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Total synthesis of malyngamide X and its 7′*S*-*epi* isomer

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Abstract—Stereoselective syntheses of malyngamide X (**1**) and its 7′(*S*)-epimer are described. A Lewis acid (Et_2AlCl) mediated *anti*-aldol reaction was employed to generate the stereocenters C-7 and C-8. The route is convergent and provides a convenient access to the synthesis of structural variants of malyngamide X. Stereochemistry at C-7′ in the molecules of natural and synthetic **1**, and 7′(*S*)-*epi* **1** was confirmed by NMR chiral solvation experiments.

1. Introduction

As part of our research program for biologically active compounds from Thai marine organisms, we have found a new malyngamide, which we named as malyngamide X (**1**) and isolated from EtOAc extract of sea hare *Bursatella leachii*.[1] Compound **1** possesses a new skeleton of malyngamide family, thus it includes an unusual tripeptide portion connecting to a methoxylated fatty acyl chain. It is active against malarial parasite *Plasmodium falciparum* (multidrug resistant strain) and tuberculous bacterium *Mycobacterium tuberculosis*. Absolute configurations of the four stereogenic centers in the tripeptide portion of **1** determined as 2*S*,5*S*,7*S*,8*R*, 14*S* were solved with various NMR spectral analyses and combined method with molecular mechanic calculations. For the remaining remote stereogenic center located in the fatty acyl chain, we have also reported that the diastereomeric solvates between **1** and the NMR chiral solvating agent (2,2,2-trifluoro-1-(9-anthryl)ethanol, TFAE, or Pirkle's alcohol)[2] showed unequivocal shifts of the 7′-OCH_3 proton signals ($\Delta\delta_{RS}<0$). Further, we have assigned 7′*R* to **1** by employing the same TFAE experiments with a known 7′*S*-isomalyngamide A and a series of two enantiomers at C-7′ of the synthetic fatty acyl fragments of **1** ($\Delta\delta_{RS}<0$ for 7′*R*-configuration and $\Delta\delta_{RS}>0$ for 7′*S*-configuration).[1] Continuation of our recent works on malyngamide X has prompted us to synthesize this unique malyngamide, which is available only in limited amount from nature. The synthesis allowed us to confirm its stereostructure and to perform further biological studies. Herein, we report a convenient and stereocontrolled total synthesis of both **1** and its 7′(*S*)-*epi* isomer.

2. Results and discussion

When we initiated the synthetic studies of malyngamide X, the C-7′ configuration was presumed to be *S* as it is the homolog of other malyngamides, which led us to adopt the synthetic route to malyngamide X having 7′*S*-configuration. Although the malyngamide 7′(*S*)-*epi* **1** exhibited completely identical ^1H and ^{13}C NMR data to that of natural malyngamide X, the specific rotation showed a little difference between each other. Fortunately, the 7′-OCH_3 signal in each compounds shifted to opposite direction (positive and negative) in the presence of the same NMR chiral solvent, thus, indicating opposite absolute configuration to each other. So that, the configuration at 7′ position in natural malyngamide X was concluded to be *R*.

2.1. Synthetic plan

As outlined in Scheme 1, the whole molecule of malyngamide X was retrosynthetically divided into four building blocks **2**–**5**; thus, the fatty acids (4*E*,7*R*)-(+)-7-methoxytetradec-4-enonic acid (**2a**) and (4*E*,7*S*)-(−)-7-methoxytetradec-4-enonic acid or lyngbic acid (**2b**)[3] could be synthesized from commercially available materials **6**–**8**. The two amino acid derivatives **3** and **4** would be generated from *N*-methyl-L-alanine and Boc-L-alanine methyl ester, respectively. The right segment, pyrrolidone derivative **5** would be derived from

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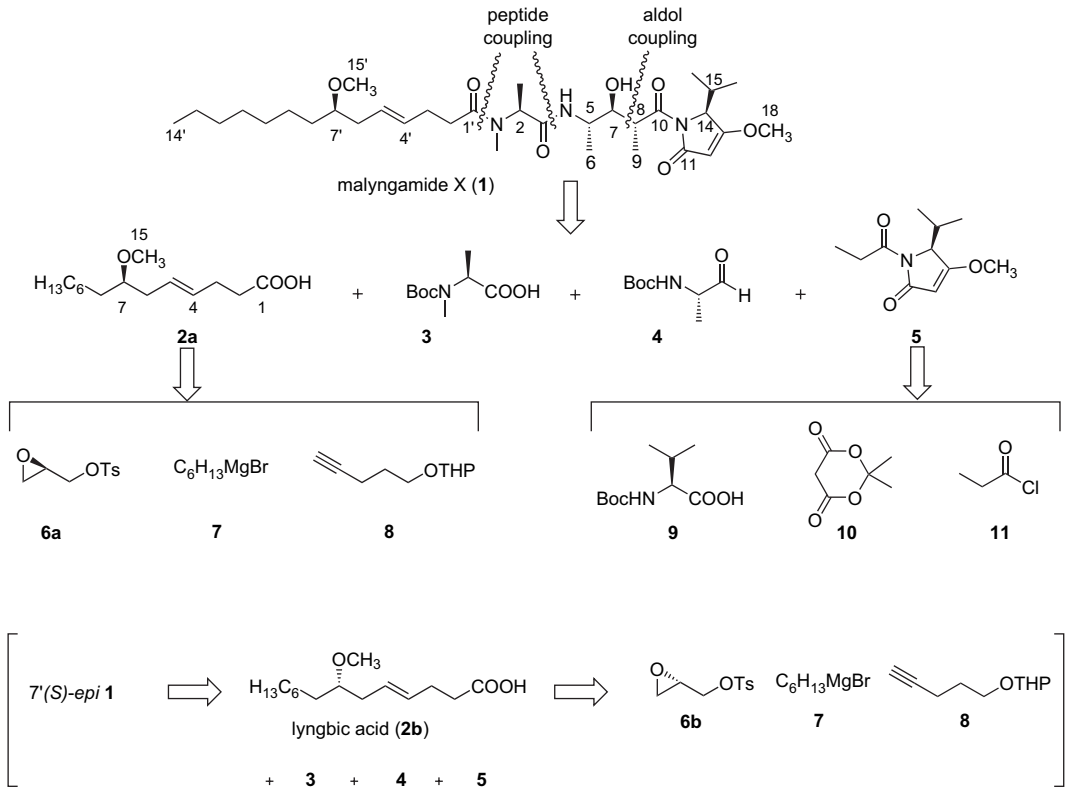


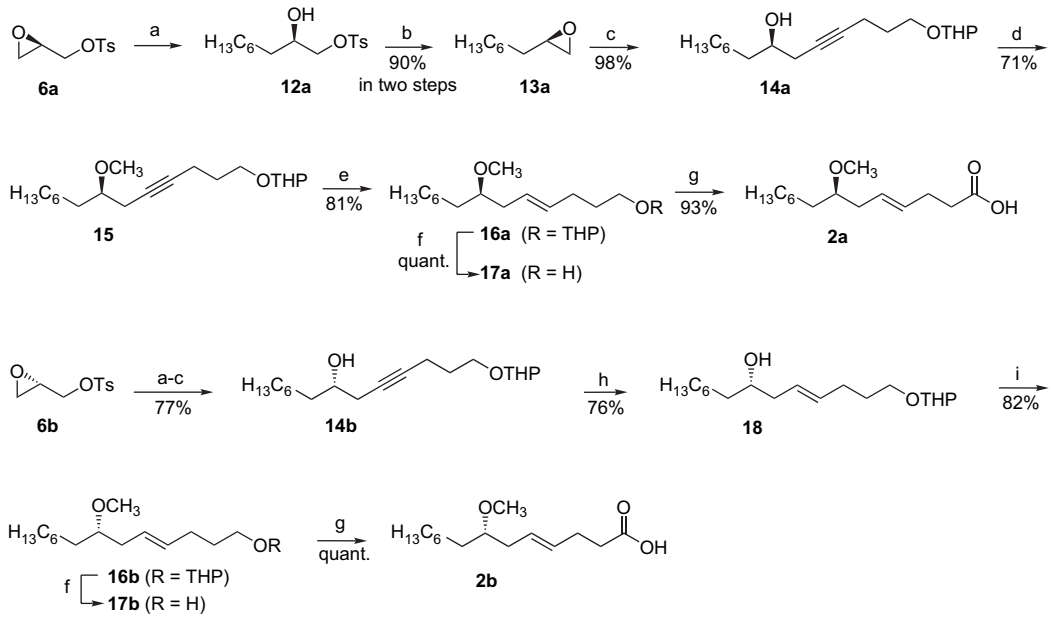
Scheme 1. Retrosynthetic analysis of malyngamide X (**1**) and its 7′(*S*)-epimer.

Boc-L-valine **9**, Meldrum's acid **10**, and propionyl chloride **11**.[4] Introduction of a stereogenic center at C7 of lyngbic acid and homologous fatty acids has been reported in various synthetic approaches, including the racemic total synthesis[5] and asymmetric total synthesis.[6] Recently, the stereogenic center of homologous fatty acid was constructed by catalytic asymmetric allylation reaction.[7] In our synthetic plan making both of the two enantiomers of fatty acid **2**, the stereogenic center at C7 in **2a** and **2b** would directly fix by employing commercially available enantiopure *R* and *S*-glycidyl tosylates (**6a** and **6b**) to couple with hexylmagnesium bromide **7** and acetylide **8**. The fragments would be connected by stepwise peptide couplings and aldol addition of aldehyde **4** with the enolate of an imide pyrrolidone **5**. Coupling of the pyrrolidone moiety at C8 of **5** is the key step as an integral part of the aldol reaction with the C7 of **4** in this synthetic route to introduce 7*S*,8*R* stereogenic centers.

2.2. Synthesis of fatty acid portion

In order to set a stereogenic center at the C-7 and the 14 carbon atoms' chain length of **2a**, the homopropargylic alcohol **14a** was generated by consecutive alkylation and alkynylation of *R*-glycidyl tosylate (**6a**) (Scheme 2). Thus, alkylation of **6a** with hexyl organocuprate generated from $C_6H_{13}MgBr$ and 0.1 mol % Li_2CuCl_4 in THF at −78 to −50 °C for 1.5 h gave only the desired alcohol **12a** (determined by ^1H NMR). The conversion of alcohol **12a** to epoxynonane **13a** was achieved by stirring with solid K_2CO_3 in MeOH at room temperature for 2 h. A mixture of **13a**, acetylide **8**, and *n*-BuLi in the presence of $BF_3\cdot Et_2O$ in a mixed solvents (Et_2O–THF=4/1) at −78 °C gave homopropargylic alcohol **14a** in 98% yield. Alcohol **14a** was converted into the corresponding methyl ether by treatment with CH_3I in the presence of dimsyl anion in THF at room temperature for 3 h to furnish the homopropargylic methyl ether **15** in 71% yield. The trans reduction of acetylene was achieved with Li metal in liq. NH_3–^{t}BuOH at temperatures between −40 and −35 °C to provide the *trans* olefinic methyl ether **16a** in 81%. The THP-protecting group was removed by treatment of **16a** with PPTS in MeOH at 40 °C for 3 h. Oxidation of the corresponding secondary alcohol **17a** proceeded under Jone's reagent in acetone at 0 °C gave fatty acid **2a** in 93% yield.

The enantiomeric synthesis of fatty acid **2b** could also be achieved in the same manner as **2a** except the use of *S*-glycidyl tosylate as starting material instead of *R*-glycidyl tosylate. The use of alternative hydride reduction of **14b** with NaOMe–LAH in refluxing THF for 24–48 h provided homoallylic alcohol **18** in 76%. The O-methylation of alcohol **18**, by refluxing its THF mixture with CH_3I and NaH–DMSO for 12 h, afforded homoallylic methyl ether **16b** in 82% yield. Subsequently, the THP was cleaved and the corresponding alcohol **17b** was oxidized to free acid **2b** in quantitative yield under the same condition for **17a**. It was noted that the reactivity toward O-methylation of homoallylic alcohol was much less than that of homopropargylic alcohol. The reason was not studied. Spectroscopic and analytical data of both **2a** and **2b** are in agreement with those reported for lyngbic acid {**2a**: $[\alpha]_D^{26}$ +11.2 (*c* 1.3, $CHCl_3$); **2b**: $[\alpha]_D^{26}$ −13.3 (*c* 2.5, $CHCl_3$); natural lyngbic acid in Ref. 8 $[\alpha]_D^{26}$ −9.0 (*c* 7.3, $CHCl_3$)}.

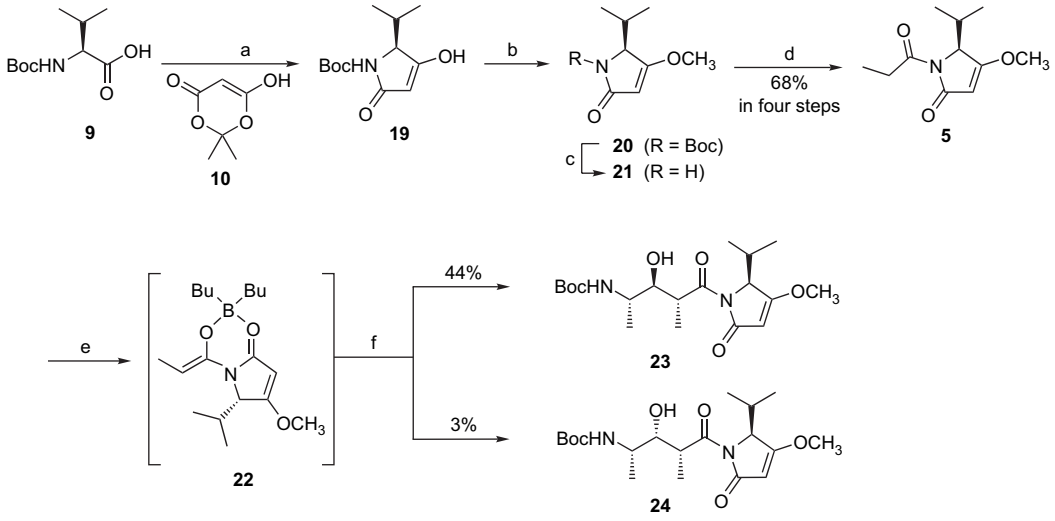


Scheme 2. Synthesis of **2a** and **2b**. (a) $C_6H_{13}MgBr$ (**7**), Li_2CuCl_4, THF, −78 to −50 °C, 1.5 h; (b) K_2CO_3, MeOH, rt, 2 h; (c) $CH{\equiv}C(CH_2)_3OTHP$ (**8**), *n*-BuLi, $BF_3{\cdot}Et_2O$, Et_2O–THF, −78 °C, 1.5 h; (d) CH_3I, NaH–DMSO, THF, rt, 3 h; (e) Li wire/liq. NH_3–^{t}BuOH, −40 to −35 °C, 2 h; (f) PTS, MeOH, 40 °C, 3 h; (g) CrO_3, H_2SO_4, acetone, 0 °C, 30 min; (h) LAH–NaOMe, THF, reflux, 24 h; (i) CH_3I, NaH–DMSO, THF, reflux, 24 h.

2.3. Synthesis of the tripeptide portion

After the synthesis of both enantiomers of fatty acid segment in **1**, the remaining tripeptide segment had to be prepared and successively connected. First, commercially available *N*-Boc-L-valine (**9**) was coupled with Meldrum's acid (**10**) using DCC and DMAP in CH_2Cl_2 at room temperature for 3 h, followed by removal of the solvent and subsequent reaction in refluxing MeOH for 1 h to furnish pyrrolidone derivative **19**. Mitsunobu condition of **19** with PPh_3 and DEAD in THF at 0 °C, addition of MeOH, and warming of the reaction mixture to room temperature afforded *O*-methyl pyrrolidone derivative **20** as the only isomer (determined by ^{1}H NMR).[9]

Removal of the Boc-protecting group performed with 50% TFA in CH_2Cl_2 at 0 °C for 0.5 h provided amine **21**. Treatment of **21** with CH_3MgBr in THF at 0 °C, followed by addition of propionyl chloride, and warming of the reaction mixture to room temperature for 2 h gave *N*-propionyl pyrrolidone **5** in 68% yield from **9**. Next step was the coupling of the pyrrolidone derivative **5** with *N*-Boc-L-alaninal (**4**). In order to generate the two stereogenic centers at the C-2 and C-3 positions of the pyrrolidone derivative **23**, the Lewis acid (Et_2AlCl) mediated *anti*-aldol reaction[9] was employed in the coupling reaction (Scheme 3). The starting material, imide pyrrolidone **5** containing a chiral isopropyl group, was converted into the (*Z*)-imide enolate **22** by treatment



Scheme 3. Synthesis of **5** and aldol coupling to C5–C18 segment of malyngamide X (**23**). (a) DCC, Meldrum's acid (**10**), DMAP, CH_2Cl_2, rt, 3 h, then MeOH, reflux, 1 h; (b) PPh_3, DEAD, CH_3OH, THF, rt, 2 h; (c) 50% TFA in CH_2Cl_2, 0 °C, 0.5 h; (d) CH_3MgBr, C_2H_5COCl, THF, 0 °C to rt, 2 h; (e) *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 1 h; (f) Et_2AlCl, Boc-L-alaninal (**4**), −78 °C.

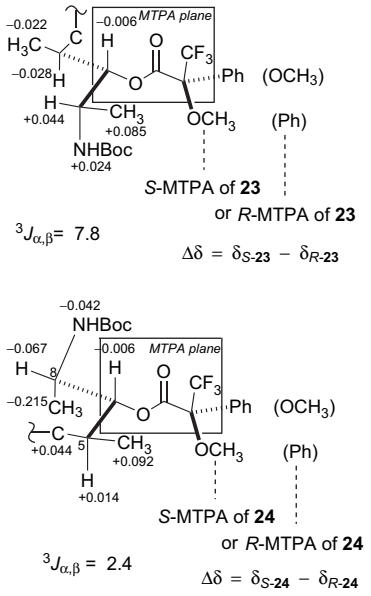


Figure 1. The $\Delta\delta$ values for the MTPA ester of **23** and **24**.

with *n*-Bu_2BOTf and *i*-Pr_2NEt at 0 °C in CH_2Cl_2 for 1 h. Exposure of **22** to alaninal derivative **4** and Et_2AlCl at −78 °C for 5 h allowed to give *anti*-aldol product **23** in 44% yield with >90% de. The use of alternative Lewis acids, such as $EtAlCl_2$, Et_3Al, $BF_3{\cdot}Et_2O$, and $SnCl_4$, lowered *anti* (**23**):*syn* (**24**) selectivity. The stereochemistry of **23** (2*S*,3*S*,4*R*) and **24** (2*S*,3*R*,4*R*) was confirmed by analysis of its MTPA esters and vicinal coupling constants of Cα/Cβ protons (Fig. 1).[10]

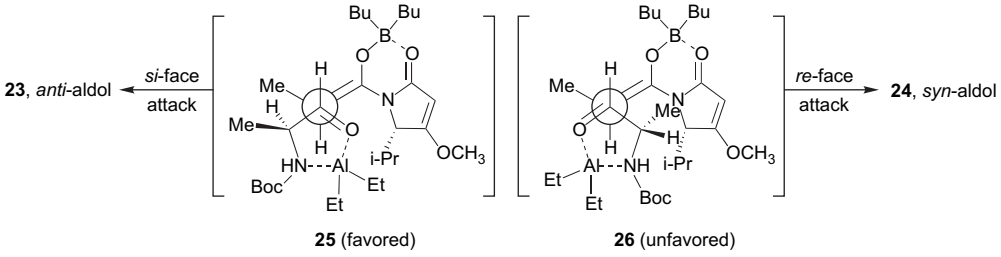
2.4. Aldol reaction and stereochemistry

From the literature, it is known that the five- or six-membered chelation proceeds with Lewis acids and aldehydes having two or more coordinating groups.[11] Thus, two models of transition state are proposed to explain the outcome of the reaction, the synclinal model **25** and the antiperiplanar model **26** (Scheme 4). The vinyl hydrogen was placed in the stereochemically most demanding position. Five-membered chelation between aldehyde **4** and Et_2AlCl seems to be crucial for facial selectivity of the attack on the (*Z*)-imide enolate **22** (chelation control). Based upon the results that indicate *si*-face attack to the aldehyde, the reaction was proposed to proceed via synclinal model **25**. In this chelation model, the participating π bonds were arranged at approx. 30° to each other. The destabilizing interactions were decreased because Lewis acid was no longer on the carbonyl group *anti* to the aldehyde substituent, but was instead *syn* to the chelated aldehyde. The antiperiplanar model **26** was disfavored due to steric, *gauche* interactions between the pyrrolidone group of the imide enolate and a chiral bulky alkyl group of the chelated aldehyde. The sterically demanding methyl group shielded the *re*-face of the aldehyde. This would favor the nucleophilic attack from the *si*-face.

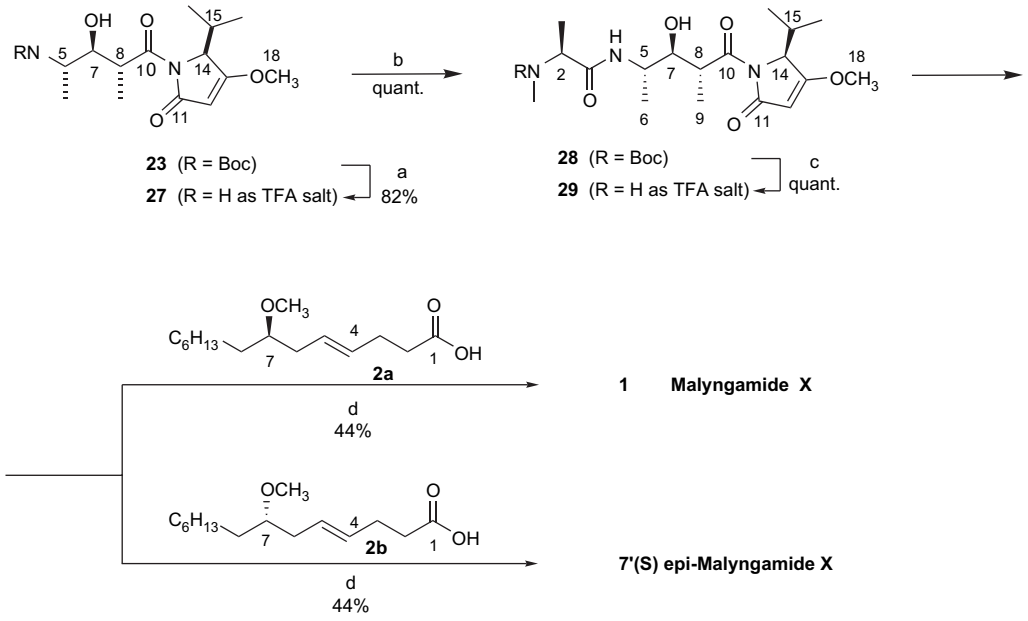
2.5. Total synthesis of malyngamide X and its epimer

With all essential pieces in hand, the linear lipopeptide of malyngamide **1** and 7′(*S*)-*epi* **1** isomer was constructed, respectively, by ligating the segments **2a** and **2b** with *N*-methyl-L-alanine and amine derivative **29**. As summarized in Scheme 5, treatment of **23** with a solution of 50% TFA in CH_2Cl_2 at 0 °C for 10 min afforded the amine **27**. Peptide formation of amine **27** and Boc-*N*-Me-L-alanine with EDC·HCl–HOAt in CH_2Cl_2 at room temperature for 3 h gave the desired tripeptide segment **28** in quantitative yield. The Boc group was cleaved with 50% TFA in CH_2Cl_2 at 0 °C for 10 min providing amine **29**. The coupling of amine **29** and *R*-lyngbic acid segment **2a** was accomplished by stirring EDC·HCl–HOAt and *i*-Pr_2NEt at room temperature for 18 h to give **1** in 44% yield. The coupling of lyngbic acid segment **2b** with amine **29** under the same reaction condition as that of **1** gave 7′(*S*)-*epi* **1** in the same yield (Scheme 6).[12]

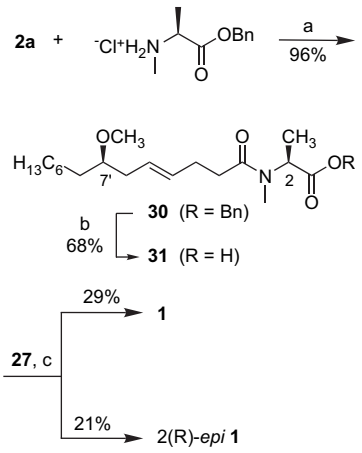
The ^1H and ^{13}C NMR data measured on the synthetic malyngamides **1** and 7′(*S*)-*epi* **1** were in good agreement with the data of natural malyngamide X (see Supplementary data). This must be due to the large distance between C-7′ and the other five stereogenic centers in the tripeptide portion. We found that only the specific rotation values and the signs of chemical shift non-equivalence ($\Delta\delta_{RS}$) in the NMR chiral solvation experiments were different. The specific rotation value of natural malyngamide X, $[\alpha]_D$ −6.2 (*c* 0.8, MeOH) only matched with that of malyngamide **1** having 7′*R*-configuration {**1**: $[\alpha]_D$ −5.9 (*c* 0.8, MeOH)} but differed from 7′(*S*)-*epi* **1**, $[\alpha]_D$ −15.4 (*c* 0.8, MeOH). When natural **1**, synthetic 7′(*S*)-*epi* **1**, and a known 7′*S*-isomalyngamide A were analyzed by ^1H NMR in $CDCl_3$ solution at 283 K in the presence of 20 equiv of 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE or Pirkle's alcohol), the $\Delta\delta_{RS}$ observed for 7′-OCH_3 protons was −0.032, +0.016, and +0.023 ppm, respectively.[1] TFAE experiments with the synthetic malyngamide **1** were carried out under the same condition. Spectral analysis of the solvated complex between **1** and *R*-TFAE gave the methoxyl protons' signal at



Scheme 4. Two model transition states of Lewis acid (Et_2AlCl) mediated *anti*-aldol reaction.



Scheme 5. Synthesis of **1a** and 7′(*S*)-*epi* **1**. (a) 50% TFA in CH_2Cl_2, 0 °C, 10 min; (b) Boc-*N*-Me-L-alanine (**3**), EDC·HCl, HOAt, CH_2Cl_2, rt, 3 h; (c) 50% TFA in CH_2Cl_2, 0 °C, 0.5 h; (d) EDC·HCl, HOAt, *i*-Pr_2NEt, CH_2Cl_2, rt, 18 h.



Scheme 6. (a) *N*-Me-L-alanine-OBn, 2-chloro-1,3-dimethyl-2-imidazolinium PF_6 (CIP), *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt, 14 h; (b) 1 N KOH, MeOH, rt, 1 h, 68%; (c) CIP, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt, 20 h.

δ_H 3.243, while in the solvated complex with *S*-TFAE at δ_H 3.255 corresponding to 7′*R*-OCH_3 $\Delta\delta_{RS}$ −0.025 (Fig. 2). These results not only confirmed the structure of **1**, but also indicated the reliability of this NMR method for determining absolute configuration at C-7′ of the malyngamide family.

3. Conclusion

We have achieved the first stereoselective total synthesis of malyngamide X, a new skeleton of the malyngamides containing a tripeptide backbone and the first 7′*R*-lyngbic acid substructure, and its 7′(*S*)-*epi* isomer. Optically active **6a** and **6b** were used to incorporate into the above synthesis to produce the optically active (4*E*,7*R*)-(+)-7-methoxytetradec-4-enonic acid, and its enantiomer (lyngbic acid). In our synthesis, the two stereogenic centers at C7(*R*) and C8(*S*) of **1** were successfully generated by Lewis acid (Et_2AlCl)

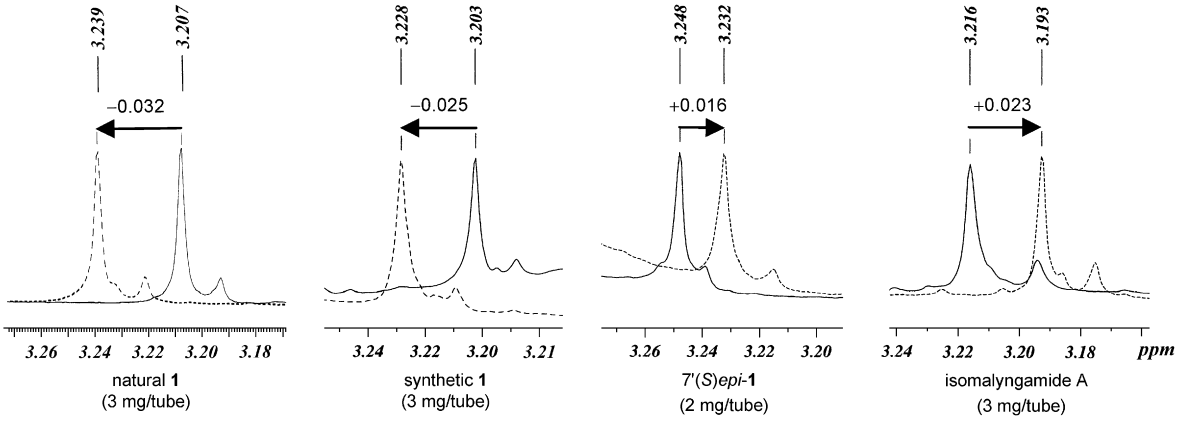


Figure 2. $\Delta\delta_{RS}$ for 7′-OCH_3 protons signal of natural and synthetic **1**, 7′(*S*)-*epi* **1**, and isomalyngamide A in the presence of 20 equiv *R*-TFAE (—) and *S*-TFAE (- - -) ($CDCl_3$, 283 K, 600 MHz). Arrows were used to indicate the unequivocal shifts of 7′-OCH_3 protons signal from *R*-TFAE to *S*-TFAE solvated complexes.

mediated stereoselective *anti*-aldol coupling reaction between alaninal derivative **4** and imide pyrrolidone **5**. The segments' coupling of fatty acids **2a** and **2b** with a tripeptide segment **29** using EDC·HCl–HOAt under careful control of reaction acidity was employed to avoid formation of ester bond. The synthetic sample of malyngamide X having 7′*R* configuration (**1**) had the same spectroscopic data, particularly the results of the TFAE experiments, and physical properties as those of natural compound. These results allowed the confirmation of the structure and stereochemistry of the natural malyngamide X to be as **1**.

4. Experimental

4.1. General

All moisture-sensitive reactions were carried out under nitrogen or argon atmosphere. Optical rotations were measured on a Perkin–Elmer 341 polarimeter using a sodium lamp operating at 589 nm. IR spectrum was obtained on a Perkin–Elmer 2000 FT-IR spectrometer. All NMR data were obtained from a Bruker AV-400 or a Bruker AMX-600 spectrometer. Chemical shifts (δ) for ^{1}H NMR spectra are given in parts per million relative to tetramethylsilane (δ 0.00) as internal standard and coupling constants (J) in hertz. Chemical shifts (δ) for ^{13}C NMR spectra are given in parts per million relative to $CDCl_3$ (δ 77.0) as internal standard. The ESI/Q/TOF/MS spectra were recorded on a Micromass LC-Q-TOF mass spectrometer. The FABMS and EIMS spectra were obtained with a JEOL JMS-700 mass spectrometer. All experiments were performed in the positive ion mode. Elemental analyses were done in the combustion analytical laboratories in Nagoya U.

4.1.1. 2*R*-Epoxynonane, 13a. To a solution of 0.10 M Li_2CuCl_4 dissolved in THF, 10.8 ml (0.001 mol) were added at −78 °C, dry THF, 140 ml, and a solution of 2.0 M hexylmagnesium bromide in ether, 12.5 ml (0.025 mol), over a 30–60 min period via dropping funnel. The yellow solution was stirred at −78 °C for 2 h. A pre-cooled solution of 2*R*-glycidyl tosylate, 5.0 g (0.02 mol), in 60 ml dry THF was added via cannula (5 ml washed). The resulting yellow-red clear solution was stirred for 0.5 h at −78 °C, then for 1 h at −50 °C. Excess hexylmagnesium bromide was quenched by the addition of 60 ml saturated ammonium chloride at −50 °C. The mixture was left to stir at room temperature for 30–60 min. The precipitate of magnesium salt was filtered and washed with cold Et_2O. The filtrate was partitioned with cold Et_2O. The combined organic extracts were washed with saturated NH_4Cl, brine, dried (Na_2SO_4), and concentrated. The residual white solid, 6.0 g, of **12a** (determined by ^{1}H NMR) was used in next step without further purification. To a solution of **12a** in 100 ml MeOH was added 3.3 g (0.024 mol) of K_2CO_3. The slurry was stirred at room temperature for 2 h. Excess K_2CO_3 was filtered and washed with cold Et_2O. The filtrate was combined and partitioned with hexane/cold 70% aq MeOH. The aqueous layer was repeatedly extracted with hexane (2–3 times). The combined hexane extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residual yellow oil was purified by column chromatography on SiO_2 (0–10% Et_2O–Hex) giving 2.6 g of **13a** (90% yield in two steps).

Compound **13a**: colorless oil; R_f 0.57, EtOAc–Hex (1:4); $[\alpha]_D^{27}$ +8.67 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (dist. t, 7.2), 1.20–1.40 (8H, br s), 1.45 (m), 1.52 (m), 2.47 (dd, 5.2, 2.4), 2.75 (dd, 5.2, 4), 2.91 (m); IR (KBr): ν 2925, 2855, 1747, 1457, 1374, 1265, 1178, 1096, 814 cm^{-1}; HRMS (EI) $C_9H_{18}O$ $[M]^+$ calcd: 142.1358, found: 142.1354.

4.1.2. 1-(Tetrahydro-pyran-2-yloxy)-tetradec-4-yn-7(*R*)-ol, 14a. To a solution of 2-pent-4-ynyloxy-tetrahydro-pyran (**8**) in a mixture of 80 ml Et_2O and 20 ml THF at −78 °C was added 1.59 M *n*-BuLi in hexane, 8.4 ml (13.39 mmol), via a dropping funnel over a 10–15 min period. The slightly cloudy solution was stirred at −78 °C for 1 h. Then 2.07 ml of **13a**, 1.73 g (12.17 mmol), was added via syringe. Then a solution of redistilled $BF_3·Et_2O$, 1.54 ml (12.17 mmol), in dry Et_2O (1:1, v/v), was added dropwise over a 15 min period. The resulting clear solution was stirred for 1.5 h at −78 °C. The reaction was quenched by the addition of 60 ml aq saturated ammonium chloride and the resulting mixture was left to stir at room temperature for 1 h. The organic layer was separated. The aqueous layer was partitioned with cold Et_2O (×2). The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on SiO_2 (0–10% EtOAc–Hex) yielding 3.69 g of **14a** (98% yield).

Compound **14a**: colorless oil; R_f 0.23, EtOAc–Hex (1:4); $[\alpha]_D^{27}$ −3.78 (*c* 1.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.87 (3H, dist. t, 7.2), 1.10–1.40 (10H, br s), 1.35–1.85 (10H, m), 2.15–2.45 (4H, m), 3.40–3.54 (2H, m), 3.66 (1H, m), 3.76–3.90 (2H, m), 4.58 (dd, 4.4, 2.4); IR (KBr): ν 3436, 2937, 2866, 1461, 1362, 1127, 1033, 899 cm^{-1}; elemental analysis calcd for $C_{19}H_{34}O_3$: C 73.50, H 11.04; found: C 73.50, H 11.62.

4.1.3. 2-((*R*)-7-Methoxytetradec-4-ynyloxy)-tetrahydro-2*H*-pyran, 15. A suspension of 50–70% sodium hydride suspension in oil, 600 mg (8.02 mmol), in 5.4 ml DMSO was transferred to a solution of **14a** (1.67 g, 5.35 mmol) in 60 ml dry THF at room temperature. Methyl iodide, 1.0 ml (16.05 mmol), was introduced into the resulting white suspension. The mixture was left to stir at room temperature for 3 h. Pre-cooled Et_2O, 10 ml, was cautiously added into the flask and the mixture was poured into crushed ice. The aqueous layer was extracted with cold Et_2O (×2). The combined organic extracts, pale yellow, were washed with satd NH_4Cl, brine, dried (Na_2SO_4), and concentrated. The residual oil was subjected to SiO_2 column (10% EtOAc–Hex) yielding 1.20 g of **15** (71% yield).

Compound **15**: Pale yellow oil; R_f 0.37, EtOAc–hexane (1:4); $[\alpha]_D^{28}$ +19.5 (*c* 2.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.88 (3H, dist. t, 7.2), 1.20–1.36 (10H, br s), 1.48–1.90 (10H, m), 2.30–2.44 (4H, m), 3.24 (1H, m), 3.37 (3H, s), 3.43–3.57 (2H, m), 3.60–3.95 (2H, m), 4.59 (1H, t, 4.4); IR (KBr): ν 2934, 2846, 1456, 1356, 1198, 1038 cm^{-1}; elemental analysis calcd for $C_{20}H_{36}O_3$: C 74.03, H 11.18; found: C 73.95, H 11.35.

4.1.4. 2-((*R*,*E*)-7-Methoxytetradec-4-enyloxy)-tetrahydro-2*H*-pyran, 16a. Gaseous NH_3 was introduced to a flame

dry two-neck flask at −78 °C condensing approximately 80 ml of liq. NH_3. Acetone–dry ice bath was, then, replaced with acetonitrile–dry ice (temp −35 to −40 °C). A solution of **15** (2.0 g, 6.4 mmol) in 3 ml of ^{t}BuOH and 10 ml of THF was added via syringe. Small piece of Li wire was added to the stirred solution until deep blue solution persists for more than 1 h. Solid NH_4Cl of 1 g was then added to neutralize ^{t}BuOLi; ammonia was allowed to evaporate overnight. The mixture was diluted with ice-water and extracted with Et_2O. Combined organic extracts were washed with aq NH_4Cl, brine, dried (Na_2SO_4), and concentrated. The pale yellow oily residue, 1.8 g, was subjected to SiO_2 column (0–10% EtOAc–Hex) yielding 1.64 g of **16a** (81% yield).

Compound **16a**: pale yellow oil; R_f 0.34, EtOAc–hexane (1:4); $[\alpha]_D^{28}$ +10.4 (*c* 2.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.88 (3H, dist. t, 7.2), 1.20–1.34 (10H, br s), 1.40–1.95 (10H, m), 2.05–2.40 (4H, m), 3.16 (1H, m), 3.35 (3H, s), 3.40–4.00 (4H, m), 4.60 (1H, t, 4.4), 5.38–5.54 (2H, dd, 15.2, 6.4); IR (KBr): ν 2923, 2858, 1456, 1353, 1101, 1036 cm^{-1}; elemental analysis calcd for $C_{20}H_{38}O_3$: C 73.57, H 11.73; found: C 73.57, H 11.94.

4.1.5. (*R*,*E*)-7-Methoxytetradec-4-en-1-ol, 17a. *p*-Toluene sulfonic acid (PTS) monohydrate, 4.3 g, was added in several portions to a solution of **16a**, 1.5 g (4.59 mmol), in 25 ml of MeOH (pH 3). The reaction mixture was stirred at 40 °C for 3 h. The reaction was neutralized with 90 ml of satd $NaHCO_3$. The aqueous phase was partitioned with cold Et_2O (×2). The combined organic extracts were washed with brine and dried (Na_2SO_4). After removal of solvent by rotary evaporation and purification by SiO_2 column (10–20% EtOAc–hexane), **17a** was obtained (1.31 g, quant. yield).

Compound **17a**: pale yellow oil; R_f 0.17, EtOAc–hexane (1:4); $[\alpha]_D^{28}$ +11.3 (*c* 1.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.89 (3H, dist. t, 7.2), 1.20–1.40 (10H, br s), 1.45 (2H, m), 1.65 (2H, m), 2.12 (2H, q, 6.8), 2.20 (2H, t, 5.6), 3.17 (1H, pent, 6.0), 3.33 (3H, s), 3.66 (2H, t, 8.8), 5.35–5.541 (2H, dd, 15.2, 6.4); IR (KBr): ν 3364, 2928, 2858, 1457, 1366, 1097, 969 cm^{-1}; elemental analysis calcd for $C_{15}H_{30}O_2$: C 74.32, H 12.47; found: C 74.33, H 12.43.

4.1.6. (*R*,*E*)-7-Methoxytetradec-4-enoic acid, 2a. To a solution of **17a**, 850 mg (3.50 mmol), in 50 ml acetone was added Jone's reagent at 0 °C until reaction color remain. Excess Jone's reagent was destroyed by slowly adding isopropanol. Top layer was decanted, and the lower layer was extracted with cold Et_2O. Combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by SiO_2 column using 1% acetic acid in EtOAc as eluting solvent giving 830 mg of **2a** (93% yield).

Compound **2a**: pale yellow oil; R_f 0.43, EtOAc–hexane (1:1); $[\alpha]_D^{28}$ +11.2 (*c* 1.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.89 (3H, dist. t, 7.2), 1.20–1.40 (10H, br s), 1.45 (2H, m), 2.21 (2H, t, 6.0), 2.36 (2H, m), 2.39 (2H, m), 3.17 (1H, pent, 6.0), 3.33 (3H, s), 5.35–5.541 (2H, dd, 15.2, 6.4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 14.1 (CH_3-14), 22.6 (CH_2-13), 25.3 (CH_2-9), 27.7 (CH_2-3), 29.3 (CH_2-10), 29.7 (CH_2-11), 31.8 (CH_2-12), 33.4 (CH_2-8), 33.7 (CH_2-2), 36.4 (CH_2-6), 56.5 (7-OCH_3), 83.8 (CH-7), 127.9 (CH-5), 130.1 (CH-4), 177.5 (C-1); IR (KBr): ν 2927, 2856, 1713, 1457, 1183, 970 cm^{-1}; HRMS (EI) $C_{15}H_{28}O_3$ $[M]^+$ calcd: 256.2038, found: 256.2032.

4.1.7. (*S*,*E*)-1-(Tetrahydro-2*H*-pyran-2-yloxy)tetradec-4-en-7-ol, 18. Using the same procedure as described for **14a**, compound **14b** (2.16 g, 77% in three steps) was obtained from **6b**. To a solution of **14b**, 2.16 g (7.0 mmol), in 60 ml THF was added 1.5 g (27.8 mmol) of NaOMe powder. The resulting slurry was heated at 40 °C for 1 h and $LiAlH_4$ powder, 580 mg (14.0 mmol), in 20 ml dry THF was then added at this temperature in several portion via syringe. The flask was heated to reflux at 80 °C under N_2 atmosphere for 24 h. The excess $LiAlH_4$ was quenched by slowly dropping 80 ml of wet Et_2O at room temperature. The mixture was poured into 40 ml cold Na–K tartrate and stirred for 1 h. The precipitate was filtered through a pad of Celite and washed with Et_2O. The filtrate was partitioned with cold Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residual oil, 2.5 g, was subjected to SiO_2 column (20% EtOAc–Hex) yielding 1.66 g of **18** (76% yield).

Compound **14b**: colorless oil; R_f 0.23, EtOAc–Hex (1:4); $[\alpha]_D^{27}$ −2.25 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) spectra were identical to **14a**; MS (EI) $C_{19}H_{33}O_3$ $[M-H]^-$ calcd: 309.24, found: 309.24.

Compound **18**: pale yellow oil; R_f 0.23, EtOAc–Hex (1:4); $[\alpha]_D^{28}$ +1.75 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.79 (3H, dist. t, 6.4), 1.30–1.90 (20H, br s), 1.95–2.30 (4H, m), 3.30.3.90 (5H, m), 4.55 (1H, m), 5.35–5.60 (2H, m); IR (KBr): ν 3452, 2943, 2857, 1456, 1353, 1120, 1035, 812 cm^{-1}; HRMS (EI) $C_{19}H_{36}O_3$ $[M]^+$ calcd: 312.2664, found: 312.2694.

4.1.8. 2-((*S*,*E*)-7-Methoxytetradec-4-enyloxy)-tetrahydro-2*H*-pyran, 16b. A suspension of 50–70% sodium hydride suspension in oil, 1.0 g (18.3 mmol), in 10 ml DMSO was transferred to a solution of **18** (1.60 g, 6.1 mmol) in 40 ml dry THF at room temperature. Methyl iodide, 1.25 ml (18.3 mmol), was introduced into the resulting white suspension. The mixture was heated to reflux for overnight. Pre-cooled Et_2O, 10 ml, was cautiously added in flask and the mixture was poured into crushed ice. The aqueous layer was extracted with cold Et_2O (×2). The combined organic extracts were washed with satd NH_4Cl, brine, dried (Na_2SO_4), and concentrated. The residual oil was subjected to SiO_2 column (10% EtOAc–Hex) yielding 1.62 g of **16b** (82% yield).

Compound **16b**: pale yellow oil; R_f 0.34, EtOAc–hexane (1:4); $[\alpha]_D^{28}$ −10.34 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) spectra were identical to **16a**; HRMS (EI) $C_{20}H_{38}O_3$ $[M]^+$ calcd: 326.2821, found: 326.2802.

4.1.9. (*R*,*E*)-7-Methoxytetradec-4-en-1-ol, 17b. Using the same procedure as described for **17a**, compound **17b** (1.0 g, 89% yield) was obtained from **16b** (1.5 g, 4.60 mmol).

Compound **17b**: pale yellow oil; R_f 0.17, EtOAc–hexane (1:4); $[\alpha]_D^{28}$ −15.79 (*c* 1.90, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) spectra were identical to **17a**; MS (EI) $C_{15}H_{29}O_2$ $[M-H]^-$ calcd: 241.2168, found: 241.22.

4.1.10. (*S*,*E*)-7-Methoxytetradec-4-enoic acid, 2b. Using the same procedure as described for **2a**, compound **2b** (0.59 g, quant.) was obtained from **16b** (0.5 g, 2.06 mmol).

Compound **2b**: pale yellow oil; R_f 0.43, EtOAc–hexane (1:1); $[\alpha]_D^{28}$ −13.3 (*c* 2.50, $CHCl_3$); ^1H ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) spectra were identical to the reported data of **2a**; HRMS (EI) $C_{15}H_{28}O_3$ $[M]^+$ calcd: 256.2038, found: 256.1990.

4.1.11. (*S*)-5-Isopropyl-4-methoxy-1-propionyl-1*H*-pyrrol-2(5*H*)-one, 5. To the stirred solution of *N*-Boc-L-valine (**9**), 2.0 g (9 mmol), in 20 ml CH_2Cl_2 were added Meldrum's acid (**10**), 1.33 g (9 mmol), DCC, 2.23 g (11 mmol), and DMAP, 2.2 g (18 mmol). The mixture was stirred at room temperature for 3 h, and then filtered. The filtrate was diluted with 30 ml CH_2Cl_2, and washed with 0.5 N HCl, H_2O, brine, dried (Na_2SO_4), and concentrated. The residual oil was then refluxed in 150 ml MeOH for 1 h. The solvent was concentrated in vacuo, and the residue of **19** was then dissolved in 50 ml THF. To this solution in an ice bath were added Ph_3P, 3 g (11.69 mmol), and 40% diethyl diazocarboxylate in toluene, 4.5 ml (9.9 mmol), and MeOH, 2.0 ml (49.5 mmol). The mixture was stirred for 0.5 h in an ice bath and 2 h at room temperature, and the solvent was removed in vacuo. The product was roughly purified by column chromatography on SiO_2 plug (Et_2O) to afford crude product of pyrrolidone **20** (determined by ^1H NMR). To the solution of **19** in CH_2Cl_2 (100 ml) in an ice bath was added TFA (30 ml), and the mixture was left to stir for 0.5 h. The TFA was removed by azeotroping with hexane (three times) to yield **21** as TFA salt.

To the stirred solution of **21** in 50 ml THF in an ice bath were added DMAP, 2.75 g (22.5 mmol), and 0.93 M MeMgBr in THF, 10.6 ml (9.9 mmol). After 0.5 h, 1.18 ml (13.5 mmol) of propionyl chloride was added. The mixture was stirred at room temperature for 2 h, and poured into 20 ml $NaHCO_3$/crushed ice. The precipitate was filtered through a pad of Celite and washed with Et_2O. The filtrate was partitioned with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residual oil was subjected to SiO_2 column (Et_2O–hexane, 1:1) yielding 1.30 g of **5** (68% overall yield).

Compound **5**: pale yellow solid; R_f 0.20, EtOAc–hexane (1:3); $[\alpha]_D^{28}$ +75.3 (*c* 0.60, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.74 (d, 7.2), 1.11 (d, 7.2), 1.15 (t, 7.2), 2.55 (m, H-6), 2.94 (q, 7.2), 3.83 (s, H_3-9), 4.37 (d, 2.4), 5.06 (s); IR (KBr): ν 3113, 2965, 2882, 1685, 1624, 1458, 1241, 997 cm^{-1}; HRMS (ESI/Q/TOF) $C_{11}H_{17}NO_3Na$ $[M+Na]^+$ calcd: 234.1106, found: 234.1108.

4.1.12. *tert*-Butyl (2*S*,3*S*,4*R*)-3-hydroxy-5-((*S*)-2-isopropyl-3-methoxy-1*H*-pyrrol-2(5*H*)-one)-4-methyl-5-oxopentan-2-ylcarbamate, 23. To a solution of 60 mg (0.28 mmol) of imide **5** in 1.0 ml of dry CH_2Cl_2 at 0 °C were added 0.3 ml (0.31 mmol) of 1 M Bu_2BOTf in CH_2Cl_2 and 0.060 ml (0.34 mmol) of freshly distilled *i*-Pr_2NEt. After 1 h at 0 °C, it was cooled to −78 °C and 0.340 ml (0.31 mmol) of 0.92 M Et_2AlCl in hexane was added. The solution of 60 mg (0.31 mmol) of *N*-Boc-L-alaninal in 1.0 ml CH_2Cl_2 was then added. After 5 h, the reaction was quenched with 1 ml of pH 7 phosphate buffer and 3 ml of ether. The mixture was allowed to warm to temperature, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and the solvent was removed in vacuo. The residue was dissolved in 4 ml of MeOH and cooled to 0 °C, and a 1 ml of 30% H_2O_2 was added dropwise. After 1 h, 4 ml of H_2O was added and then MeOH was removed under vacuo. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with cold saturated aq NH_4Cl, saturated aq $NaHCO_3$, brine, and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by preparative TLC (lower phase of CH_2Cl_2–MeOH–H_2O, 90:10:5) to give 47 mg (44% yield) of **23** and 3.1 mg of **24** (2.9%).

Compound **23**: yellow oil; R_f 0.28, lower phase of CH_2Cl_2–MeOH–H_2O (90:10:5); $[\alpha]_D^{29}$ +8.15 (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.76 (d, 6.8), 1.10 (d, 6.8), 1.19 (d, 6.8), 1.21 (d, 6.8), 1.46 (s, Boc), 2.61 (m), 3.59 (dd, 8.0, 2.4), 3.82 (m), 3.85 (s), 3.98 (dq, 8.0, 6.8), 4.54 (d, 2.8), 4.80 (br s), 5.09 (s); IR (KBr): ν 3365, 2977, 2938, 1695, 1622, 1507, 1456, 1319, 1173, 955 cm^{-1}; HRMS (TOF) $C_{19}H_{32}N_2O_6Na$ $[M+Na]^+$ calcd: 385.2339, found: 407.2167.

Compound **24**: yellow oil; R_f 0.16, lower phase of CH_2Cl_2–MeOH–H_2O (90:10:5); $[\alpha]_D^{29}$ +8.15 (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.75 (d, 6.8), 1.10 (d, 6.8), 1.19 (d, 6.8), 1.21 (d, 6.8), 1.46 (s, Boc), 2.52 (m), 3.79 (m), 3.84 (m), 3.84 (s), 4.05 (m), 4.59 (d, 2.8), 4.80 (br s), 5.08 (s); HRMS (TOF) $C_{19}H_{33}N_2O_6$ $[M+H]^+$ calcd: 385.2339, found: 385.2368.

4.1.13. *tert*-Butyl (*S*)-1-((2*S*,3*S*,4*R*)-3-hydroxy-5-((*S*)-2-isopropyl-3-methoxy-1*H*-pyrrol-2(5*H*)-one)-4-methyl-5-oxopentan-2-ylcarbamoyl)ethylmethylcarbamate, 28. To the solution of **23**, 240 mg (0.62 mmol), in CH_2Cl_2 (20 ml) in an ice bath was added TFA (5 ml), and the mixture was left to stir for 10 min. The TFA was removed by azeotroping with hexane (three times) to yield **27** as a light yellow oil.

To the stirred solution of Boc-*N*-methyl-L-alanine (144 mg, 0.71 mmol), HOAt (102 mg, 0.75 mmol), and EDC·HCl (136 mg, 0.71 mmol) in CH_2Cl_2 (20 ml) at room temperature was added a solution of **27**, 200 mg (0.50 mmol), and *i*-Pr_2NEt (60 µl, 0.35 mmol) in 15 ml CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C to room temperature over 3 h period, and the solvent was removed in vacuo. The residue was extracted with CH_2Cl_2, and the organic layer was washed with 0.5 N HCl, H_2O, brine, dried (Na_2SO_4), and concentrated. The residual oil was subjected to SiO_2 column (2.5% MeOH–EtOAc) yielding 237 mg of **28** (quant.).

Compound **28**: pale yellow oil; R_f 0.57, 2.5% MeOH in EtOAc; $[\alpha]_D^{29}$ +8.15 (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.76 (d, 7.2), 1.10 (d, 6.4), 1.11 (d, 10.0), 1.20

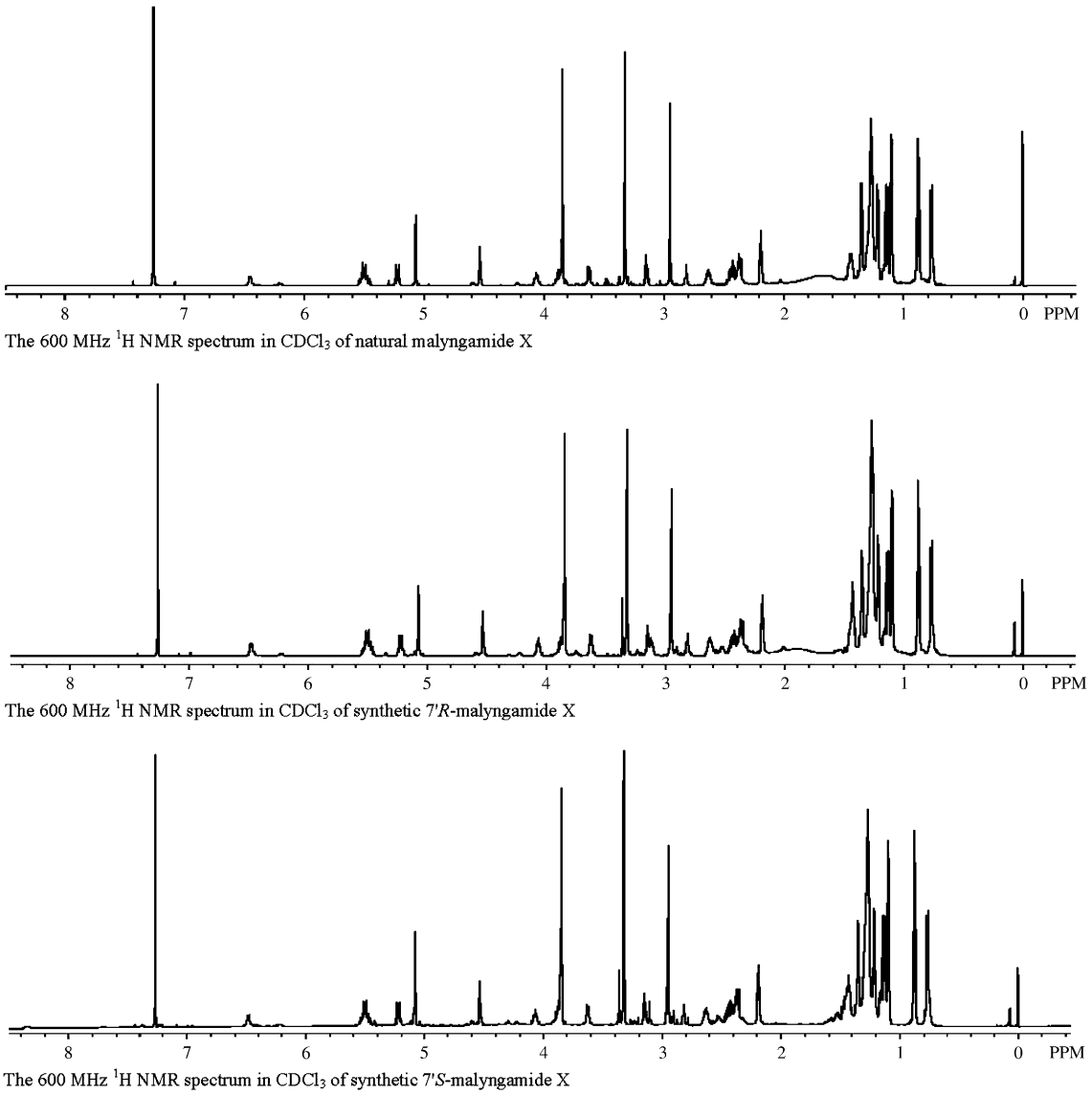


Figure 3. NMR spectra of malyngamide X: *Upper*, natural; *Middle*, synthetic; and *Bottom*, 7′*S*-epimer.

(d, 6.8), 1.53 (d, 7.2), 2.62 (m), 2.99 (s), 3.63 (br d, 8.0), 3.85 (s), 3.89 (m), 4.16 (m), 4.19 (q, 6.8), 4.52 (d, 2.8), 5.07 (s), 6.40 (br); IR (KBr): ν 3395, 2979, 2932, 1702, 1624, 1508, 1458, 1319, 1173, 988 cm^{-1}; HRMS (TOF) *m/z* $C_{23}H_{40}N_3O_7$ $[M+H]^+$ calcd: 470.2866, found: 470.2871.

4.1.14. Malyngamide X, 1[13] (Fig. 3). To the solution of **28**, 70 mg (0.15 mmol), in CH_2Cl_2 (3 ml) in an ice bath was added TFA (0.5 ml), and the mixture was left to stir for 10 min. The TFA was removed by azeotroping with hexane (three times) to yield **29** as a light yellow oil.

To the stirred solution of fatty acid **2a** (20.0 mg, 0.078 mmol), HOAt (9.0 mg, 0.082 mmol), and EDC·HCl (12.0 mg, 0.078 mmol) in CH_2Cl_2 (1 ml) at room temperature was added a solution of **29**, 38 mg (0.078 mmol), and *i*-Pr_2NEt (20 µl, 0.12 mmol) in CH_2Cl_2 1 ml at 0 °C. The mixture was stirred at 0 °C to room temperature over 18 h period, and the solvent was removed in vacuo. The residue was extracted with CH_2Cl_2, and the organic layer was washed with 0.5 N HCl, H_2O, brine, dried (Na_2SO_4), and concentrated. The residual oil was purified by preparative TLC (EtOAc) to give 20 mg of **1** (44%).

Compound **1**: pale yellow oil; R_f 0.34, EtOAc; $[\alpha]_D^{27}$ −5.9 (*c* 0.8, MeOH); ^{1}H (600 MHz) δ 0.77 (d, 7.2), 0.88 (t, 6.6), 1.10 (d, 6.6), 1.14 (d, 6.6), 1.21 (d, 6.6), 1.23–1.33 (m), 1.35 (d, 7.2), 1.44 (m), 2.19 (t), 2.37 (m), 2.43 (m), 2.63 (m), 2.95 (s), 3.15 (pentet, 6.0), 3.32 (s), 3.63 (dd, 9.0, 2.4), 3.85 (s), 3.88 (dq, 9.0, 6.6), 4.07 (m), 4.53 (d, 2.4), 5.08 (s), 5.23 (q, 7.2), 5.48 (dt, 15.6, 6.0), 5.53 (dt, 15.6, 6.0), 6.48 (d, 9.0); ^{13}C (150 MHz); δ 13.7 (C-3), 14.2 (C-9), 14.1 (C-14′), 15.4 (C-16), 18.1 (C-6), 18.7 (C-17), 22.6 (C-13′), 25.3 (C-9′), 28.1 (C-3′), 29.0 (C-15), 29.3 (C-10′), 29.7 (C-11′), 30.6 (C-1), 31.8 (C-12′), 33.4 (C-8′), 33.8 (C-2′), 36.4 (C-6′), 42.4 (C-8), 46.7 (C-5), 51.9 (C-2), 56.5 (C-15′), 58.5 (C-18), 64.5 (C-14), 77.4 (C-7), 80.8 (C-7′), 94.6 (C-12), 127.3 (C-4′), 131.1 (C-5′), 171.0 (C-11), 171.4 (C-4), 173.5 (C-1′), 175.7 (C-10), 179.9 (C-13); IR (KBr): ν 3336, 2929, 2855, 1719, 1680, 1624, 1457, 1379, 1319, 1247, 1101, 953 cm^{-1}; HRMS (FAB) $C_{33}H_{58}N_3O_7$ $[M+H]^+$ calcd: 608.4275, found: 608.4294.

4.1.15. 7′(*S*)-Malyngamide X, 7′(*S*)-*epi* 1. Using the same procedure as described for **1**, compound 7′(*S*)-*epi* **1** (20 mg, 44% yield) was obtained from **2b** (20 mg, 0.078 mmol).

Compound 7′(*S*)-*epi* **1**: pale yellow oil; R_f 0.34, EtOAc; $[\alpha]_D^{27}$ −15.4 (*c* 0.8, MeOH); ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were identical to that of **1**; IR (KBr): *ν* 3336, 2931, 2856, 1719, 1684, 1624, 1457, 1379, 1319, 1248, 1097, 953 cm^{-1}; HRMS (FAB) $C_{33}H_{58}N_3O_7$ $[M+H]^+$ calcd: 608.4275, found: 608.4305.

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Supplementary data

^{1}H NMR spectra for compounds **2a**, **23**, **24**, **28**, **1** (natural and synthetic), and 7′(*S*)-*epi* **1**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.01.035.

References and notes

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2. NMR chiral solvating agents (CSAs) are optically pure compounds that bind in situ to the substrate through nonconvalent, intermolucular forces. The solvated complexes between CSA and a pair of enantiomers are diastereomers, which showed non-equivocal shits of the ^{1}H NMR signals; see for instance: (a) Wenzel, T. J.; Wilcox, J. D. *Chirality* **2003**, *15*, 256–270; (b) Latypov, Sh.; Franck, X.; Jullian, J.-C.; Hocquemiller, R.; Figadére, B. *Chem.—Eur. J.* **2002**, *8*, 5662–5666; (c) Jullian, J.-C.; Franck, X.; Latypov, S.; Hocquemiller, R.; Figadére, B. *Tetrahedron: Asymmetry* **2003**, *14*, 963–966; (d) Pirkle, W. H.; Beare, S. D. *J. Am. Chem. Soc.* **1969**, *91*, 5150–5155.
3. Lyngbic acid is the major fatty acid substructure in the malyngamides. See: (a) Tan, L. T.; Okino, T.; Gerwick, W. H. *J. Nat. Prod.* **2000**, *63*, 952–955; (b) Nogle, L. M.; Gerwick, W. H. *J. Nat. Prod.* **2003**, *66*, 217–220; (c) Milligan, K. E.; Márquez, B.; Williamson, T.; Davies-Coleman, M.; Gerwick, W. H. *J. Nat. Prod.* **2000**, *63*, 965–968; (d) Kan, Y.; Sakamoto, B.; Fujita, T.; Nagai, H. *J. Nat. Prod.* **2000**, *63*, 1599–1602.
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10. For α-methyl-β-hydroxycarbonyl compounds, the observed vicinal coupling constants for *anti* C_α/C_β protons is large ($^3J_{H,H}$=7–12 Hz) whereas that of the *gauche* C_α/C_β protons is small ($^3J_{H,H}$=0–4 Hz); see: (a) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294–4299; (b) Paik, S.; Carmeli, S.; Cullingham, J.; Moore, R. E.; Patterson, G. M. L.; Tius, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 8116–8125 (see Fig. 1).
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12. The different segments' coupling method was applied to **1**. Sequentially, lyngbic acid **2a** was coupled to *N*-Me-L-alanine-OBn using 2-chloro-1,3-dimethyl-2-imidazolinium PF_6 (CIP) and *i*-Pr_2NEt, debenzylation of the corresponding lipopeptide **30** by basic hydrolysis provided free acid **31**, final coupling of **31** with amine derivative **27** by reaction with CIP and *i*-Pr_2NEt accomplishing in 50% yield as a 1:1 mixture of diastereomers (determined by ^{1}H NMR). Fortunately, the isomers could be isolated by preparative TLC (EtOAc–Hex–Et_3N, 4:5:0.1). Thus, the malyngamide **1** was isolated in 29% yield. Another isomer would be its C-2(*R*) epimer because of the propensity for racemization of the *N*-Me-L-alanine residue after activation with CIP (see Scheme 6).
13. The tripeptide moiety was numbered with respect to janolusimide, a very similar tripeptide. See: Sodano, G.; Spinella, A. *Tetrahedron Lett.* **1986**, *27*, 2505–2508.