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Total Synthesis of Malyngamides K, L, and 5″-*epi*-C and Absolute Configuration of Malyngamide L

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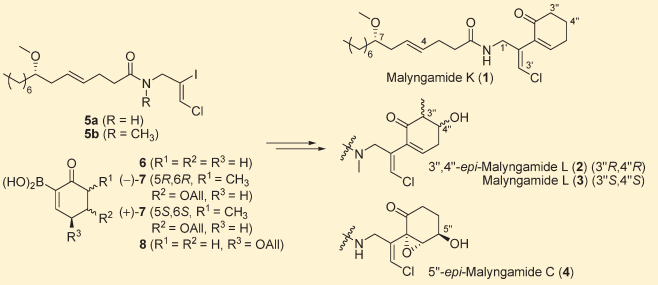
Supporting Information

ABSTRACT: An accelerated, enantioselective, and general synthetic route to a class of malyngamides, K (**1**), L (**3**), and 5″-*epi*-C (**4**), bearing a cyclohexenone ring or a heavily oxygenated six-membered ring and a vinyl chloride structural motif was developed. The key step was the Suzuki cross-coupling reaction of boronic acids **6**−**8** with unsaturated carboxylic amides **5a,b** possessing the chlorovinyl iodide functionality for the construction of the skeletons of **1**−**4**. The key intermediates **10a,b** were prepared using Ogilvie's method for the construction of the chlorovinyl iodide functionality. The NMR data of the synthetic compound **2** were in full agreement with those of the reported product, and the discrepancy in the specific rotation data suggested that the correct structure of malyngamide L should be **3**, in which the absolute configuration of the amine part was enantiomeric to that in compound **2**. Then the absolute configuration of the stereogenic center at C(3″) and C(4″) in malyngamide L was confirmed by synthesis of compound **3**.



INTRODUCTION

Malyngamide K (**1**), malyngamide L (**3**),[1] and 5″-*epi*-malyngamide C (**4**)[2,3] are members of a class of marine natural products isolated from the marine cyanophyte *Lyngbya majuscula*. Malyngamides K and L were isolated from a sample of *L. majuscula* collected from Curacao in the Southern Caribbean by Gerwick's group in 1997.[1] These compounds displayed cytotoxicity to brine shrimp (the former: IC_{50} 6 μM; the latter: IC_{50} 8 μM) and goldfish (the former: IC_{50} 7 μM; the latter: IC_{50} 15 μM). However, the absolute configurations of C(3″) and C(4″) chiral centers on the amine moiety of malyngamide L were not determined because of the unresolved multiplet nature of proton resonances for the C(3″) and C(4″) positions. 5″-*epi*-Malyngamide C was isolated from a sample of *L. majuscula* collected near Bush Key, Dry Tortugas, Florida, by Luesch's group in 2010.[2] It was found to be cytotoxic to HT29 colon cancer cells (IC_{50} 15.4 μM) and to inhibit bacterial quorum sensing in a reporter gene assay. Malyngamide K and 5″-*epi*-malyngamide C were also isolated from a sample of the marine cyanobacterium *L. majuscula* collected from shallow water in True Blue Bay, Grenada, by Gerwick's group in 2010[3] and found to be moderately cytotoxic to NCI-H460 human lung tumor (the former: IC_{50} 1.1 μM; the latter: IC_{50} 4.5 μM) and neuro-2a cancer cell lines (the former: IC_{50} 0.49 μM; the latter: IC_{50} 10.9 μM). Structurally, these malyngamides consist of a fatty acid side chain containing a 4*E* double bond and a 7*S* stereogenic center connected via an amide linkage to a cyclohexenone ring or a heavily oxygenated six-membered ring with a functional unit of vinylic chloride. This group also includes malyngamides C, deoxy-C,[4] 5″-*O*-acetyl-5″-*epi*-C acetate,[3] C acetate,[4] D,[5] G,[6] I acetate,[7] iso-K,[8] M, N,[7] and 2[9] (Figure 1), which along with another 24 malyngamides were found to possess a wide range of biological properties.[10]

The scarcity of malyngamides from natural sources has hampered biological evaluation of these fascinating molecules. To provide materials for more extensive biological evaluation and to confirm the absolute configuration of unsecured stereogenic centers, we were interested in establishing a generally applicable protocol for the preparation of malyngamides. To date, the synthesis of malyngamides U[11,12] and W,[13] bearing a heavily oxygenated six-membered ring or a cyclohexenone ring functionality, and malyngamides M,[14] O, P, Q, and R,[15] bearing a vinyl chloride motif, have been realized by us. However, the synthesis of malyngamides bearing both a heavily oxygenated six-membered ring or cyclohexenone ring and a vinyl chloride functionality (i.e., malyngamides K and L) is still challenging. Although our previous method for the construction of the vinyl chloride motif used the Wittig reaction,[14,15] this approach would not be so efficient in the synthesis of such molecules possessing a cyclohexenone motif. Analysis of the structure of malyngamides K, L, and 5″-*epi*-C in detail revealed that a coupling reaction between the cyclohexenone and chlorovinyl iodide would be the best approach. Herein, we report the synthesis of malyngamides K (**1**), L (**3**), and 5″-*epi*-C (**4**) and the confirmation of the absolute configuration of malyngamide L.

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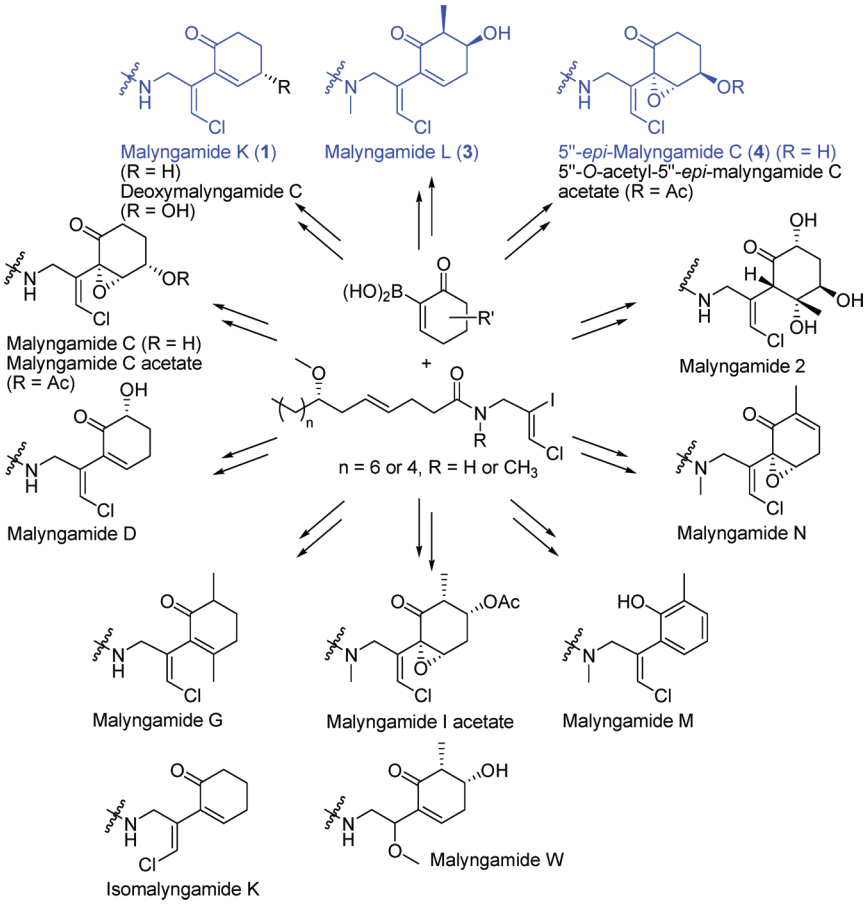
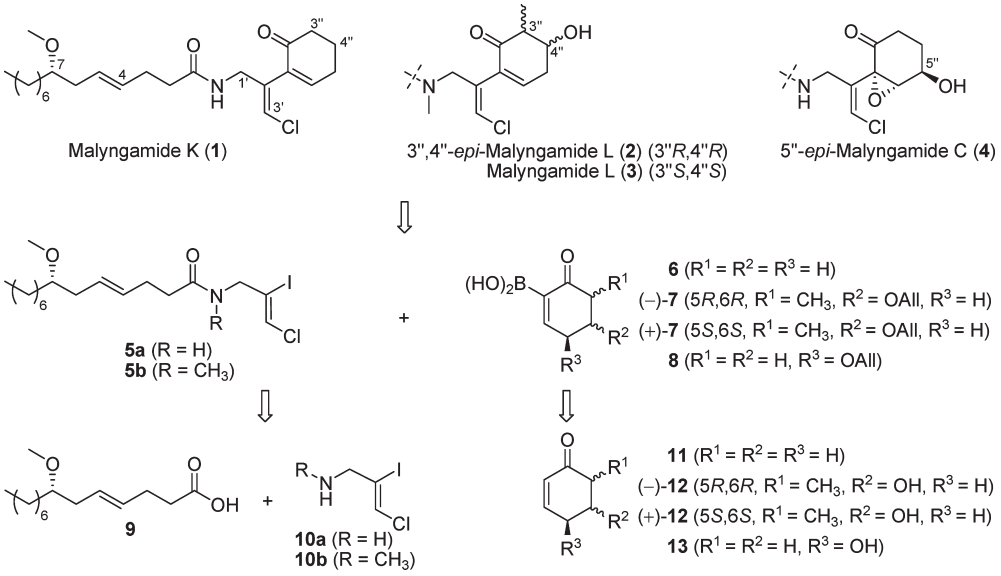


Figure 1. Structure of malyngamides K, L, 5′′-*epi*-C, deoxy-C, 5′′-*O*-acetyl-5′′-*epi*-C acetate, C, C acetate, D, G, I acetate, iso-K, M, N, and 2, which could be prepared with Suzuki cross-coupling reaction, and malyngamide W.

Scheme 1. Retrosynthetic Analysis



RESULTS AND DISCUSSION

As outlined in Scheme 1, malyngamides K, L, and 5′′-*epi*-malyngamide C are retrosynthetically divided into unsaturated carboxylic amide components **5a,b** that bear the chlorovinyl iodide part, and boronic acids **6**−**8**. Suzuki cross-coupling reaction between two of them would furnish the skeleton of

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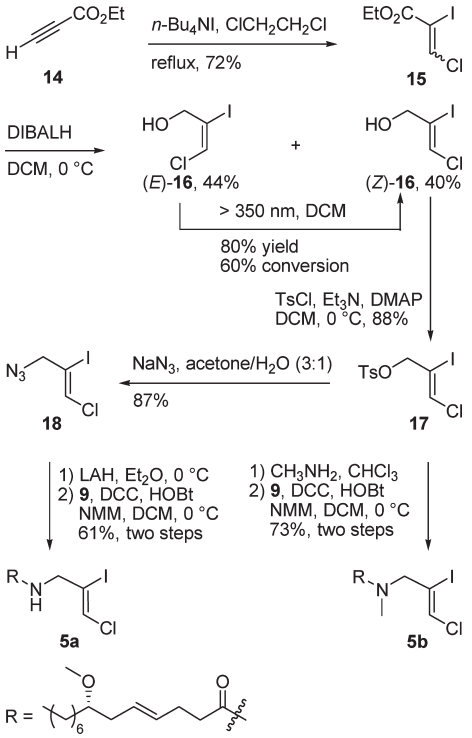
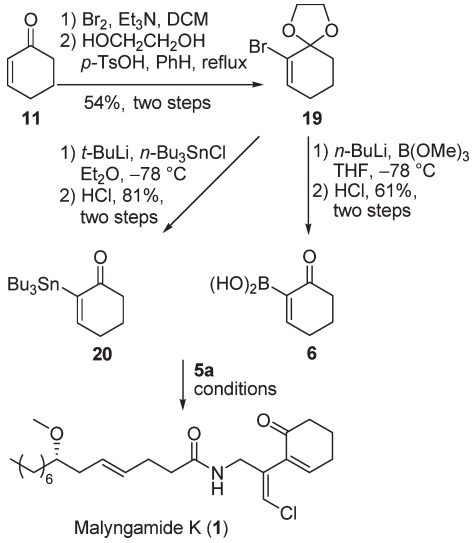
Scheme 2. Preparation of Key Intermediates 5a and 5b



Scheme 3. Preparation of Malyngamide K



the target malyngamides. **5a,b** could be formed by an amide linkage between acid **9** and amines **10a,b**. In turn, the chlorovinyl iodide functionality of amines **10a,b** could be generated from ethyl propiolate (**14**) using Ogilvie's method,[16,17] and the chiral fatty acid **9**, (−)-(4*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.[12] **6**−**8** could be prepared from cyclohexenone ring derivatives via functional transformations.[18]

The preparation of amides **5a,b** began with ethyl propiolate (**14**) (Scheme 2).[16] Thus, compound **14** was converted to ester **15** by exposure to *n*-tetrabutylammonium iodide (*n*-Bu_4NI) in refluxing 1,2-dichloroethane. Subsequent reduction of the ester **15** with diisobutylaluminum hydride (DIBALH) in DCM at 0 °C gave the intermediate alcohol **16** in 84% yield as a mixture of *E*- and *Z*-isomers (*E*:*Z* = 1.1:1). This mixture could be separated carefully by flash chromatography over silica gel, and the *E*-isomer could be converted to the desired *Z*-isomer in 80% yield (based on 60% conversion) by irradiation with UV light (>350 nm) in DCM.[16] The *Z*-configuration of the vinyl chloride was consistent with that in natural malyngamides K, L, and 5″-*epi*-C, which provided a foundation for the preparation of these malyngamides. Then activation of the hydroxyl group in alcohol (*Z*)-**16** with *p*-toluenesulfonyl chloride (*p*-TsCl) in the presence of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in DCM at 0 °C afforded the tosylate **17** in 88% yield,[19] which was followed by azidation with sodium azide in acetone/water (3:1) to give the azide **18** in 87% yield.[20] Reduction of azide **18** with lithium aluminum hydride (LAH) in diethyl ether at 0 °C generated the corresponding amine,[21] which was directly condensed with the acid **9** in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole (HOBt), and *N*-methylmorpholine (NMM) in DCM at 0 °C to afford amide **5a** in 61% yield in two steps.[11] The synthesis of amide **5b** was also achieved by treatment of tosylate **17** with an excess of aqueous methylamine in chloroform,[22] followed by amidation with acid **9** in 73% yield in two steps.[11]

With the key intermediate **5a** in place, we sought to construct the C(2′)−C(1″) framework of malyngamide K via transition metal-catalyzed cross-coupling reaction initially (Scheme 3), so the synthesis of stannane **20** and boronic acid **6** was pursued. The preparation of stannane **20** and boronic acid **6** both began with 2-cyclohexen-1-one (**11**). Thus, bromination of enone **11** with bromine in the presence of triethylamine generated the bromoenone,[23] followed by protection of the carbonyl group with ethylene glycol ($HOCH_2CH_2OH$) in the presence of *p*-toluenesulfonic acid (*p*-TsOH) in refluxing benzene to afford the ketal **19** in 54% yield in two steps.[24] Ketal **19** was easily transformed to viable intermediates stannane **20** and boronic acid **6** by treatment with tri-*n*-butyltin chloride (*n*-Bu_3SnCl) in the presence of *tert*-butyllithium (*t*-BuLi),[25] or trimethyl borate [$B(OMe)_3$] in the presence of *n*-butyllithium (*n*-BuLi), and then treatment with hydrogen chloride,[18] in 81% and 61% yield, respectively. On the basis of the preparation of the key intermediates **20** and **6**, we focused our efforts on the synthesis of malyngamide K by the Stille coupling reaction;[26] several conditions were examined (Supporting Information, Table S1). No desired product resulted when stannane **20** was reacted with the amide **5a** using tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] as catalyst in the presence of copper(I) chloride[27] in THF, cesium fluoride[28] in THF at 50 °C, or copper(I) iodide in DMF at rt to 50 °C[29] (entries 1−3). The same result was obtained using bis(acetonitrile)dichloropalladium [$PdCl_2(MeCN)_2$] as catalyst under various conditions (entries 4−6).[26,30,25] A survey of the literature prompted us to turn our attention to the Suzuki coupling reaction,[31] which is very sensitive to the palladium source and ligand. However, no favorable results were obtained when using $Pd(PPh_3)_4$ or $Pd(PhCN)_2Cl_2$ as catalyst in ethanol,[32] DME/H_2O,[33] or THF/H_2O[34] (entries 7−9). No reaction occurred when using palladium diacetate [$Pd(OAc)_2$] as catalyst without ligand or using triphenylphosphine as ligand (entries 10 and 11).[35] Fortunately, malyngamide K was achieved in 89% yield when $Pd(OAc)_2$ and

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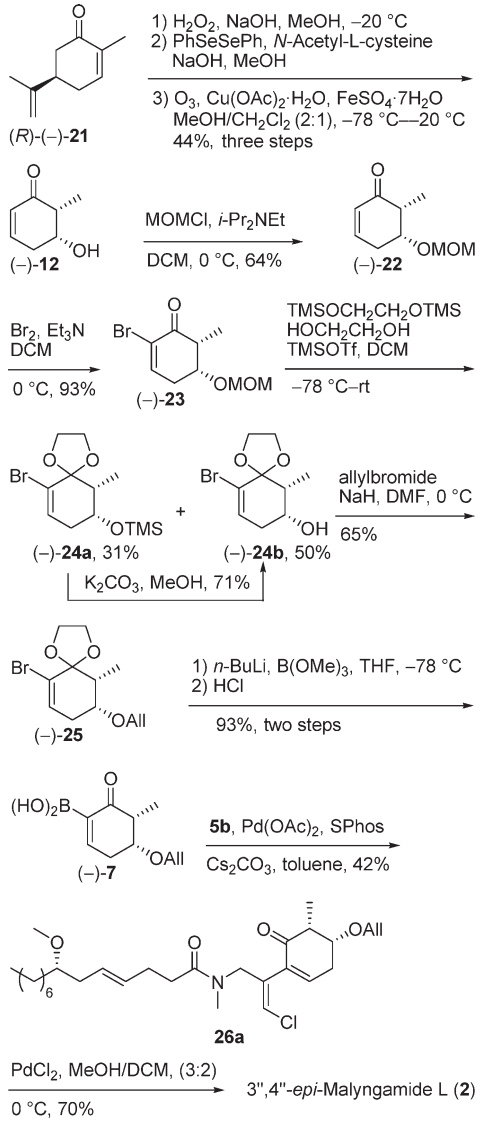
Scheme 4. Preparation of 2



tri-*tert*-butylphosphonium tetrafluoroborate (t-$Bu_3P·HBF_4$) were used in the presence of cesium carbonate (entry 13), while the use of the biphenyl ligand 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos) resulted in a lower yield (entry 12).[35] The spectral data of synthetic malyngamide K (**1**) were in good agreement with that reported in the literature.[1] As expected, the preparation of the relatively simple malyngamide K was accomplished smoothly in seven steps in 23% yield.

Encouraged by the synthesis of malyngamide K, we continued to synthesize malyngamide L, possessing a more challenging structure, in which the absolute configurations of C(3″) and C(4″) have not been confirmed. At the onset of this project, our initial speculation was that the structure of malyngamide L should be that of compound **2**, with the absolute configuration at the C(3″) and C(4″) center being syn, bearing *R* stereochemistry for both centers, on the basis of biogenesis analysis and other "normal" malyngamides such as malyngamides I acetate and W (see Figure 1).[7,36] Hence, target compound **2** was pursued first (Scheme 4). Thus, boronic acid (−)-**7** was first prepared, using a reaction sequence similar to that used previously, from the enone (−)-**12**, which was prepared in three steps from (*R*)-(−)-carvone [(−)-**21**] as follows:[13] Stereoselective epoxidation of enone (−)-**21** with hydrogen peroxide in the presence of sodium hydroxide in methanol at −20 °C generated the desired α,β-epoxide ketone;[37] subsequently, reductive ring-opening of the resulting epoxide ketone by a catalytic amount of diphenyl diselenide (PhSeSePh) in the presence of *N*-acetyl-L-cysteine and sodium hydroxide in methanol[38] followed by ozonization in methanol/DCM (2:1) at −78 °C followed by treatment with copper(II) acetate monohydrate [$Cu(OAc)_2·H_2O$] and iron sulfate heptahydrate ($FeSO_4·7H_2O$) at −20 °C resulted in the desired enone (−)-**12**[39] in 44% yield in three steps. Then protection of the hydroxyl group in enone (−)-**12** with methoxymethyl chloride (MOMCl) in the presence of *N*,*N*-diisopropylethylamine in DCM at 0 °C gave the corresponding ether (−)-**22** in 64% yield,[40] which underwent bromination to afford the bromoenone (−)-**23** in 93% yield.[23] In order to protect the carbonyl group of bromoenone (−)-**23**, several conditions were tested. Initially, aromatization of the α,β-unsaturated cyclohexenone moiety in bromoenone (−)-**23** occurred when treated with $HOCH_2CH_2OH$ and *p*-TsOH in benzene at reflux,[24] and the starting material was recovered when using 1,2-bis(trimethylsilyloxy)ethane ($TMSOCH_2CH_2OTMS$) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) even if $HOCH_2CH_2OH$ was added at −78 °C.[41] Fortunately, when the reaction temperature was maintained at −78 °C for 4 h and then raised to rt for 20 h, ketal (−)-**24a** and (−)-**24b** were achieved in 31% and 50% yields, respectively. Then deprotection of the TMS group of ketal (−)-**24a** with potassium carbonate in methanol afforded ketal (−)-**24b** in 71% yield,[42] and this was a spontaneous reaction when exposed to the air. The stereochemistry of ketal (−)-**24b** was unambiguously established to be 9*R* and 10*R* by X-ray crystallographic analysis (Supporting Information, Figure S1). Subsequently, protection of the hydroxyl group of ketal (−)-**24b** using allyl bromide in the presence of sodium hydride in DMF at 0 °C furnished the allyl ether (−)-**25** in 65% yield.[43] Finally, boronic acid (−)-**7** was prepared by a procedure similar to that for the preparation of boronic acid **6**; treatment of allyl ether (−)-**25** with $B(OMe)_3$ in the presence of *n*-BuLi followed by hydrogen chloride produced desired intermediate (−)-**7** in 93% yield in two steps.[18] The allyl ether was the most suitable protecting group among those tested. At this stage, we were faced with the task of the construction of the skeleton of compound **2** via Suzuki coupling reaction of boronic acid (−)-**7** and amide **5b**. Surprisely, compound **26a** was achieved using SPhos as ligand in 42% yield,[35] but no desired product resulted when t-$Bu_3P·HBF_4$ was used. Perhaps the coupling reaction of boronic acid (−)-**7** and amide **5b** failed with t-Bu_3P as ligand because of competing π-allyl complex formation between Pd catalyst and allyl group in compound (−)-**7**.[44,45] SPhos was used as ligand, because the L_2Pd complex is too large to allow for the Pd−C interaction and is most likely much too hindered to participate in an oxidative addition process. One of the ligands must dissociate to arrive at a complex similar to L·Pd prior to oxidative addition, and the Pd possibly coordinated to the aromatic ring.[46] The LPd cannot form the competing π-allyl complex, so compound **26a** was achieved. Finally, removal of the allyl group with palladium(II) chloride in methanol/DCM (3:2) completed the synthesis of 3″,4″-*epi*-malyngamide L (**2**) in 70% yield.[47] Thus, the preparation of the 3″,4″-*epi*-malyngamide L (**2**) was finished in ten steps in 3.4% yield.

The ^1H and ^{13}C NMR data of synthetic malyngamide L (**2**) were in complete agreement with the data reported for the

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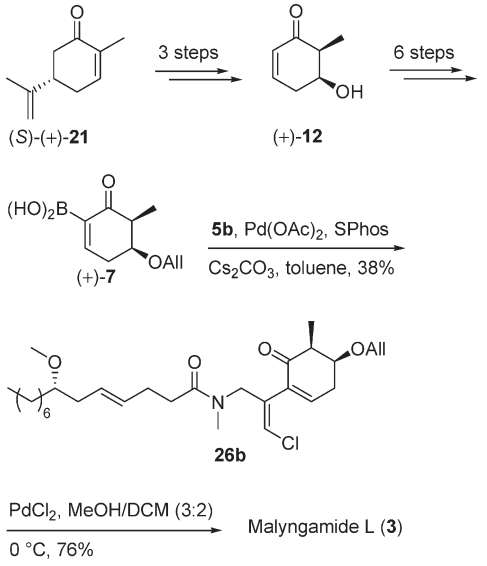
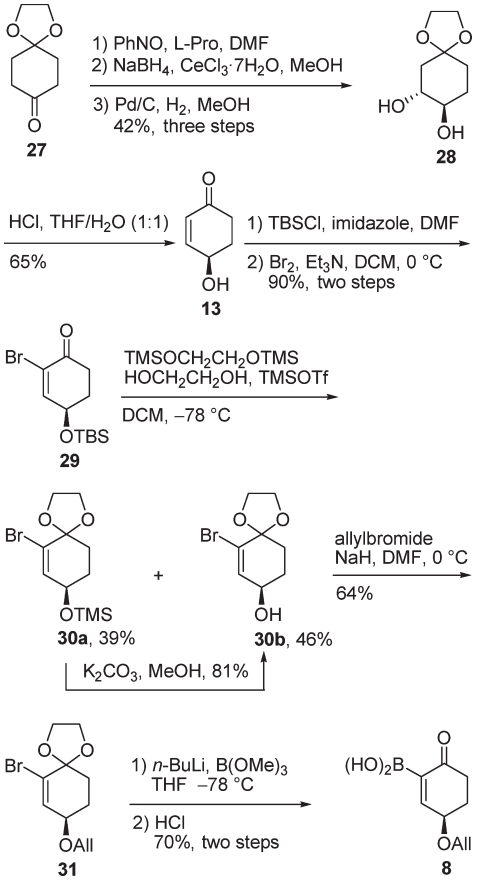
Scheme 5. Preparation of Malyngamide L



Scheme 6. Preparation of Key Intermediate 8



isolated malyngamide L. However, the specific rotation of compound **2** was found to be $[\alpha]^{20}_{D}$ −16 (*c* 0.3, EtOH), which was opposite to the reported value of $[\alpha]^{20}_{D}$ +17.3 (*c* 0.1, EtOH).[1] The acid portion of malyngamide L was determined to be (−)-(4*E*,7*S*)-7-methoxytetradec-4-enoic acid from biosynthetic considerations. The only possible explanation was that the opposite configuration of the amine portion of the isolated malyngamide L was enantiomeric with the amine part of compound **2** (i.e., *S* instead of *R*). Hence, the structure and absolute configuration of malyngamide L should be that in compound **3**. The chiral centers between the fatty acid part and the amine part were too remote from each other, and hence compounds **2** and **3** would have identical ^{1}H and ^{13}C NMR spectral features. This deduction was further confirmed by our similar observations of the spectral data of serinol-derived malyngamides,[48] malyngamides U,[11,12] Q, and R, derived by total synthesis.[15] Thus, the key intermediate (+)-**7** was prepared from (*S*)-(+)-carvone [(+)-**21**] in nine steps in 13% overall yield. After Suzuki cross-coupling reaction and deprotection, compound **3** was accomplished in 29% yield from boronic acid (+)-**7** (Scheme 5). In the synthesis of the compound **3**, the stereochemistry of ketal (+)-**24b** was also established as 9*S* and 10*S* by X-ray crystallographic analysis (Supporting Information, Figure S2). The NMR data of synthetic compound **3** were identical with those reported for the isolated malyngamide L and compound **2**. The specific rotation of compound **3** was found to be $[\alpha]^{20}_{D}$ +20 (*c* 0.3, EtOH), which is consistent with the reported value $[\alpha]^{20}_{D}$ +17.3 (*c* 0.1, EtOH).[1] These results revealed that the absolute configuration of malyngamide L should be that observed in compound **3**.

On the basis of the successful access to malyngamides K and L, the Suzuki cross-coupling could also be applied to the synthesis of 5″-*epi*-malyngamide C in our project (Schemes 6 and 7). First, the synthesis of key intermediate **8** could begin with the known ketone **13**, which was prepared from monoketal **27** in four steps. Thus, oxidation of the monoketal **27** using nitrosobenzene in the presence of L-proline in DMF gave the corresponding hydroxylamine. The resultant hydroxylamine was reduced to afford a single alcohol using Luche conditions,[49] followed by reductive cleavage of the N−O bond in the presence of palladium on activated carbon (Pd/C) in methanol under H_2 atmosphere (1 atm) to give diol **28**[50] in 42% yield in three steps. Subsequently, deketalization and elimination of diol **28** with hydrogen chloride in THF/water (1:1) afforded enone **13** in 65% yield.[49] Protection of the hydroxyl group in enone **13** with *tert*-butyldimethylsilyl chloride (TBSCl)[50] in the presence of imidazole in DMF followed by bromination of the corresponding silyl ether gave bromoenone **29**[23] in 90% yield in two steps. Then treatment of ketone **29** with $TMSOCH_2CH_2OTMS$, $HOCH_2CH_2OH$, and TMSOTf at 20 °C for 5 h gave **30a** and **30b** in 39% and 46% yields, respectively.[41] Note that the control of reaction temperature was very important; aromatization of the substrate occurred when the reaction temperature was raised to 30 °C, and the reaction was very slow below 10 °C. Deprotection of ketal **30a** also afforded ketal **30b** in 81% yield. The hydroxyl group in alcohol **30b** was protected again as the allyl ether **31** by allyl bromide in 64% yield.[43] Then the boronic acid **8** was prepared by a procedure similar to that for the preparation of boronic acid **6** in 70% yield in two steps. Again, the allyl ether gave a satisfactory result in the preparation of desired boronic acid **8**.

With the key intermediates **5a** and **8** in hand, the skeleton of the 5″-*epi*-malyngamide C could be constructed via Suzuki cross-coupling reaction. Thus, using the same conditions as those used for the preparation of **26a** and **26b**, compound **32** was obtained in 56% yield.[35] The remaining task was to complete stereoselective epoxidation to finish the preparation of 5″-*epi*-malyngamide

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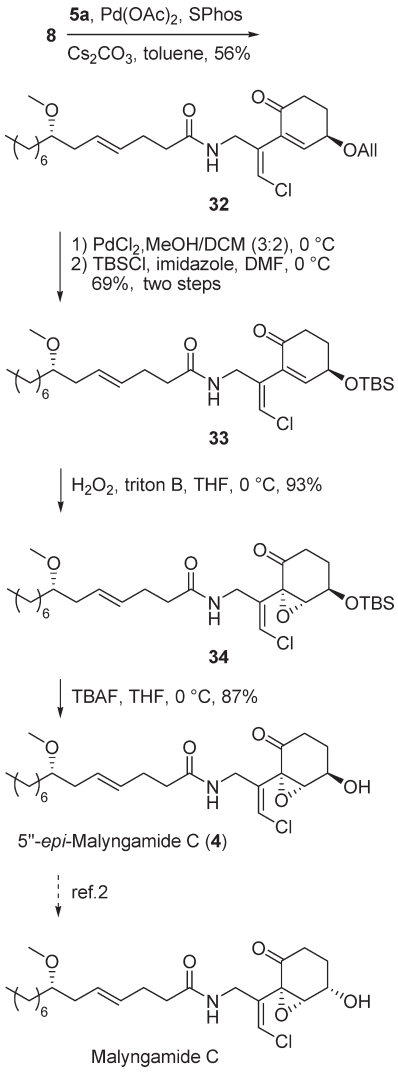
Scheme 7. Preparation of 5″-*epi*-Malyngamide C (4) and Malyngamide C



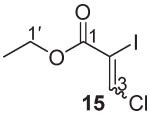
C. A survey of the literature revealed that stereoselectivity in favor of C(1″)−C(6″) double bond epoxidation seemed plausible, because the epoxidation was certain to be impeded by the presence of the adjacent steric hindrance from the protective group of the C-5″ hydroxyl group. Thus, the allyl ether was converted to silyl ether **33**, bearing more steric bias, by treatment with $PdCl_2$[47] and then TBSCl and imidazole[50] in 69% yield in two steps. Then stereoselective epoxidation of **33** with hydrogen peroxide and benzyltrimethylammonium hydroxide (triton B)[50] in THF at 0 °C smoothly provided the corresponding epoxide **34** as a single stereoisomer in 93% yield (only one stereoisomer was observed by ^{1}H NMR analysis of the crude product). Finally, removal of the TBS protecting group with tetrabutylammonium fluoride (TBAF)[51] in THF at 0 °C in 87% yield finished the synthesis of 5″-*epi*-malyngamide C. The spectral data of synthetic 5″-*epi*-malyngamide C (**4**) were in good agreement with the reported data for the isolated 5″-*epi*-malyngamide C.[2] 5″-*epi*-Malyngamide C could be converted to malyngamide C via the Mitsunobu reaction.[2] Malyngamide C could also be achieved by the same route as that used for the synthesis of 5″-*epi*-malyngamide C, using D-proline-mediated oxygenation to introduce the stereocenter in the cyclohexenone. Then completely stereoselective Sharpless epoxidation of the allylic alcohol finished the preparation of malyngamide C.

CONCLUSION

The enantioselective total synthesis of malyngamide K, malyngamide L, and 5″-*epi*-malyngamide C have been accomplished via a highly convergent strategy in seven steps in 23% yield, in ten steps in 3.7% yield, and in fourteen steps in 2.7% yield, respectively. The key step was the Suzuki cross-coupling reaction for the construction of the skeletons of **1**−**4**. The determination of the absolute configuration of C(3″) and C(4″) in the amine portion of malyngamide L was accomplished by the synthesis of compounds **2** and **3**. Further application of this strategy toward the synthesis of the structurally related malyngamides containing a cyclohexenone ring or a heavily oxygenated six-membered ring and with a vinylic chloride functionality, such as C, C acetate, deoxy-C, D, G, I acetate, N, and 2, is currently underway and will be presented in due course.

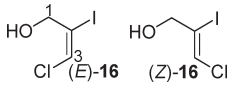
EXPERIMENTAL SECTION

Ethyl 3-Chloro-2-iodoprop-2-enoate (15).[16]



To a stirred solution of ethyl propiolate (**14**) (2.00 g, 20.41 mmol) in DCM (80 mL) was added *n*-Bu_4NI (22.59 g, 61.23 mmol). The reaction mixture was heated at reflux for 18 h. Then the reaction mixture was cooled to rt, diluted with EtOAc, and washed with $NaHSO_3$ (20 wt % solution), saturated $NaHCO_3$ solution, and brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 10:1) afforded ester **15** (3.82 g, 72% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.01 (s, 1H, H-3), 4.31 (dd, J = 14.0, 7.2 Hz, 2H, H-1′), 1.35 (t, J = 7.2 Hz, 3H, H-2′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.4 (C, C-1), 128.7 (CH, C-3), 85.0 (C, C-2), 62.6 (CH_2, C-1′), 13.9 (CH_3, C-2′); MS (EI) m/z (%) 260 (M^+, 23), 225 (32), 215 (78), 133 (6), 53 (100).

(*E*)-3-Chloro-2-iodoprop-2-en-1-ol and (*Z*)-3-Chloro-2-iodoprop-2-en-1-ol [(*E*)-16 and (*Z*)-16].[16]



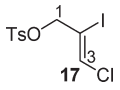
To a stirred solution of ester **15** (4.50 g, 17.31 mmol) in DCM (100 mL) was added DIBALH (52 mL, 1 M in hexanes, 52 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and then maintained for 2 h. Then MeOH (5 mL) was carefully added dropwise to quench the reaction. A saturated solution of Rochelle's salt (100 mL) was introduced, and the resulting mixture was stirred until both layers became clear. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 5:1) afforded alcohol (*E*)-**16** (1.66 g, 44% yield) and alcohol (*Z*)-**16** (1.51 g, 40% yield) as a colorless oil. For (*E*)-**16**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.60 (d, J = 0.4 Hz, 1H, H-3), 4.38 (s, 2H, H-1), 2.80 (br, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 120.2 (CH, C-3), 102.6 (C, C-2), 63.6 (CH_2, C-1); MS (EI) m/z (%) 218 (M^+, 23), 127 (56), 91 (100), 55 (31), 39 (28). For (*Z*)-**16**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.75 (s, 1H, H-3), 4.32 (s, 2H, H-1), 2.85 (br, 1H,

dx.doi.org/10.1021/jo2003852 |J. Org. Chem. 2011, 76, 3946–3959

OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 125.4 (CH, C-3), 109.4 (C, C-2), 69.7 (CH_2, C-1); MS spectra data of (*Z*)-**16** is identical to that of (*E*)-**16**.

A stirred solution of alcohol (*E*)-**16** (300 mg, 1.38 mmol) in DCM (50 mL) was irradiated with UV light (>350 nm) for 3 h, then the solvent was evaporated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 5:1) afforded alcohol (*Z*)-**16** (144 mg, 80% yield on the basis of 60% conversion).

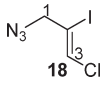
(*Z*)-3-Chloro-2-iodoallyl 4-Methylbenzenesulfonate (17).



17

To a stirred solution of alcohol (*Z*)-**16** (2.10 g, 9.63 mmol) in Et_3N (30 mL) and DCM (60 mL) were added *p*-TsCl (7.34 g, 38.52 mmol) and DMAP (117 mg, 0.96 mmol) at 0 °C, The reaction mixture was allowed to warm to rt and then maintained for 20 h. The reaction mixture was washed with H_2O (100 mL × 3). The organic layer was dried over Mg_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 10:1) afforded compound **17** (3.15 g, 88% yield) as a white solid. Mp 76−77 °C; IR (KBr) 3051, 1594, 1364, 1175, 950, 843, 666, 533 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, *J* = 8.4 Hz, 2H, 2ArH), 7.37 (d, *J* = 8.4 Hz, 2H, 2ArH), 6.76 (s, 1H, H-3), 4.77 (s, 2H, H-1), 2.46 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.3 (C, ArC), 132.8 (C, ArC), 130.1 (CH, C-3), 129.9 (CH, ArCH), 128.0 (CH, ArCH), 99.0 (C, C-2), 74.7 (CH_2, C-1), 21.6 (CH_3); HRMS (ESI) *m*/*z* $C_{10}H_{14}ClINO_3S$ $[M + NH_4]^+$ calcd 389.9422, found 389.9419.

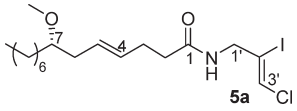
(*Z*)-3-Chloro-2-iodoprop-2-en-1-azide (18).



18

To a stirred solution of compound **17** (1.60 g, 4.30 mmol) in acetone and H_2O (48 mL, acetone/H_2O 3:1) was added NaN_3 (1.12 g, 17.20 mmol), and the reaction mixture was maintained at this temperature for 5 h. After removal of acetone, the reaction mixture was extracted with EtOAc (50 mL × 3). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 5:1) afforded azide **18** (909 mg, 87% yield) as a colorless oil. IR (KBr) 3044, 2102, 1589, 1279, 825, 588 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.72 (d, *J* = 0.8 Hz, 1H, H-3), 4.17 (s, 2H, H-1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 127.7 (CH, C-3), 102.0 (C, C-2), 60.1 (CH_2, C-1); HRMS (ESI) *m*/*z* $C_3H_7ClIN_4$ $[M + NH_4]^+$ calcd 260.9398, found 260.9400.

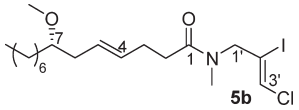
(−)-(4*E*,7*S*)-*N*-[(*Z*)-3-Chloro-2-iodoprop-2-ene]-7-methoxytetradec-4-enamide (5a).



5a

To a suspension of LAH (125 mg, 3.30 mmol) in Et_2O (20 mL) was added a solution of azide **18** (534 mg, 2.20 mmol) in Et_2O (10 mL) dropwise at 0 °C, and the reaction mixture was maintained at this temperature for 2 h. NaOH (1 mL, 3% in water) was added, and the mixture was stirred for an additional 1 h. The resulting mixture was filtered through Celite, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the amine **10a** as a colorless oil. To a stirred solution of this amine in DCM (5 mL) was added acid **9** (353 mg, 1.38 mmol) in DCM (5 mL), followed by DCC (314 mg, 1.50 mmol), HOBt (224 mg, 1.7 mmol), and NMM (154 mg, 1.50 mmol) at 0 °C. The mixture was allowed to warm to rt over 3 h, stirring was continued for 10 h, and then the mixture was concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 2:1) afforded amide **5a** (611 mg, 61% yield in two steps) as a colorless oil. $[\alpha]^{20}_D$ −5 (*c* 1.0, $CHCl_3$); IR (KBr) 3286, 3049, 2927, 1653, 1543, 1460, 1097, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.66 (s, 1H, H-3′), 5.98 (s, 1H, NH), 5.52−5.49 (m, 2H, H-4 and H-5), 4.21 (d, *J* = 6.0 Hz, 2H, H-1′), 3.32 (s, 3H, H-15), 3.19−3.14 (m, 1H, H-7), 2.36 (t, *J* = 5.6 Hz, 2H, H-2), 2.29 (dd, *J* = 12.8, 6.0 Hz, 2H, H-6), 2.21 (t, *J* = 5.2 Hz, 2H, H-3), 1.44−1.43 (m, 2H, H-8), 1.27 (s, 10H, H-9, H-10, H-11, H-12, and H-13), 0.88 (t, *J* = 7.2 Hz, 3H, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2 (C, C-1), 130.7 (CH, C-4), 128.0 (CH, C-5), 126.5 (CH, C-3′), 106.2 (C, C-2′), 80.6 (CH, C-7), 56.4 (CH_3, C-15), 49.1 (CH_2, C-1′), 36.3 (CH_2, C-2), 36.2 (CH_2, C-6), 33.3 (CH_2, C-8) 31.8 (CH_2, C-9), 29.7 (CH_2, C-12), 29.3 (CH_2, C-11), 28.5 (CH_2, C-3), 25.3 (CH_2, C-10), 22.6 (CH_2, C-13), 14.1 (CH_3, C-14); HRMS (ESI) *m*/*z* $C_{18}H_{32}ClINO_2$ $[M + H]^+$ calcd 456.1161, found 456.1155.

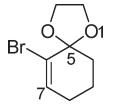
(−)-(4*E*,7*S*)-*N*-[(*Z*)-3-Chloro-2-iodoprop-2-ene]-7-methoxy-*N*′-methyltetradec-4-enamide (5b).



5b

To a stirred solution of compound **17** (1.2 g, 3.23 mmol) in $CHCl_3$ (12 mL) was added $MeNH_2$ (12 mL, 40% in H_2O), and the reaction mixture was maintained at rt for 2 d. The $CHCl_3$ layer was separated, and the H_2O layer was extracted with $CHCl_3$ (10 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the amine **10b** as a yellow oil. Then according to the procedure for the preparation of amide **5a**, acid **9** (691 mg, 2.70 mmol) afforded amide **5b** (1.11 g, 73% yield in two steps) as a colorless oil. $[\alpha]^{20}_D$ −10 (*c* 1.0, $CHCl_3$); IR (KBr) 3734, 3396, 2926, 1651, 1460, 1099, 971, 827, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.58/6.55 (s, 1H, H-3′), 5.52−5.48 (m, 2H, H-4 and H-5), 4.38 (4.22) (s, 2H, H-1′), 3.32 (s, 3H, H-15), 3.15 (t, *J* = 5.6 Hz, 1H, H-7), 2.98/2.88 (s, 3H, NCH_3), 2.41−2.37 (m, 4H, H-2 and H-6), 2.19 (t, *J* = 5.6 Hz, 2H, H-3), 1.43 (s, 2H, H-8), 1.27 (s, 10H, H-9, H-10, H-11, H-12, and H-13), 0.87 (t, *J* = 6.8 Hz, 3H, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6/172.5 (C, C-1′), 131.0/130.9 (CH, C-4), 127.3/127.5 (CH, C-5), 126.3/125.7 (CH, C-3′), 105.2/105.6 (C, C-2′), 80.7 (CH, C-7), 56.47/56.50 (CH_3, C-15), 56.3/59.3 (CH_2, C-1), 36.3/32.9 (CH_2, C-2), 35.0/33.1 (CH_3, NCH_3), 33.4 (CH_2, C-6), 33.3 (CH_2, C-8) 31.8 (CH_2, C-9), 29.7 (CH_2, C-12), 29.3 (CH_2, C-11), 28.0 (28.2) (CH_2, C-3), 25.3 (CH_2, C-10), 22.6 (CH_2, C-13), 14.1 (CH_3, C-14); HRMS (ESI) *m*/*z* $C_{19}H_{34}ClINO_2$ $[M + H]^+$ calcd 470.1317, found 470.1305.

6-Bromo-1,4-dioxaspiro[4.5]dec-6-ene (19).[22,23]

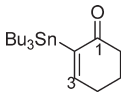


19

To a stirred solution of 2-cyclohexenone **11** (1.40 g, 14.58 mmol) in DCM (40 mL) was added a solution of Br_2 (0.8 mL, 16.10 mmol) in DCM (10 mL) in a dropwise fashion at 0 °C, followed by Et_3N (2.2 mL, 16.10 mmol). After stirring for 5 min, the reaction mixture was washed with H_2O (50 mL × 3). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 3:1) afforded 2-bromo-2-cyclohexen-1-one as a colorless oil. To a solution of this ketone (1.90 g, 10.86 mmol) in benzene (60 mL) were added $HOCH_2CH_2OH$ (1.35 g, 21.72 mmol) and *p*-TsOH (93 mg, 0.54 mmol). The reaction mixture was refluxed for 12 h under a Dean−Stark setup. The mixture was concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 5:1) afforded compound **19** (1.72 g, 54% in two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ

6.34 (t, J = 4.0 Hz, 1H, H-7), 4.21−4.18 (m, 2H, H-3), 4.01−3.97 (m, 2H, H-2), 2.12−2.08 (m, 2H, H-8), 1.94−1.91 (m, 2H, H-10), 1.82−1.76 (m, 2H, H-9); ^{13}C NMR (400 MHz, $CDCl_3$) δ 135.9 (CH, C-7), 124.5 (C, C-6), 105.7 (C, C-5), 65.7 (CH_2, C-3), 65.7 (CH_2, C-2), 35.5 (CH_2, C-10), 27.4 (CH_2, C-8), 20.2 (CH_2, C-9); MS (EI) m/z (%) 218 (M^+, 1), 190 (100), 139 (8), 109 (3) 79 (5).

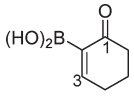
2-Tri-*n*-butylstannyl-2-cyclohexen-1-one (20).[24]



20

To a stirred solution of compound **19** (168 mg, 0.77 mmol) in Et_2O (5 mL) was added *t*-BuLi (1.9 mL, 0.8 M in hexane, 1.54 mmol) via syringe under argon at −78 °C, and the reaction mixture was maintained at this temperature for 30 min. Then a cooled solution of *n*-Bu_3SnCl (277 mg, 0.85 mmol) was added, and the reaction mixture was maintained at this temperature for 1 h. To the reaction mixture was added HCl (5 mL, 2 M), and the mixture was stirred for 3 h. The reaction mixture was extracted with EtOAc (8 mL × 4). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 1:1) afforded stannane **20** (241 mg, 81% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (t, J = 3.6 Hz, 1H, H-3), 2.43 (t, J = 6.4 Hz, 2H, H-6), 2.35 (dd, J = 10.0, 5.6 Hz, 2H, H-4), 2.02−1.95 (m, 2H, H-5), 1.51−1.43 (m, 6H, 3 × CH_2), 1.34−1.25 (m, 6H, 3 × CH_2), 0.95−0.86 (m, 15H, 3 × CH_2 and 3 × CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.5 (C, C-1), 159.4 (CH, C-3), 145.3 (CH, C-2), 38.1 (CH_2, C-6), 29.0 (CH_2), 27.9 (CH_2, C-4), 27.3 (CH_2), 23.0 (CH_2, C-5), 13.6 (CH_3), 9.6 (CH_2); MS (ESI) m/z 387.1 ([M + H]$^+$)

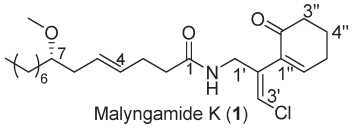
2-Dihydroxyboryl-2-cyclohexen-1-one (6).



6

To a stirred solution of compound **19** (805 mg, 3.69 mmol) in THF (10 mL) was added *n*-BuLi (1.5 mL, 2.5 M in hexane, 3.7 mmol) via syringe under argon at −78 °C, and the reaction mixture was maintained at this temperature for 1 h. Then a cooled solution of $B(OMe)_3$ (426 mg, 4.10 mmol) in THF (10 mL) was added, and the reaction mixture was maintained at this temperature for 2 h and then diluted with HCl (9 mL, 2 M) and extracted with EtOAc (20 mL × 4). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 1:1) afforded boronic acid **6** (315 mg, 61% yield) as a white solid. Mp 52−54 °C; IR (KBr) 3362, 2955, 1629, 1411, 1334, 1100, 552 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (t, J = 4 Hz, 1H, H-3), 7.45 (s, 2H, 2 × OH), 2.49−2.46 (m, 4H, H-4 and H-6), 2.07−2.00 (m, 2H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.0 (C, C-1), 165.5 (CH, C-3), 37.9 (CH_2, C-6), 27.1 (CH_2, C-4), 22.4 (CH_2, C-5); HRMS (ESI) m/z $C_6H_{10}BO_3$ [M + H]$^+$ calcd 141.0717, found 141.0715.

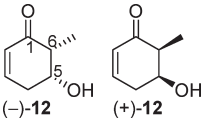
(−)-(4*E*,7*S*)-*N*-[(2*Z*)-2-Chloromethyleneethyl-(2-oxocyclohex-1-enyl)]-7-methoxytetradec-4-enamide [malyngamide K (1)].



Malyngamide K (**1**)

To a stirred solution of boronic acid **6** (54 mg, 0.44 mmol) and amide **5a** (101 mg, 0.22 mmol) in toluene (3 mL) were added *t*-$Bu_3P\cdot HBF_4$ (13 mg, 0.04 mmol) and Cs_2CO_3 (143 mg, 0.44 mmol), the reaction vessel was purged for 10 min with argon, $Pd(OAc)_2$ (5 mg, 0.02 mmol) was added, and the reaction mixture was maintained at rt for 30 h under argon. The mixture was concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 2:1) afforded malyngamide K (**1**) (83 mg, 89%) as a colorless oil. $[\alpha]^{20}_D$ −5.7 (*c* 0.4, $CHCl_3$); IR (KBr) 3370, 2926, 1673, 1543, 1457, 1364, 1256, 1095, 972, 809 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.94 (t, J = 4.0 Hz, 1H, H-6″), 6.28 (s, 1H, H-3′), 6.12 (s, 1H, NH), 5.48−5.45 (m, 2H, H-4 and H-5), 3.93 (dd, J = 5.2, 0.8 Hz, 2H, H-1′), 3.32 (s, 3H, H-15), 3.17−3.11 (m, 1H, H-7), 2.54−2.47 (m, 4H, H-3″ and H-5″), 2.33−2.29 (m, 2H, H-3), 2.23−2.17 (m, 4H, H-2 and H-6), 2.10−2.04 (m, 2H, H-4″), 1.44−1.42 (m, 2H, H-8), 1.30−1.27 (m, 10H, H-9, H-10, H-11, H-12, and H-13), 0.88 (t, J = 7.2 Hz, 3H, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.7 (C, C-2″), 172.5 (C, C-1), 151.5 (CH, C-6″), 136.7 (C, C-2′), 136.5 (C, C-1″), 130.9 (CH, C-4), 127.9 (CH, C-5), 119.7 (CH, C-3′), 81.0 (CH, C-7), 56.7 (CH_3, C-15), 44.0 (CH_2, C-1′) 38.6 (CH_2, C-3″), 36.7 (CH_2, C-2), 36.6 (CH_2, C-6), 33.6 (CH_2, C-8), 32.1 (CH_2, C-9), 30.0 (CH_2, C-12), 29.5 (CH_2, C-11), 28.8 (CH_2, C-3), 26.3 (CH_2, C-5″), 25.5 (CH_2, C-10), 22.9 (CH_2, C-13), 22.9 (CH_2, C-4″), 14.3 (CH_3, C-14); HRMS (ESI) m/z $C_{24}H_{39}ClNO_3$ [M + H]$^+$ calcd 424.2613, found 424.2607.

(−)-(5*R*,6*R*)-5-Hydroxy-6-methylcyclohex-2-enone and (+)-(5*S*,6*S*)-5-Hydroxy-6-methylcyclohex-2-enone [(−)-12 and (+)-12].[13]



(−)-**12** (+)-**12**

To a stirred solution of (*R*)-(−)-carvone [(−)-**21**] (5.00 g, 33.33 mmol) in MeOH (80 mL) was added NaOH (2.5 mL, 4 M) at −20 °C, followed by the dropwise addition of H_2O_2 (45.3 mL, 30% purity, 40 mmol) over 50 min. The reaction mixture was quenched by saturated Na_2SO_3 solution. The mixture was then extracted with DCM (100 mL × 4). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 50:1) afforded the corresponding epoxy ketone as a colorless oil. To a stirred and degassed solution of this epoxy ketone (5.15 g, 31.00 mmol), *N*-acethyl-L-cysteine (15.16 g, 93.00 mmol), and PhSeSePh (967 mg, 3.10 mmol) in MeOH (300 mL) was added NaOH (15.5 mL, 6 M) under argon, and the reaction mixture was maintained at rt for 1.5 h. The reaction mixture was then diluted with H_2O (200 mL), saturated with NaCl, and extracted with DCM (200 mL × 4). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 5:1) afforded corresponding β-alcohol ketone as a white solid. A stirred solution of this β-alcohol ketone (3.59 g, 21.39 mmol) in MeOH and DCM (90 mL, MeOH/DCM 2:1) was bubbled with O_3 at −78 °C. After consumption of the β-alcohol ketone (monitored by TLC), argon was purged and the reaction mixture was allowed to warm to −20 °C. Then $Cu(OAc)_2\cdot H_2O$ (8.51 g, 42.78 mmol) was added, the reaction mixture was maintained at this temperature for 20 min, and $FeSO_4\cdot 7H_2O$ (7.14 g, 25.67 mmol) was added in small portions. The suspension was stirred at −20 °C for 7 h and then allowed to warm to rt, this temperature was maintained for 3 h, H_2O (30 mL) was added, and the mixture was extracted with DCM (80 mL × 3). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 1:1) afforded α,β-unsaturated cyclohexenone (−)-**12** (1.85 g, 44% yield in three steps) as a colorless oil. $[\alpha]^{20}_D$ −48 (*c* 1.0, $CHCl_3$); IR (KBr) 3426, 2935, 1670, 1394, 1209, 1054, 897 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85−6.81 (m, 1H, H-3), 6.04 (dt, J = 10.0, 2.0 Hz, 1H, H-2), 4.29 (s, 1H, H-5), 2.71−2.53

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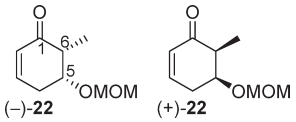
(m, 4H, H-4, H-6, and OH), 1.20 (d, J = 7.2 Hz, 3H, H-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.2 (C, C-1), 145.4 (CH, C-3), 129.2 (CH, C-2), 70.6 (CH, C-5), 47.6 (CH, C-6), 33.3 (CH_2, C-4), 10.5 (CH_3, C-7); HRMS (ESI) m/z calcd for $C_7H_{14}NO_2$ $[M + NH_4]^+$ 144.1019, found 144.1023.

According to the above procedure, (+)-**21** (1.60 g, 10.67 mmol) afforded (+)-**12** (605 mg, 45% yield in three steps) as a colorless oil. $[\alpha]^{20}_D$ +42 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz), ^{13}C NMR ($CDCl_3$, 100 MHz), and MS spectra data of (+)-**12** are identical with those of (−)-**12**.

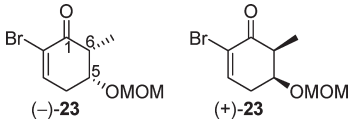
(−)-(5*R*,6*R*)-5-Methoxymethoxy-6-methylcyclohex-2-enone and (+)-(5*S*,6*S*)-5-Methoxymethoxy-6-methylcyclohex-2-enone [(−)-22] and (+)-22].



To a stirred solution of ketone (−)-**12** (1.50 g, 11.90 mmol) in DCM (50 mL) were added MOMCl (2.6 mL, 35.70 mmol) and i-Pr_2NEt (6.2 mL, 35.70 mmol) at 0 °C. The reaction mixture was allowed to warm to rt, and this temperature was maintained for 4 h. Then the reaction mixture was diluted with H_2O (40 mL) and extracted with DCM (50 mL × 3). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 5:1) afforded the MOM ether (−)-**22** (1.30 g, 64%) as a colorless oil. $[\alpha]^{20}_D$ −18 (c 1.0, $CHCl_3$); IR (KBr) 3347, 2937, 1681, 1389, 1208, 1149, 1104, 1046, 917 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.75 (dd, J = 9.2, 3.6 Hz, 1H, H-3), 6.00 (t, J = 5.6 Hz, 1H, H-2), 4.65−4.55 (m, 2H, OCH_2), 4.08 (s, 1H, H-5), 3.31 (t, J = 2.4 Hz, 3H, OCH_3), 2.64−2.52 (m, 3H, H-4 and H-6), 1.16−1.13 (m, 3H, H-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.5 (C, C-1), 144.9 (CH, C-3), 129.3 (CH, C-2), 95.5 (OCH_2), 76.1 (CH, C-5), 55.5 (OCH_3), 46.6 (CH, C-6), 30.5 (CH_2, C-4), 10.7 (CH_3, C-7); HRMS (ESI) m/z calcd for $C_9H_{18}NO_3$ $[M + NH_4]^+$ 188.1281, found 188.1285.

According to the above procedure, (+)-**12** (259 mg, 2.05 mmol) afforded (+)-**22** (310 mg, 89%) as a colorless oil. $[\alpha]^{20}_D$ +26 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz), ^{13}C NMR ($CDCl_3$, 100 MHz), and MS spectra data of (+)-**22** are identical with those of (−)-**22**.

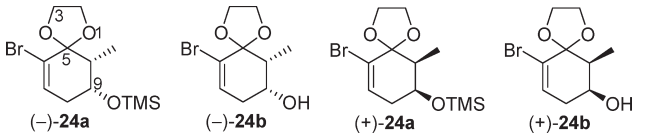
(−)-(5*R*,6*R*)-2-Bromo-5-methoxymethoxy-6-methylcyclohex-2-enone and (+)-(5*S*,6*S*)-2-Bromo-5-methoxymethoxy-6-methylcyclohex-2-enone [(−)-23 and (+)-23].



According to the bromination procedure for the preparation of **19**, (−)-**22** (531 mg, 3.12 mmol) afforded (−)-**23** (720 mg, 93% yield) as a colorless oil. $[\alpha]^{20}_D$ −20 (c 0.2, $CHCl_3$); IR (KBr) 3373, 2936, 1694, 1148, 1095, 1033, 916 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (t, J = 4.4 Hz, 1H, H-3), 4.64 (dd, J = 26.8, 6.8 Hz, 2H, OCH_2), 4.13 (dd, J = 7.6, 3.6 Hz, 1H, H-5), 3.35 (s, 3H, OCH_3), 2.86−2.80 (m, 1H, H-6), 2.78−2.61 (m, 2H, H-4), 1.26 (d, J = 6.8 Hz, 3H, H-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.3 (C, C-1), 145.0 (CH, C-3), 123.4 (CH, C-2), 95.7 (OCH_2), 75.9 (CH, C-5), 55.7 (OCH_3), 47.5 (CH, C-6), 33.0 (CH_2, C-4), 11.3 (CH_3, C-7); HRMS (ESI) m/z calcd for $C_9H_{17}BrNO_3$ $[M + NH_4]^+$ 266.0386, found 266.0389.

According to the above procedure, (+)-**22** (291 mg, 1.71 mmol) afforded (+)-**23** (411 mg, 97%) as a colorless oil. $[\alpha]^{20}_D$ +2 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz), ^{13}C NMR ($CDCl_3$, 100 MHz), and MS spectra data of (+)-**23** are identical with those of (−)-**23**.

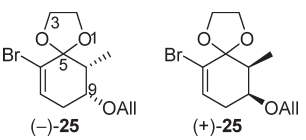
(−)-(9*R*,10*R*)-6-Bromo-10-methyl-9-trimethylsilyloxyspiro[4.5]dec-6-ene, (−)-(9*R*,10*R*)-6-Bromo-9-hydroxy-10-methylspiro[4.5]dec-6-ene, (+)-(9*S*,10*S*)-6-Bromo-10-methyl-9-trimethylsilyloxyspiro[4.5]dec-6-ene, and (+)-(9*S*,10*S*)-6-Bromo-9-hydroxy-10-methylspiro[4.5]dec-6-ene [(−)-24a, (−)-24b, (+)-24a, and (+)-24b].



To a stirred solution of ketone (−)-**23** (504 mg, 2.03 mmol) in DCM (20 mL) were added $TMSOCH_2CH_2OTMS$ (1.3 mL, 5.30 mmol), $HOCH_2CH_2OH$ (0.2 mL, 3.20 mmol), and TMSOTf (0.02 mL, 0.06 mmol) at −78 °C, and the reaction mixture was maintained at this temperature for 4 h. Then the reaction mixture was allowed to warm to rt, and it was maintained at this temperature for 12 h. The reaction mixture was diluted with Et_3N (2 mL) and extracted with DCM (30 mL × 3). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 5:1) afforded compounds (−)-**24a** (202 mg, 31% yield) as a pale yellow oil and (−)-**24b** (252 mg, 50% yield) as a white solid. To a stirred solution of compound (−)-**24a** (646 mg, 2.01 mmol) in MeOH (20 mL) was added K_2CO_3 (277 mg, 2.01 mmol) at 0 °C, and the reaction mixture was maintained at this temperature for 2 h. Then the solvent was concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 2:1) also afforded compound (−)-**24b** (354 mg, 71% yield). For (−)-**24a**: $[\alpha]^{20}_D$ −32 (c 1.0, $CHCl_3$); IR (KBr) 3520, 2956, 1336, 1253, 1151, 1085, 1020, 899, 842, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.17 (dd, J = 5.6, 3.2 Hz, 1H, H-7), 4.25−3.88 (m, 5H, H-2, H-3, and H-9), 2.17−2.02 (m, 3H, H-8 and H-10), 0.97 (d, J = 7.2 Hz, 3H, H-11), 0.11 (s, 9H, 3 × CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.1 (CH, C-7), 123.9 (C, C-6), 109.0 (C, C-5), 67.3 (CH, C-9), 66.3 (CH_2, C-2), 65.2 (CH_2, C-3), 45.2 (CH, C-10), 32.6 (CH_2, C-8), 7.1 (CH_3, C-11), 0.0 (CH_3). For (−)-**24b**: Mp 79−81 °C; $[\alpha]^{20}_D$ −11 (c 1.0, $CHCl_3$); IR (KBr) 3413, 2897, 1638, 1337, 1148, 1067, 867, 589 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.18 (t, J = 4.0 Hz, 1H, H-7), 4.30−4.28 (m, 2H, H-2), 4.05−4.01 (m, 3H, H-3 and H-9), 2.57 (br, 1H, OH), 2.32−2.24 (m, 3H, H-8 and H-10), 1.08 (d, J = 7.2 Hz, 3H, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 131.3 (CH, C-7), 124.6 (C, C-6), 107.9 (C, C-5), 69.0 (CH, C-9), 67.3 (CH_2, C-2), 66.3 (CH_2, C-3), 44.0 (CH, C-10), 35.2 (CH_2, C-8), 10.2 (CH_3, C-11); HRMS (ESI) m/z calcd for $C_9H_{14}BrO_3$ $[M + H]^+$ 249.0121, found 249.0123.

According to the above procedure, (+)-**23** (309 mg, 1.25 mmol) afforded (+)-**24a** (132 mg, 33% yield) as a pale yellow oil {$[\alpha]^{20}_D$ +25 (c 1.0, $CHCl_3$)} and (+)-**24b** (143 mg, 46% yield) as a white solid {Mp 79−81 °C; $[\alpha]^{20}_D$ +16 (c 1.0, $CHCl_3$)}. (+)-**24a** (332 mg, 1 mmol) afforded (+)-**24b** (201 mg, 81% yield). ^{1}H NMR ($CDCl_3$, 400 MHz), ^{13}C NMR ($CDCl_3$, 100 MHz), and MS spectra data of (+)-**24a** and (+)-**24b** are identical with those of (−)-**24a** and (−)-**24b**.

(−)-(9*R*,10*R*)-9-Allyloxy-6-bromo-10-methylspiro[4.5]dec-6-ene and (+)-(9*S*,10*S*)-9-Allyloxy-6-bromo-10-methylspiro[4.5]dec-6-ene [(−)-25 and (+)-25].



To a stirred solution of ketone (−)-**24b** (411 mg, 1.66 mmol) in DMF (6 mL) was added NaH (74 mg, 55% purity, 1.70 mmol) at 0 °C, the reaction mixture was maintained at this temperature for 1 h, and allyl

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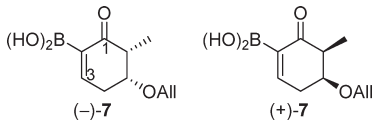
bromide (0.2 mL, 1.70 mmol) was then added. The reaction mixture was allowed to warm to rt, and this temperature was maintained for 8 h. Then the reaction mixture was diluted with H_2O (6 mL) and extracted with EtOAc (20 mL × 3). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 10:1) afforded compound (−)-**25** (337 mg, 65% yield) as a colorless oil. $[\alpha]^{20}_D$ −23 (*c* 2.0, $CHCl_3$); IR (KBr) 3431, 2896, 1727, 1336, 1147, 1075, 865, 588 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.21−6.19 (m, 1H, H-7), 5.96−5.87 (m, 1H, CH), 5.30−5.16 (m, 2H, $=CH_2$), 4.28−3.88 (m, 7H, H-2, H-3, H-9, and CH_2), 2.39−2.10 (m, 3H, H-8 and H-10), 0.99 (d, *J* = 6.8 Hz, 3H, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.9 (CH), 131.7 (CH, C-7), 124.0 (C, C-6), 116.8 (CH_2, $=CH_2$), 108.8 (C, C-5), 73.8 (CH, C-9), 69.4 (CH_2), 66.4 (CH_2, C-2), 65.3 (CH_2, C-3), 41.8 (CH, C-10), 29.9 (CH_2, C-8), 7.7 (CH_3, C-11); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{18}BrO_3$ $[M + H]^+$ 289.0434, found 289.0441.

According to the above procedure, (+)-**24b** (159 mg, 0.64 mmol) afforded (+)-**25** (120 mg, 65% yield) as a colorless oil. $[\alpha]^{20}_D$ +35 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz), ^{13}C NMR ($CDCl_3$, 100 MHz), and MS spectra data of (+)-**25** are identical with those of (−)-**25**.

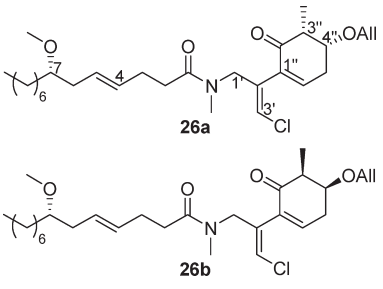
(−)-(5*R*,6*R*)-5-Allyloxy-2-dihydroxyboryl-6-methyl-2-cyclohexen-1-one and (+)-(5*S*,6*S*)-5-Allyloxy-2-dihydroxyboryl-6-methyl-2-cyclohexen-1-one [(−)-7 and (+)-7].



According to the procedure for the preparation of **6**, (−)-**25** (263 mg, 0.91 mmol) afforded (−)-7 (178 mg, 93% yield) as a colorless oil. $[\alpha]^{20}_D$ −6 (*c* 1.0, $CHCl_3$); IR (KBr) 3385, 2926, 2026, 1652, 1342, 1072, 926, 783 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (t, *J* = 3.6 Hz, 1H, H-3), 7.12 (s, 2H, 2 × OH), 5.91−5.82 (m, 1H, CH), 5.29−5.12 (m, 2H, $=CH_2$), 4.04−3.89 (m, 3H, H-5 and CH_2), 2.78−2.63 (m, 3H, H-6 and H-4), 1.18 (d, *J* = 6.8 Hz, 3H, H-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.1 (C, C-1), 159.8 (CH, C-3), 134.5 (CH), 117.1 (CH_2, $=CH_2$), 76.7 (CH, C-5), 70.1 (CH_2), 46.1 (CH, C-6), 31.0 (CH_2, C-4), 10.5 (CH_3, C-7); HRMS (ESI) *m*/*z* calcd for $C_{10}H_{16}BO_4$ $[M + H]^+$ 211.1136, found 211.1138.

According to the procedure for the preparation of **6**, (+)-**25** (166 mg, 0.58 mmol) afforded (+)-7 (87 mg, 71% yield) as a colorless oil. $[\alpha]^{20}_D$ +10 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz), ^{13}C NMR ($CDCl_3$, 100 MHz), and MS spectra data of (+)-7 are identical with those of (−)-7.

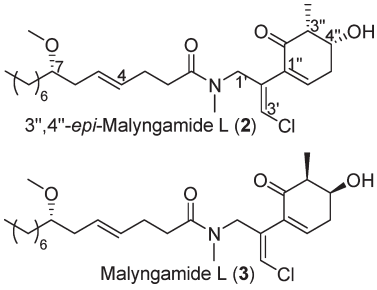
(−)-(4*E*,7*S*)-*N*-{(2*Z*)-[(3*R*,4*R*)-4-Allyloxy-3-methyl-2-oxocyclohex-1-enyl]-2-chloromethyleneethyl}-*N*-methyl-7-methoxytetradec-4-enamide and (−)-(4*E*,7*S*)-*N*-{(2*Z*)-[(3*S*,4*S*)-4-allyloxy-3-methyl-2-oxocyclohex-1-enyl]-2-chloromethyleneethyl}-*N*-methyl-7-methoxytetradec-4-enamide (26a and 26b).



According to the procedure for the preparation of **1**, except using Sphos as the ligand, (−)-7 (113 mg, 0.54 mmol) and **5b** (125 mg, 0.27 mmol) afforded **26a** (58 mg, 42% yield) as a colorless oil. $[\alpha]^{20}_D$ −5.0 (*c* 1.0, $CHCl_3$); IR (KBr) 3464, 2985, 2256, 1741, 1375, 1242, 1408, 919, 735, 608 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.66/6.61 (t, *J* = 4.4 Hz, 1H, H-6″), 6.13/6.12 (s, 1H, H-3′), 5.88−5.83 (m, 1H, CH), 5.50−5.45 (m, 2H, H-4 and H-5), 5.28−5.14 (m, 2H, $=CH_2$), 4.25−3.91 (m, 5H, H-1′, H-4″, and CH_2), 3.32 (s, 3H, H-15), 3.16−3.13 (m, 1H, H-7), 2.94/2.87 (s, 3H, NCH_3), 2.83−2.77 (m, 1H, H-3″), 2.69−2.62 (m, 2H, H-5″), 2.31−2.27 (m, 4H, H-3 and H-2), 2.20−2.16 (m, 2H, H-6), 1.44−1.41 (m, 2H, H-8), 1.27−1.25 (m, 10H, H-9, H-10, H-11, H-12, and H-13), 1.19 (t, *J* = 6.8 Hz, 3H, H-7″), 0.88 (t, *J* = 6.8 Hz, 3H, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.4/198.7 (C, C-2″), 172.4/172.9 (C, C-1), 144.7/145.7 (CH, C-6″), 135.4/136.0 (C, C-2′), 135.1/134.3 (C, C-1″), 134.6/134.5 (CH), 131.1 (CH, C-4), 127.1/127.2 (CH, C-5), 118.0/118.2 (CH, C-3′), 116.8/117.0 ($=CH_2$), 80.7/80.8 (CH, C-7), 76.47/76.49 (CH, C-4″), 69.8/70.0 (CH_2), 56.45/56.48 (CH_3, C-15), 51.1/53.5 (CH_2, C-1′), 46.4/46.6 (CH, C-3″), 36.3/36.4 (CH_2, C-6), 35.2/33.4 (CH_3, NCH_3), 33.31/33.36 (CH_2, C-2), 33.28/32.7 (CH_2, C-5″), 31.8 (CH_2, C-8), 29.6/29.8 (CH_2, C-12), 29.7 (CH_2, C-10), 29.24/29.27 (CH_2, C-11), 28.1/28.3 (CH_2, C-3), 25.2/25.3 (CH_2, C-9), 22.6 (CH_2, C-13), 14.1 (CH_3, C-14), 10.4/10.5 (CH_3, C-7″); HRMS (ESI) *m*/*z* $C_{29}H_{47}ClNO_4$ $[M + H]^+$ calcd 508.3188, found 508.3183.

According to the procedure for the preparation of **1**, except using Sphos as the ligand, (+)-7 (80 mg, 0.38 mmol) and **5b** (89 mg, 0.19 mmol) afforded **26b** (37 mg, 38% yield) as a colorless oil. $[\alpha]^{20}_D$ −5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz), ^{13}C NMR ($CDCl_3$, 100 MHz), and MS spectra data of **26b** are identical with those of **26a**.

(−)-(4*E*,7*S*)-*N*-{(2*Z*)-[(3*R*,4*R*)-4-Hydroxy-3-methyl-2-oxocyclohex-1-enyl]-2-chloromethyleneethyl}-*N*-methyl-7-methoxytetradec-4-enamide and (+)-(4*E*,7*S*)-*N*-{(2*Z*)-[(3*S*,4*S*)-4-Hydroxy-3-methyl-2-oxocyclohex-1-enyl]-2-chloromethyleneethyl}-*N*-methyl-7-methoxytetradec-4-enamide [3″,4″-*epi*-malyngamide L (2) and malyngamide L (3)].



To a stirred solution of allyl ether **26a** (22 mg, 0.04 mmol) in MeOH and DCM (2 mL, MeOH/DCM 3:2) was added $PdCl_2$ (50 mg, 0.28 mmol). The dark brown suspension was stirred at rt for 7 h, and then toluene (2 mL) was added. The reaction mixture was concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 1:2) afforded 3″,4″-*epi*-malyngamide L (**2**) (13 mg, 70% yield) as a colorless oil. $[\alpha]^{20}_D$ −17 (*c* 0.3, EtOH); IR (KBr) 3414, 2928, 1678, 1634, 1460, 1358, 1097, 970, 812, 601 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.59/6.63 (s, 1H, H-6″), 6.21/6.15 (s, 1H, H-3′), 5.47−5.43 (m, 2H, H-4 and H-5), 4.28−4.15 (m, 2H, H-1′), 4.15−3.98 (m, 1H, H-4″), 3.317/3.324 (s, 1H, H-15), 3.19−3.11 (m, 1H, H-7), 2.97/2.87 (s, 3H, NCH_3), 2.75/2.80 (t, *J* = 3.2 Hz, 1H, H-3″), 2.72−2.63 (m, 2H, H-5″), 2.35−2.22 (m, 4H, H-2 and H-3), 2.18−2.14 (m, 2H, H-6), 1.43−1.42 (m, 2H, H-8), 1.30−1.22 (m, 13H, H-9, H-10, H-11, H-12, H-13, and H-7″), 0.88 (t, *J* = 6.4 Hz, 3H, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.53 (C, C-2″), 173.72/172.98 (C, C-1), 143.70/145.39 (CH, C-6″), 136.32 (C, C-2′), 135.66 (C, C-1″), 131.03/129.74 (CH, C-4), 127.15/126.77 (CH, C-5), 118.66 (CH, C-3′), 80.74 (CH, C-7), 71.57 (70.55) (CH, C-4″), 56.48/56.25 (CH_3, C-15), 52.39/53.47 (CH_2, C-1′), 48.12/47.84 (CH, C-3″), 36.36/36.18

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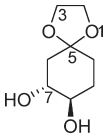
(CH_2, C-6), 34.91/33.20 (CH_3, NCH_3), 34.63/33.92 (CH_2, C-5″), 33.43/33.58 (CH_2, C-2), 33.30/32.51 (CH_2, C-8), 31.80/31.04 (CH_2, C-12), 29.72 (CH_2, C-10), 29.27 (CH_2, C-11), 27.79/28.20 (CH_2, C-3), 25.24/25.38 (CH_2, C-9), 22.63/22.77 (CH_2, C-13), 14.08 (CH_3, C-14), 11.22/10.71 (CH_3, C-7″); HRMS (ESI) m/z $C_{26}H_{43}ClNO_4$ $[M + H]^+$ calcd 468.2875, found 468.2872.

According to the above procedure, **26b** (12 mg, 0.02 mmol) afforded malyngamide L (**3**) (7 mg, 76% yield) as a colorless oil. $[\alpha]^{20}_D$ +20 (*c* 0.25, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz), ^{13}C NMR ($CDCl_3$, 100 MHz), and MS spectra data of **3** are identical with **2**.

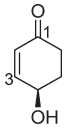
(7*R*,8*R*)-1,4-Dioxaspiro[4.5]decane-7,8-diol (28).[45,46]



28

To a stirred solution of 1,4-cyclohexanedione monoethyleneketal (**27**) (1.00 g, 6.41 mmol) and L-proline (110 mg, 0.96 mmol) in DMF (15 mL) was added a solution of nitrosobenzene (343 mg, 3.21 mmol) in DMF (4 mL) over 15 h by syringe pump at 0 °C, and the reaction mixture was maintained at this temperature for 2 h. Then MeOH (8 mL) and $CeCl_3 \cdot 7H_2O$ (2.61 g, 7.00 mmol) were added to the mixture, followed by $NaBH_4$ (266 mg, 7.00 mmol). The reaction mixture was stirred for 30 min at 0 °C, diluted with H_2O (10 mL), and extracted with EtOAc (30 mL × 3). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 2:1) afforded the alcohol. To a solution of this alcohol in MeOH (10 mL) was added Pd/C (30 mg, 10% purity), and the mixture was stirred under H_2 atmosphere at rt for 5 h. The reaction mixture was filtered and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 1:1) afforded diol **28** (469 mg, 42% yield in three steps) as a light brown oil. $[\alpha]^{20}_D$ 0 (*c* 0.3, $CHCl_3$); IR (KBr) 3393, 2924, 1456, 1359, 1053, 923, 808, 599 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.99−3.91 (m, 4H, H-3 and H-2), 3.75 (br, 2H, OH), 3.64−3.58 (m, 1H, H-7), 3.48−3.42 (m, 1H, H-8), 2.08−2.03 (m, 1H, H-6a), 1.92−1.87 (m, 1H, H-6b), 1.84−1.73 (m, 1H, H-9a), 1.73−1.61 (m, 3H, H-9b and H-10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 108.7 (C, C-5), 74.0 (CH, C-8), 72.6 (CH, C-7), 64.32 (CH_2, C-3), 64.28 (CH_2, C-2), 40.3 (CH_2, C-6), 32.4 (CH_2, C-10), 28.0 (CH_2, C-9); MS (ESI) m/z 197.1 ($[M + Na]^+$).

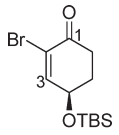
(+)-(*R*)-4-Hydroxycyclohex-2-enone (13).[45]



13

To a stirred solution of diol **28** (456 mg, 2.62 mmol) in THF and H_2O (50 mL, THF/H_2O 1:1) was added HCl (3.3 mL, 2 M), and the mixture was stirred at rt for 24 h. A saturated aqueous solution of $(NH_4)_2SO_4$ (25 mL) was added to quench the reaction. Then the mixture was extracted with EtOAc (80 mL × 3). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 1:1) afforded ketone **13** (189 mg, 65% yield) as a colorless oil. $[\alpha]^{20}_D$ +89 (*c* 0.7, $CHCl_3$); IR (KBr) 3392, 2924, 2140, 1672, 1456, 1378, 1254, 1205, 1065, 943, 862, 760, 547 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.98 (d, *J* = 10.0 Hz, 1H, H-3), 5.96 (d, *J* = 10.0 Hz, 1H, H-2), 4.58 (dd, *J* = 4.4, 2.4 Hz, 1H, H-4), 3.50 (br, 1H, OH), 2.61−2.55 (m, 1H, H-6a), 2.43−2.32 (m, 2H, H-6b and H-5a), 2.05−1.95 (m, 1H, H-5b); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.4 (C, C-1), 153.6 (CH, C-3), 128.8 (CH, C-2), 66.0 (CH, C-4), 35.3 (CH_2, C-5), 32.2 (CH_2, C-6); MS (ESI) m/z 135.1 ($[M + Na]^+$).

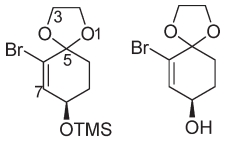
(+)-(*R*)-2-Bromo-4-*tert*-butyldimethylsilyloxycyclohex-2-enone (29).



29

To a stirred solution of ketone **13** (110 mg, 0.98 mmol) in DMF (2 mL) were added TBSCl (369 mg, 2.45 mmol) and imidazole (180 mg, 2.65 mmol) at 0 °C, and the reaction mixture was maintained at this temperature for 4 h. Then the reaction mixture was diluted with H_2O (4 mL) and extracted with EtOAc (5 mL × 3). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 5:1) afforded silyl ether as a colorless oil. According to the bromination procedure for the preparation of **19**, the silyl ether afforded **29** (268 mg, 90% yield in two steps) as a colorless oil. $[\alpha]^{20}_D$ +12 (*c* 1.0, $CHCl_3$); IR (KBr) 3379, 2955, 1700, 1601, 1468, 1360, 1256, 1105, 972, 873, 837, 779, 669, 490 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (dd, *J* = 2.8, 1.2 Hz, 1H, H-3), 4.55−4.51 (m, 1H, H-4), 2.81−2.74 (m, 1H, H-6a), 2.50−2.42 (m, 1H, H-6b), 2.26−2.19 (m, 1H, H-5a), 2.07−1.98 (m, 1H, H-5b), 0.89 (s, 9H, 3 × CH_3), 0.11 (3H, CH_3), 0.10 (3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.4 (C, C-1), 153.7 (CH, C-3), 123.8 (C, C-2), 68.3 (CH, C-4), 34.7 (CH_2, C-5), 32.7 (CH_2, C-6), 25.6 (CH_3), −4.8 (CH_3), −4.9 (CH_3); HRMS (ESI) m/z calcd for $C_{12}H_{25}BrNO_2Si$ $[M + NH_4]^+$ 322.0832, found 322.0824.

(+)-(*R*)-6-Bromo-8-trimethylsilyloxy-spiro[4.5]dec-6-ene and (−)-(*R*)-8−6-Bromo-hydroxyspiro[4.5]dec-6-ene (30a and 30b).

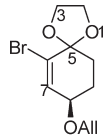


30a **30b**

To a stirred solution of ketone **29** (297 mg, 0.98 mmol) in DCM (10 mL) were added $TMSOCH_2CH_2OTMS$ (0.8 mL, 3.30 mmol), $HOCH_2CH_2OH$ (0.1 mL, 2.00 mmol), and TMSOTf (9 mg, 0.04 mmol) at 0 °C, and the reaction mixture was maintained at this temperature for 1 h. Then the reaction mixture was allowed to warm to 20 °C, and this temperature was maintained for 5 h. The reaction mixture was diluted with Et_3N (1 mL) and extracted with DCM (20 mL × 3). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 2:1) afforded compounds **30a** (117 mg, 39% yield) and **30b** (105 mg, 46% yield) as a colorless oil. According to the procedure for the preparation of (−)-**24b**, **30a** (156 mg, 0.51 mmol) also afforded compound **30b** (97 mg, 81% yield). For **30a**: $[\alpha]^{20}_D$ +2 (*c* 1.0, $CHCl_3$); IR (KBr) 3396, 2957, 1638, 1463, 1364, 1257, 1090, 1019, 946, 882, 839, 800, 540 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.24 (d, *J* = 2.8 Hz, 1H, H-7), 4.23−4.16 (m, 3H, H-3 and H-8), 4.04−3.91 (m, 2H, H-2), 2.12−1.91 (m, 2H, H-10), 1.85−1.76 (m, 2H, H-9), 0.13 (s, 9H, 3 × CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0 (CH, C-7), 126.7 (C, C-6), 105.5 (C, C-5), 67.9 (CH, C-8), 66.1 (CH_2, C-3), 65.8 (CH_2, C-2), 32.4 (CH_2, C-10), 30.5 (CH_2, C-9), 0.1 (CH_3). For **30b**: $[\alpha]^{20}_D$ −10 (*c* 1.0, $CHCl_3$); IR (KBr) 3392, 2923, 1634, 1460, 1345, 1155, 1085, 940, 747, 523 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.38 (d, *J* = 2.8 Hz, 1H, H-7), 4.24−4.18 (m, 3H, H-3 and H-8), 4.06−3.93 (m, 2H, H-2), 2.19 (br, 1H, OH), 2.15−2.05 (m, 2H, H-10), 1.87−1.73 (m, 2H, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.3 (CH, C-7), 127.6 (C, C-6),

105.4 (C, C-5), 67.5 (CH, C-8), 66.2 (CH_2, C-3), 65.8 (CH_2, C-2), 32.2 (CH_2, C-10), 30.1 (CH_2, C-9); MS (EI) *m*/*z* (%) 234 (M^+, 1), 208 (9)/206 (10), 192 (12)/190 (39), 155 (89), 127 (28), 99 (100)/97 (22). Elemental Anal. Calcd for $C_8H_{11}BrO_3$: C, 40.87; H, 4.72. Found: C, 41.23; H, 4.52.

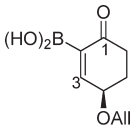
(+)-(*R*)-8-Allyloxy-6-bromospiro[4.5]dec-6-ene (31).



31

According to the procedure for the preparation of (−)-**25**, **30b** (263 mg, 1.12 mmol) afforded **31** (196 mg, 64% yield) as a colorless oil. $[\alpha]^{20}_D$ +37 (*c* 0.3, $CHCl_3$); IR (KBr) 3393, 2923, 1740, 1643, 1459, 1358, 1161, 1088, 1024, 946, 791 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.40 (d, *J* = 2.8 Hz, 1H, H-7), 5.95−5.85 (m, 1H, CH), 5.31−5.16 (m, 2H, =CH_2), 4.23−4.16 (m, 2H, CH_2), 4.03−3.90 (m, 5H, H-2, H-3, and H-8), 2.14−1.91 (m, 2H, H-10), 1.89−1.77 (m, 2H, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.9 (CH, C-7), 134.5 (CH), 128.1 (C, C-6), 117.0 (=CH_2), 105.5 (C, C-5), 73.6 (CH, C-8), 69.3 (CH_2), 66.0 (CH_2, C-3), 65.8 (CH_2, C-2), 32.1 (CH_2, C-10), 26.7 (CH_2, C-9); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{15}BrO_3Na$ $[M + Na]^+$ 297.0097, found 297.0093.

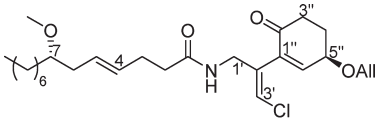
(+)-(*R*)-6-Allyloxy-2-dihydroxyboryl-2-cyclohexen-1-one (8).



8

According to the procedure for the preparation of **6**, **31** (200 mg, 0.73 mmol) afforded **8** (100 mg, 70% yield) as a yellow oil. $[\alpha]^{20}_D$ +41 (*c* 0.3, $CHCl_3$); IR (KBr) 3302, 2926, 1655, 1536, 1417, 1094, 925 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.81 (s, 1H, H-3), 6.33 (s, 2H, 2 × OH), 5.99−5.90 (m, 1H, CH), 5.36−5.23 (m, 2H, =CH_2), 4.28−4.24 (m, 1H, H-4), 4.16−4.10 (m, 2H, CH_2), 2.72−2.03 (m, 4H, H-5 and H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.7 (C, C-1), 164.3 (CH, C-3), 134.3 (CH), 117.7 (CH_2, =CH_2), 73.2 (CH, C-4), 70.1 (CH_2), 36.0 (CH_2, C-6), 29.3 (CH_2, C-5); MS (EI) *m*/*z* (%) 196 (M^+, 1), 195 (5), 151 (14), 111 (100), 96 (33), 94 (9). Elemental Anal. Calcd for $C_9H_{13}BO_4$: C, 55.15; H, 6.69. Found: C, 55.23; H, 7.02.

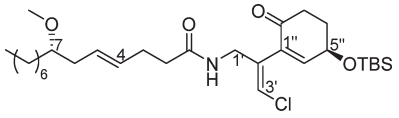
(+)-(4*E*,7*S*)-*N*-[(2*Z*)-(*R*-5-Allyloxy-2-oxocyclohex-1-enyl)-2-chloromethyleneethyl]-7-methoxytetradec-4-enamide (32).



32

According to the procedure for the preparation of **1**, except using Sphos as the ligand, **5a** (64 mg, 0.14 mmol) afforded **32** (38 mg, 56% yield) as a colorless oil. $[\alpha]^{20}_D$ +8 (*c* 0.5, $CHCl_3$); IR (KBr) 3372, 2923, 2854, 1661, 1460, 1378, 1096, 1027, 402 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.91(d, *J* = 1.2 Hz, 1H, H-6″), 6.31 (s, 1H, H-3′), 6.05 (br, 1H, NH), 5.97−5.90 (m, 1H, CH), 5.48−5.45 (m, 2H, H-4 and H-5), 5.35−5.22 (m, 2H, =CH_2), 4.33−4.29 (m, 1H, H-5″), 4.14−4.12 (m, 2H, CH_2), 4.02−3.97 (m, 1H, H-1′a), 3.91−3.86 (m, 1H, H-1′b), 3.32 (s, 3H, H-15), 3.16−3.13 (m, 1H, H-7), 2.73−2.42 (m, 2H, H-3″), 2.40−2.04 (m, 8H, H-3, H-6, H-2, and H-4″), 1.42 (s, 2H, H-8), 1.27 (s, 10H, H-9, H-10, H-11, H-12, and H-13), 0.88 (t, *J* = 6.8 Hz, 3H, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.3 (C, C-2″), 172.3 (C, C-1), 150.8 (CH, C-6″), 135.9 (C, C-2′), 135.7 (C, C-1″), 134.3 (CH), 130.7 (CH, C-4), 127.7 (CH, C-5), 119.8 (CH, C-3′), 117.6 (=CH_2), 80.7 (CH, C-7), 72.5 (CH, C-5″), 70.0 (CH_2), 56.4 (CH_3, C-15), 43.4 (CH_2, C-1′), 36.4 (CH_2, C-6), 36.3 (CH_2, C-2), 35.6 (CH_2, C-8), 33.3 (CH_2, C-3″), 31.8 (CH_2, C-12), 29.7 (CH_2, C-10), 29.3 (CH_2, C-11), 29.2 (CH_2, C-3), 28.5 (CH_2, C-4″), 25.3 (CH_2, C-9), 22.6 (CH_2, C-13), 14.1 (CH_3, C-14); HRMS (ESI) *m*/*z* calcd for $C_{27}H_{43}ClNO_4$ $[M + H]^+$ 480.2875, found 480.2887.

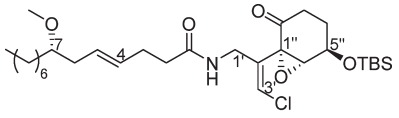
(+)-(4*E*,7*S*)-*N*-[(2*Z*)-(*R*-5-*tert*-Butyldimethylsilyloxy-2-oxocyclohex-1-enyl)-2-chloromethyleneethyl]-7-methoxytetradec-4-enamide (33).



33

According to the procedure for the preparation of **2**, **32** (19 mg, 0.04 mmol) afforded corresponding alcohol (17 mg, 75% yield) as a colorless oil. To a stirred solution of this alcohol (13 mg, 0.03 mmol) in DMF (1 mL) were added TBSCl (12 mg, 0.09 mmol) and imidazole (6 mg, 0.09 mmol) at 0 °C, and the reaction mixture was maintained at this temperature for 4 h. Then the reaction mixture was diluted with H_2O (4 mL) and extracted with EtOAc (5 mL × 3). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 5:1) afforded silyl ether **33** (15 mg, 69% yield in two steps) as a colorless oil. $[\alpha]^{20}_D$ +5 (*c* 0.1, $CHCl_3$); IR (KBr) 3369, 2923, 2854, 1660, 1460, 1378, 1097, 1025, 723 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.77 (s, 1H, H-6″), 6.31 (s, 1H, H-3′), 6.05 (br, 1H, NH), 5.49−5.46 (m, 2H, H-4 and H-5), 4.63−4.59 (m, 1H, H-5″), 4.03−3.98 (m, 1H, H-1′a), 3.91−3.86 (m, 1H, H-1′b), 3.33 (s, 3H, H-15), 3.18−3.12 (m, 1H, H-7), 2.72−2.40 (m, 2H, H-3″), 2.35−2.31 (m, 2H, H-3), 2.27−2.01 (m, 6H, H-6, H-2, and H-4″), 1.43 (s, 2H, H-8), 1.28−1.27 (m, 10H, H-9, H-10, H-11, H-12, and H-13), 0.93−0.88 (m, 12H, 3 × CH_3 and H-14), 0.14 (s, 3H, CH_3), 0.15(s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.6 (C, C-2″), 172.3 (C, C-1), 154.0 (CH, C-6″), 135.8 (C, C-2′), 135.0 (C, C-1″), 130.7 (CH, C-4), 127.7 (CH, C-5), 120.0 (CH, C-3′), 80.7 (CH, C-7), 67.0 (CH, C-5″), 56.5 (CH_3, C-15), 43.5 (CH_2, C-1′), 36.5 (CH_2, C-6), 36.4 (CH_2, C-2), 35.8 (CH_2, C-8), 33.4 (CH_2, C-3″), 32.8 (CH_2, C-12), 31.8 (CH_2, C-10), 29.8 (CH_2, C-11), 29.3 (CH_2, C-3), 28.6 (CH_2, C-4″), 25.7 (CH_3), 25.3 (CH_2, C-9), 22.7 (CH_2, C-13), 14.1 (CH_3, C-14), −4.6 (CH_3), −4.7 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{30}H_{53}ClNO_4Si$ $[M + H]^+$ 554.3427, found 554.3416.

(−)-(4*E*,7*S*)-*N*-[(2*Z*)-2-(1*S*,5*R*,6*S*-5-*tert*-Butyldimethylsilyloxy-2-oxo-7-oxabicyclo[4.1.0]heptan-1-yl)-2-chloromethyleneethyl]methoxytetradec-4-enamide (34).



34

To a stirred solution of silyl ether **33** (3 mg, 5.42 μmol) in THF (1 mL) at 0 °C were added H_2O_2 (0.5 mL) and triton B (0.1 mg, 1.00 μmol). The reaction mixture was stirred for 30 min at 0 °C, and then NH_4Cl (2.0 mg) was added. The mixture was concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 2:1) afforded the corresponding epoxide **34** (3 mg, 93% yield) as a colorless oil. $[\alpha]^{20}_D$ −8 (*c* 0.2, MeOH); IR (KBr) 3394, 2923, 2854, 1740, 1650, 1541, 1460, 1377, 1094, 722 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.37 (s, 1H, H-3′), 6.11 (br, 1H, NH), 5.48−5.46 (m, 2H, H-4 and H-5), 4.87−4.46 (m, 1H, H-5″), 4.00−3.95 (m, 1H, H-1′a), 3.85−3.80 (m, 1H, H-1′b), 3.42 (d, *J* = 2.4 Hz, 1H, H-6″), 3.32

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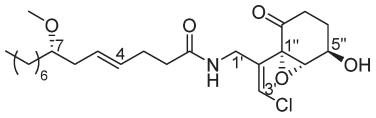
(s, 3H, H-15), 3.17−3.11 (m, 1H, H-7), 2.40−2.31 (m, 3H, H-3″ and H-3a), 2.26−2.22 (m, 2H, H-3b and H-6a), 2.19−2.17 (m, 2H, H-6b and H-2a), 2.07−1.99 (2H, H-2b and H-4″a), 1.82−1.75 (m, 1H, H-4″b), 1.44−1.42 (m, 2H, H-8), 1.27 (br, 10H, H-9, H-10, H-11, H-12, and H-13), 0.93−0.86 (m, 12H, 3 × CH_3 and H-14), 0.132 (s, 3H, CH_3), 0.126 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.2 (C, C-2″), 172.2 (C, C-1), 133.2 (C, C-2′), 130.7 (CH, C-4), 127.6 (CH, C-5), 122.5 (CH, C-3′), 80.8 (CH, C-7), 64.9 (CH, C-6″), 64.3 (CH, C-5″), 60.5 (CH_3, C-1″), 56.5 (CH_3, C-15), 40.8 (CH_2, C-1′), 36.5 (CH_2, C-6), 36.4 (CH_2, C-2), 33.4 (CH_2, C-8), 32.2 (CH_2, C-3″), 31.8 (CH_2, C-12), 29.8 (CH_2, C-10), 29.3 (CH_2, C-11), 28.5 (CH_2, C-3), 25.8 (CH_2, C-4″), 25.7 (CH_3), 25.3 (CH_2, C-9), 22.7 (CH_2, C-13), 14.1 (CH_3, C-14), −4.7 (CH_3), −5.0 (CH_3); HRMS (ESI) m/z calcd for $C_{30}H_{53}ClNO_5Si$ $[M + H]^+$ 570.3376, found 570.3366.

(−)-(4*E*,7*S*)-*N*-[(2*Z*)-2-(1*S*,5*R*,6*S*-5-Hydroxy-2-oxo-7-oxabicyclo[4.1.0]heptan-1-yl)-2-chloromethyleneethyl]methoxytetradec-4-enamide [5″-*epi*-malyngamide C (4)].



5"-*epi*-Malyngamide C (**4**)

To a stirred solution of epoxide **34** (3 mg, 5.26 μmol) in THF (1 mL) at 0 °C was added TBAF (5 mg, 0.02 mmol). The reaction mixture was stirred for 30 min at 0 °C, and then the reaction mixture was concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc 1:1) afforded **4** (2 mg, 87% yield) as a colorless oil. $[\alpha]^{20}_D$ −6 (*c* 0.1, MeOH); IR (KBr) 3367, 2924, 2854, 1714, 1652, 1541, 1459, 1074 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.42 (s, 1H, H-3′), 6.05 (br, 1H, NH), 5.49−5.45 (m, 2H, H-4 and H-5), 4.49 (s, 1H, H-5″), 4.03−3.97 (m, 1H, H-1′a), 3.88−3.83 (m, 1H, H-1′b), 3.60 (d, J = 2 Hz, 1H, H-6″), 3.33 (s, 3H, H-15), 3.19−3.13 (m, 1H, H-7), 2.87 (br, 1H, OH), 2.51−2.47 (m, 2H, H-3″), 2.32−2.29 (m, 2H, H-3), 2.24−2.10 (m, 5H, H-6, H-2, and H-4″a), 1.93−1.86 (m, 1H, H-4″b), 1.44−1.42 (m, 2H, H-8), 1.27−1.25 (m, 10H, H-9, H-10, H-11, H-12, and H-13), 0.88 (m, 3H, H-14); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 202.6 (C, C-2″), 173.0 (C, C-1), 133.0 (C, C-2′), 130.7 (CH, C-4), 127.8 (CH, C-5), 123.6 (CH, C-3′), 80.7 (CH, C-7), 64.4 (CH, C-6″), 64.1 (CH, C-5″), 61.0 (C, C-1″), 56.4 (CH_3, C-15), 41.6 (CH_2, C-1′), 36.3 (CH_2, C-6), 36.2 (CH_2, C-2), 33.4 (CH_2, C-8), 31.8 (CH_2, C-3″), 29.74 (CH_2, C-12), 29.69 (CH_2, C-10), 29.3 (CH_2, C-11), 28.3 (CH_2, C-3), 26.1 (CH_2, C-4″), 25.4 (CH_2, C-9), 22.7 (CH_2, C-13), 14.1 (CH_3, C-14); HRMS (ESI) m/z calcd for $C_{24}H_{39}ClNO_5$ $[M + H]^+$ 456.2511, found 456.2515.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Table S1, Figure S1, and Figure S2. Comparison of ^1H and ^{13}C NMR spectral data for malyngamide K (isolated **1** and synthetic **1**). Comparison of ^1H NMR spectral data for malyngamide L [isolated malyngamide L (**3**) and synthetic malyngamide L (**3**)] and 3″,4″-*epi*-malyngamide L (**2**). Comparison of ^{13}C NMR spectral data for malyngamide L [isolated malyngamide L (**3**) and synthetic malyngamide L (**3**)] and 3″,4″-*epi*-malyngamide L (**2**). Comparison of ^1H and ^{13}C NMR spectral data for 5″-*epi*-malyngamide C (**4**) (isolated **4** and synthetic **4**). ^1H, ^{13}C NMR spectra, DEPT 135 experiments of compounds **15**, (*E*)-**16**, (*Z*)-**16**, **17**, **18**, **5a**, **5b**, **19**, **20**, **6**, **1**, (−)-**12**, (+)-**12**, (−)-**22**, (+)-**22**, (−)-**23**, (+)-**23**, (−)-**24a**, (−)-**24b**, (+)-**24a**, (+)-**24b**, (−)-**25**, (+)-**25**, (−)-**7**, (+)-**7**, **26a**, **26b**, **2**, **3**, **28**, **13**, **29**, **30a**, **30b**, **31**, **8**, **32**, **33**, **34**, and **4**. Comparison of ^1H and ^{13}C NMR spectra of malyngamide L (**3**) and 3″,4″-*epi*-malyngamide L. Comparison of ^1H and ^{13}C NMR spectra of 5″-*epi*-malyngamide C (**4**) (isolated **4** and synthetic **4**). This material is available free of charge via the Internet at http://pubs.acs.org.

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