpha]^{20}_D$ −55.6 (*c* 0.018, MeOH)]; IR (KBr) 2927, 2854, 1711, 1649, 1627, 1282, 1141, 824 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J* = 6.9 Hz, 3H, H-14), 1.21−1.31 (m, 10H, 5 × CH_2, H-9, H-10, H-11, H-12, and H-13), 1.38−1.44 (m, 2H, H-8), 2.19 (t, *J* = 5.6 Hz, 2H, H-6), 2.35−2.42 (m, 4H, H-2 and H-3), 2.85/2.90 (s, 3H, NCH_3), 3.15 (t, *J* = 5.6 Hz, 1H, H-7), 3.33 (s, 3H, OCH_3, H-15), 3.51/3.54 (s, 2H, H-3′), 3.64 (s, 3H, OCH_3, H-8′), 3.66/3.68 (s, 3H, OCH_3), 4.18/4.33 (s, 2H, H-1′), 5.10 (s, 1H, H-5′), 5.47−5.53 (m, 2H, H-4 and H-5), 6.07/6.19 (s, 1H, H-7′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1 (CH_3, C-14), 22.7 (CH_2, C-13), 25.3 (CH_2, C-9), 28.1/28.3 (CH_2, C-3), 29.3 (CH_2, C-11), 29.7 (CH_2, C-10), 31.8 (CH_2, C-12), 33.0/33.9 (NCH_3), 33.3 (CH_2, C-2), 33.3 (CH_2, C-8), 33.9/34.3 (CH_2, C-3′), 36.3 (CH_2, C-6), 45.2/48.8 (CH_2, C-1′), 50.9/51.1 (OCH_3), 55.7 (OCH_3, C-8′), 56.5 (OCH_3, C-15), 80.8 (CH, C-7), 92.1 (CH, C-5′), 117.7/118.8 (CH, C-7′), 127.0 (CH, C-4), 131.3/131.4 (CH, C-5), 133.6/134.5 (C, C-2′), 167.6 (C, C-6′), 171.5/171.6 (C, C-4′), 172.8 (C, C-1); MS (ESI) *m*/*z* 472.4 ([M + H]$^+$).

***E*,(7*S*)-*N*-{(2*Z*)-(Chloromethylene)-4-hydroxy-6-oxo-[(5*S*)-(*tert*-butyldimethylsilyloxymethyl)-4-methoxy-2-oxo-1*H*-pyrrol-1(5*H*)-yl]hexyl}-7-methoxy-*N*′-methyltetradec-4-enamide and *E*,(7*S*)-*N*-{(2*Z*)-(Chloromethylene)-4-hydroxy-6-oxo-[(5*R*)-(*tert*-butyldimethylsilyloxymethyl)-4-methoxy-2-oxo-1*H*-pyrrol-1(5*H*)-yl]hexyl}-7-methoxy-*N*′-methyltetradec-4-enamide (23 and 5″-*epi*-23).** To a stirred solution of compound **22** (35 mg, 0.07 mmol) in CH_2Cl_2 (3 mL) was added TFA (1 mL) at 0 °C, and the mixture was stirred at this temperature for 1 h, followed by the addition of saturated $NaHCO_3$ solution (6 mL), and extracted with CH_2Cl_2 (3 × 6 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated to afford the crude methylamine as a pale yellow oil. To a stirred solution of the methylamine in CH_2Cl_2 (2 mL) was added acid **5** (18 mg, 0.07 mmol) in CH_2Cl_2 (1 mL), DCC (17 mg, 0.08 mmol), HOBt (11 mg, 0.08 mmol), and NMM (8 mg, 0.08 mmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h, and the stirring was continued for 8 h, followed by concentration in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 1:1) afforded alcohol **23** (3 mg, 6% yield) as a colorless oil. Compound **23** had also been prepared by the below method. Then, to a solution of compound **27** (364 mg, 0.94 mmol) in dry EtOAc (15 mL) was added IBX (790 mg, 2.82 mmol) under argon atmosphere. The resulting suspension was reflux for 8 h. The reaction was then cooled to rt and filtered through a short column with EtOAc as an eluent to give the crude aldehyde **31**. To a stirred solution of (*S*)-**8** (255 mg, 0.85 mmol) in dry CH_2Cl_2 (4.5 mL) was added $TiCl_4$ (0.10 mL, 0.94 mmol) dropwise in CH_2Cl_2 (1 mL) under argon atmosphere at −78 °C, and the mixture was stirred for 10 min at this temperature. Diisopropylethylamine (0.35 mL, 2.13 mmol) was then added dropwise slowly, and the mixture was stirred at the same temperature for 2.5 h. Subsequently, a solution of aldehyde **31** in CH_2Cl_2 (2 mL) was added dropwise, and the reaction was stirred at −78 °C for 30 min. The reaction mixture was allowed to warm to 0 °C slowly and stirred at 0 °C for another 2 h, followed by the addition of saturated NH_4Cl solution (10 mL) at 0 °C. The solution was then warmed to rt and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 3:1 to 1:1) afforded the secondary alcohol **23** (325 mg, 56% yield) as a colorless oil. $[\alpha]^{20}_D$ +34 (*c* 1.0, $CHCl_3$); IR (KBr) 3405, 2929, 1729, 1632, 1321, 1114 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.09 (s, 3H, CH_3), −0.07 (s, 3H, CH_3), 0.76 (s, 9H, 3 × CH_3), 0.83 (t, *J* = 6.4 Hz, 3H, H-14), 1.21−1.25 (m, 10H, 5 × CH_2, H-9, H-10, H-11, H-12, and H-13), 1.38−1.40 (m, 2H, H-8), 2.13−2.16 (m, 4H, 2 × CH_2), 2.30−2.36 (m, 4H, 2 × CH_2), 2.81−2.88 (m, 4H, NCH_3 and H-5′a), 3.11 (t, *J* = 5.6 Hz, 1H, H-7), 3.18 (dd, *J* = 17.6 and 3.2 Hz, 1H, H-5′b), 3.28 (s, 3H, OCH_3, H-15), 3.81−3.87 (m, 4H, H-4′ and H-7″), 4.19−4.29 (m, 3H, H-1′ and H-6″a), 4.39 (d, *J* = 14.4 Hz, 1H, H-6″b), 4.50−4.53 (m, 1H, H-5″), 5.07/5.05 (s, 1H, H-3″), 5.41−5.52 (m, 2H, H-4 and H-5), 6.16 (s, 1H, H-7′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.8 (CH_3), −5.7 (CH_3), 14.0 (CH_3, C-14), 17.9 (C), 22.5 (CH_2), 25.2 (CH_2), 25.5 (CH_3), 28.1 (CH_2), 29.2 (CH_2), 29.7 (CH_2), 31.7 (CH_2), 33.2 (CH_2), 33.3 (CH_2), 34.4 (NCH_3), 36.3 (CH_2), 39.1 (CH_2, C-3′), 43.7 (CH_2, C-5′), 45.1 (CH_2, C-1′), 56.4 (OCH_3, C-15), 58.6 (CH and CH_2, C-5″ and C-6″), 61.1 (OCH_3, C-7″), 65.9 (CH, C-4′), 80.7 (CH, C-7), 94.8 (CH, C-3″), 118.0 (CH, C-7′), 127.1 (CH, C-5), 131.1 (CH, C-4), 135.0 (C, C-2′), 170.4 (C, C-4″), 171.7 (C, C-2″), 172.9 (C, C-1), 177.2 (C, C-6′); HRMS (ESI) *m*/*z* $C_{35}H_{62}ClN_2O_7Si$ [M + H]$^+$ calcd 685.4009, found 685.4020. (A mixture of diastereomeric alcohol **23**, which could be used in the next step for oxidation directly, could be separated by flash chromatography. The large amount of isomers was used for spectral determination. Though absolute configuration of compound **23** was not comfirmed. The same phenomenon was found in compound 5″-*epi*-**23**.)

According to the preceding procedure (the second method), **27** (407 mg, 1.05 mmol) and (*R*)-**8** (285 mg, 0.95 mmol) afforded alcohols 5″-*epi*-**23** (364 mg, 56% yield) as a colorless oil. $[\alpha]^{20}_D$ −38 (*c* 1.0, $CHCl_3$); IR (KBr) 3404, 2928, 2855, 1631, 1321, 1114, 835, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.09 (s, 3H, CH_3), −0.08 (s, 3H, CH_3), 0.76 (s, 9H, 3 × CH_3), 0.83 (t, *J* = 6.3 Hz, 3H, H-14), 1.20−1.24 (m, 10H, 5 × CH_2, H-9, H-10, H-11, H-12, and H-13), 1.36−1.40 (m, 2H, H-8), 2.12−2.14 (m, 4H, 2 × CH_2), 2.31−2.34 (m, 4H, 2 × CH_2), 2.83−2.87 (m, 4H, NCH_3 and H-5′a), 3.11 (t, *J* = 6.0 Hz, 1H, H-7), 3.18 (dd, *J* = 17.7 and 3.6 Hz, 1H, H-5′b), 3.28 (s, 3H, OCH_3, H-15), 3.81−3.85 (m, 4H, H-4′ and H-7″), 4.19−4.24 (m, 3H, H-1′ and H-6″a), 4.36−4.41 (m, 1H, H-6″b), 4.50−4.53 (m, 1H, H-5″), 5.05/5.10 (s, 1H, H-3″), 5.44−5.46 (m, 2H, H-4 and H-5), 6.16 (s, 1H, H-7′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.8 (CH_3), −5.7 (CH_3), 14.0 (CH_3, C-14), 17.9 (C), 22.5 (CH_2), 25.2 (CH_2), 25.5 (CH_3), 28.0 (CH_2), 29.2 (CH_2), 29.6 (CH_2), 31.7 (CH_2), 33.3 (2 × CH_2), 34.4 (NCH_3), 36.3 (CH_2), 39.1 (CH_2), 43.6 (CH_2, C-5′), 45.1 (CH_2, C-1′), 56.4 (OCH_3, C-15), 58.5 (CH, C-5″), 58.6 (CH_2, C-6″), 61.1 (OCH_3, C-7″), 65.8 (CH, C-4′), 80.6 (CH, C-7), 94.8 (CH, C-3″), 118.0 (CH, C-7′), 127.1 (CH, C-5), 131.1 (CH, C-4), 135.0 (C, C-2′), 170.4 (C, C-4″), 171.6 (C, C-2″), 173.0 (C, C-1), 177.2 (C, C-6′); HRMS (ESI) *m*/*z* $C_{35}H_{62}ClN_2O_7Si$ [M + H]$^+$ calcd 685.4009, found 685.4015.

***E*,(7S)-*N*-{(2*Z*,4*E*)-2-(Chloromethylene)-4-methoxy-6-oxo-[(5*S*)-hydroxymethyl-4-methoxy-2-oxo-1*H*-pyrrol-1(5*H*)-yl]-4-hexenyl}-7-methoxy-*N*′-methyltetradec-4-enamide and *E*,(7*S*)-*N*-{(2*Z*,4*E*)-2-(Chloromethylene)-4-methoxy-6-oxo-[(5*R*)-hydroxymethyl-4-methoxy-2-oxo-1*H*-pyrrol-1(5*H*)-yl]-4-hexenyl}-7-methoxy-*N*′-methyltetradec-4-enamide [Malyngamide R (4)[1d] and 5″-*epi*-4].** To a stirred solution of β-keto ester **34** (35 mg, 0.05 mmol) in MeOH (1.1 mL) was added trimethylorthoformate (0.22 mL, 2.02 mmol)

and sulfuric acid (2 mg, 0.02 mmol). The reaction mixture was stirred for 30 h at rt, followed by the addition of saturated $NaHCO_3$ solution (1 mL), and extracted with EtOAc (3 × 5 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 1:2) afforded pure malyngamide R (**4**) (15 mg, 52% yield) and β-keto ester **36** (10 mg, 36% yield) as a colorless oil. $[\alpha]^{20}_D$ +4 (*c* 1.0, MeOH) [lit.[1d] $[\alpha]^{20}_D$ +2 (*c* 0.9, MeOH)]; IR (KBr) 3397, 2929, 1718, 1629, 1460, 1389, 1316, 1164, 1075, 976, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 6.0 Hz, 3H, H-14), 1.23−1.32 (m, 10H, 5 × CH_2, H-9, H-10, H-11, H-12, and H-13), 1.37−1.40 (m, 2H, H-8), 2.14−2.31 (m, 6H, H-2, H-3 and H-6), 2.78/2.82 (s, 3H, NCH_3), 2.92 (d, J = 14.8 Hz, 1H, H-3′a), 3.09−3.11 (m, 1H, H-7), 3.29 (s, 3H, OCH_3, H-15), 3.65/3.70 (s, 3H, OCH_3, H-8′), 3.79 (d, J = 14.7 Hz, 1H, H-6″a), 3.86 (s, 3H, OCH_3, H-7″), 3.97 (d, J = 13.6 Hz, 1H, H-1′a), 4.31−4.55 (m, 4H, H-3′b, H-1′b, H-5″, H-6″b), 5.08/5.10 (s, 1H, H-3″), 5.41−5.43 (m, 2H, H-4 and H-5), 6.14/6.16 (s, 1H, H-7′), 6.82/6.96 (s, 1H, H-5′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (CH_3, C-14), 22.6 (CH_2, C-12), 25.3 (CH_2, C-9), 28.0 (CH_2, C-3), 29.3 (CH_2, C-10), 29.8 (CH_2, C-13), 31.8 (CH_2, C-11), 33.4 (CH_2, C-2), 33.4 (CH_2, C-8), 33.8 (NCH_3), 36.4 (CH_2, C-3′), 36.7 (CH_2, C-6), 44.7 (CH_2, C-1′), 55.7 (OCH_3, C-8′), 56.5 (OCH_3, C-15), 58.6 (OCH_3, C-7″), 59.2 (CH_2, C-6″), 62.5 (CH, C-5″), 80.8 (CH, C-7), 95.1 (2 × CH, C-5′ and C-3″), 119.9 (CH, C-7′), 127.4 (CH, C-5), 130.8 (CH, C-4), 133.5 (C, C-2′), 165.3 (C, C-6′), 170.9 (C, C-4′), 170.9 (C, C-2″), 173.5 (C, C-1), 176.9 (C, C-4″); HRMS (ESI) *m/z* $C_{30}H_{48}ClN_2O_7$ $[M + H]^+$ calcd 583.3145, found 583.3150. (The data of ^{13}C NMR spectrum were identified via following ref 1d, as for 5″-*epi*-**4**.)

According to the preceding procedure, 5″-*epi*-**34** (21 mg, 0.03 mmol) afforded amide 5″-*epi*-**4** (9 mg, 53% yield) as a pale yellow oil. $[\alpha]^{20}_D$ −46 (*c* 1.0, MeOH); IR (KBr) 3398, 2929, 1717, 1630, 1389, 1316, 1248, 1212, 1163, 1097, 975, 844 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 6.0 Hz, 3H, H-14), 1.23−1.30 (m, 10H, 5 × CH_2, H-9, H-10, H-11, H-12, and H-13), 1.38−1.40 (m, 2H, H-8), 2.14−2.32 (m, 6H, H-2, H-3, and H-6), 2.78/2.83 (s, 3H, NCH_3), 2.94 (d, J = 14.8 Hz, 1H, H-3′a), 3.09−3.12 (m, 1H, H-7), 3.29 (s, 3H, OCH_3, H-15), 3.65/3.70 (s, 3H, OCH_3, H-8′), 3.79 (d, J = 12.0 Hz, 1H, H-6″a), 3.86 (s, 3H, OCH_3, H-7″), 3.98 (d, J = 13.6 Hz, 1H, H-1′a), 4.30−4.55 (m, 4H, H-3′b, H-1′b, H-5″, H-6″b), 5.09/5.10 (s, 1H, H-3″), 5.40−5.45 (m, 2H, H-4 and H-5), 6.14/6.16 (s, 1H, H-7′), 6.82/6.96 (s, 1H, H-5′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (CH_3, C-14), 22.6 (CH_2, C-12), 25.3 (CH_2, C-9), 28.1 (CH_2, C-3), 29.3 (CH_2, C-10), 29.8 (CH_2, C-13), 31.8 (CH_2, C-11), 33.4 (CH_2, C-2), 33.5 (CH_2, C-8), 33.9 (NCH_3), 36.4 (CH_2, C-3′), 36.7 (CH_2, C-6), 44.7 (CH_2, C-1′), 55.7 (OCH_3, C-8′), 56.5 (OCH_3, C-15), 58.6 (OCH_3, C-7″), 59.3 (CH_2, C-6″), 62.5 (CH, C-5″), 80.8 (CH, C-7), 95.1 (CH, C-3″), 95.2 (CH, C-5′), 119.8 (CH, C-7′), 127.5 (CH, C-5), 130.8 (CH, C-4), 133.6 (C, C-2′), 165.3 (C, C-6′), 170.9 (C, C-4′), 170.9 (C, C-2″), 173.5 (C, C-1), 176.9 (C, C-4″); HRMS (ESI) *m/z* $C_{30}H_{48}ClN_2O_7$ $[M + H]^+$ calcd 583.3145, found 583.3148.

***E*,(7*S*)-*N*-{(2*Z*,4*E*)-2-(Chloromethylene)-4-methoxy-6-oxo-[(5*S*)-hydroxymethyl-4-methoxy-2-oxo-1*H*-pyrrol-1(5*H*)-yl]-4-hexenyl}-7-methoxytetradec-4-enamide and *E*,(7*S*)-*N*-{(2*Z*,4*E*)-2-(Chloromethylene)-4-methoxy-6-oxo-[(5*R*)-hydroxymethyl-4-methoxy-2-oxo-1*H*-pyrrol-1(5*H*)-yl]-4-hexenyl}-7-methoxytetradec-4-enamide [Malyngamide Q (3)[1d] and 5″-*epi*-3].** To a stirred solution of enol methyl ether **37** (27 mg, 0.04 mmol) in CH_3CN (1 mL) was added $Mg(ClO_4)_2$ (4 mg, 0.02 mmol). The reaction mixture was heated to 50 °C for 10 h, then cooled to rt and diluted with $NaHCO_3$ (5 drops), then the solvent was concentrated in vavuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 1:4) afforded malyngamide Q (**3**) (18 mg, 78% yield) as a colorless oil. $[\alpha]^{20}_D$ +4.5 (*c* 1.0, MeOH) [lit.[1d] $[\alpha]^{20}_D$ +2.1 (*c* 0.8, MeOH)]; IR (KBr) 3314, 2928, 1718, 1632, 1318, 1214, 1163, 975, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 6.8 Hz, 3H, H-14), 1.23−1.25 (m, 10H, 5 × CH_2, H-9, H-10, H-11, H-12, and H-13), 1.38−1.39 (m, 2H, H-8), 2.13−2.27 (m, 6H, H-2, H-3 and H-6), 3.07−3.12 (m, 2H, H-3′a and H-7), 3.28 (s, 3H, OCH_3, H-15), 3.68 (s, 3H, OCH_3, H-8′), 3.80 (dd, J = 12.0 and 2.4 Hz, 1H, H-6″a), 3.87 (s, 3H, OCH_3, H-7″), 3.96 (dd, J = 14.0 and 5.2 Hz, 1H, H-1′a), 4.12 (dd, J = 14.0 and 6.8 Hz, 1H, H-1′b), 4.18 (d, J = 13.6 Hz, 1H, H-3′b), 4.36 (dd, J = 12.0 and 2.4 Hz, 1H, H-6″b), 4.59−4.61 (m, 1H, H-5″), 5.11 (s, 1H, H-3″), 5.40−5.44 (m, 2H, H-4 and H-5), 5.95 (br, 1H, NH), 6.04 (s, 1H, H-7′), 6.90 (s, 1H, H-5′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (CH_3, C-14), 22.6 (CH_2, C-12), 25.3 (CH_2, C-9), 28.4 (CH_2, C-3), 29.3 (CH_2, C-11), 29.7 (CH_2, C-10), 31.8 (CH_2, C-13), 33.3 (CH_2, C-8), 36.2 (CH_2, C-2), 36.3 (CH_2, C-6), 36.6 (CH_2, C-3′), 37.8 (CH_2, C-1′), 56.0 (OCH_3, C-8′), 56.4 (OCH_3, C-15), 58.7 (OCH_3, C-7″), 59.6 (CH_2, C-6″), 62.4 (CH, C-5″), 80.7 (CH, C-7), 95.1 (CH, C-3″), 95.4 (CH, C-5′), 118.3 (CH, C-7′), 127.6 (CH, C-5), 130.6 (CH, C-4), 135.3 (C, C-2′), 165.7 (C, C-6′), 170.8 (C, C-2″), 171.6 (C, C-4′), 172.7 (C, C-1), 176.7 (C, C-4″); HRMS (ESI) *m/z* $C_{29}H_{45}ClN_2O_7Na$ $[M + Na]^+$ calcd 591.2808, found 591.2804.

According to the preceding procedure, 5″-*epi*-**37** (20 mg, 0.03 mmol) afforded 5″-*epi*-**3** (13 mg, 76% yield) as a pale yellow oil. $[\alpha]^{20}_D$ −37 (*c* 0.4, MeOH); IR (KBr) 3315, 2929, 1718, 1631, 1606, 1317, 1215, 1162, 1076, 974, 843 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 0.85 (t, J = 6.8 Hz, 3H, H-14), 1.22−1.24 (m, 10H, 5 × CH_2, H-9, H-10, H-11, H-12, and H-13), 1.39−1.40 (m, 2H, H-8), 2.13−2.26 (m, 6H, H-2, H-3, and H-6), 3.08−3.13 (m, 2H, H-3′a and H-7), 3.28 (s, 3H, OCH_3, H-15), 3.69 (s, 3H, OCH_3, H-8′), 3.80 (dd, J = 12.0 and 2.4 Hz, 1H, H-6″a), 3.87 (s, 3H, OCH_3, H-7″), 3.97 (dd, J = 14.0 and 5.2 Hz, 1H, H-1′a), 4.09−4.34 (m, 2H, H-1′b and H-3′b), 4.36 (dd, J = 12.0 and 2.4 Hz, 1H, H-6″b), 4.58−4.60 (m, 1H, H-5″), 5.11 (s, 1H, H-3″), 5.40−5.44 (m, 2H, H-4 and H-5), 5.97 (br, 1H, NH), 6.05 (s, 1H, H-7′), 6.89 (s, 1H, H-5′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (CH_3, C-14), 22.6 (CH_2, C-12), 25.3 (CH_2, C-9), 28.4 (CH_2, C-3), 29.3 (CH_2, C-11), 29.7 (CH_2, C-10), 31.8 (CH_2, C-13), 33.3 (CH_2, C-8), 36.3 (CH_2, C-2), 36.4 (CH_2, C-6), 36.7 (CH_2, C-3′), 37.9 (CH_2, C-1′), 56.0 (OCH_3, C-8′), 56.4 (OCH_3, C-15), 58.7 (OCH_3, C-7″), 59.8 (CH_2, C-6″), 62.5 (CH, C-5″), 80.7 (CH, C-7), 95.2 (CH, C-3″), 95.5 (CH, C-5′), 118.4 (CH, C-7′), 127.8 (CH, C-5), 130.6 (CH, C-4), 135.2 (C, C-2′), 165.7 (C, C-6′), 170.8 (C, C-2″), 171.6 (C, C-4′), 172.9 (C, C-1), 176.7 (C, C-4″); HRMS (ESI) *m/z* $C_{29}H_{45}ClN_2O_7Na$ $[M + Na]^+$ calcd 591.2808, found 591.2801.

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Supporting Information Available: Experimental procedures; list of spectral data for other compound; comparison of ^1H and ^{13}C NMR spectral data for malyngamides O and P (isolated **1** and **2**, synthetic **1** and **2**); ^1H NMR spectral data for malyngamides Q and R (isolated **3** and **4**, synthetic **3** and **4**) and 5″-*epi*-**3** and 5″-*epi*-**4**; ^{13}C NMR spectral data for malyngamides Q and R (isolated **3** and **4**, synthetic **3** and **4**) and 5″-*epi*-**3** and 5″-*epi*-**4**; ^1H, ^{13}C NMR, and DEPT 135 spectra of compounds **12**, **13**, **9**, **6**, **14**, **15**, **17**, **18**, **2**, **1**, (*S*)-**21**, (*R*)-**21**, (*S*)-**8**, (*R*)-**8**, **22**, **23**, 5″-*epi*-**23**, **24**, **26**, **27**, **28**, **29**, **30**, **33**, 5″-*epi*-**33**, **34**, 5″-*epi*-**34**, **35**, 5″-*epi*-**35**, **4**, **4** (NOE), 5″-*epi*-**4**, **37**, 5″-*epi*-**37**, **3**, and 5″-*epi*-**3**; comparison of ^1H and ^{13}C NMR spectra for malyngamides Q and R (isolated **3** and **4**, synthetic **3** and **4**) and 5″-*epi*-**3** and 5″-*epi*-**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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