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PAPER

Total synthesis and absolute configuration of malyngamide W†

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A concise enantioselective synthesis of malyngamide W (**1**) and its 2′-epimer was described. The strategy was based on three key steps: (1) ozonolysis of compound **11** which was derived from (*R*)-(−)-carvone **8**, followed by copper-iron-catalyzed rearrangement to give the key cyclohex-2-enone intermediate **5**, (2) Nozaki–Hiyama–Kishi coupling reaction between aldehyde **4** and iodide **14** to afford alcohol **3**, and (3) asymmetric (*R*)-CBS reduction of the ketone functionality in compound **21** to establish the C-2′ chiral center in the target compound **1**. The absolute configuration of malyngamide W (**1**) was thus confirmed *via* the synthesis of **1** and 2′-*epi*-**1**.

Introduction

The malyngamides are a class of complex lipopeptides, which are both broadly represented and highly varied within various strains of the marine cyanobacterium *Lyngbya majuscula*. Up to now, 30 variants of this structure type were known from collections made around the world, including malyngamides A–X, serinol-derived malyngamides, toxic-type malyngamides (hermitamides A and B), and isomalyngamides.[1] Most of the malyngamides consist of an optically active (4*E*,7*S*) 12- or 14-carbon methoxylated monounsaturated fatty acid moiety in the form of an amide. The amino end is usually appended to a heavily oxygenated six-membered ring or heterocycle and/or with a vinylic chloride function.[1] Malyngamide W, together with U and V, were isolated from a shallow water *L. majuscula* Harvey ex Gomont (Oscillatoriaceae) by Gerwick's group in 2003.[2] The absolute stereochemistry of the 2′-position on the amine portion of malyngamide W was not determined due to a lack of material. At the same time, the scarcity of **1** in natural sources had hampered the biological evaluation of this fascinating molecule. Thus far, the synthetic studies on malyngamides are centered on the synthesis of the acid part[3] and only a few on total synthesis have appeared. Isobe disclosed the synthesis of malyngamide X in 2007.[4a] The other total syntheses of malyngamides such as malyngamides M, O, P, Q, R, U and several serinol-derived malyngamides were mainly completed by our group,[4b–e] however, there are no reports on the synthesis of malyngamide W (**1**). Hence, we were interested in the synthesis of malyngamide W (**1**) to provide materials for the confirmation of the absolute configuration of its stereogenic centers and more extensive biological evaluation.

Malyngamide W (**1**) has a polyoxygenated cyclohexane ring similar to its congeners H, I, J, L, N, U, and V (Fig. 1).[2,5] We envisioned that a previously reported α,β-unsaturated cyclohexanone **5**[6] was a key intermediate towards the synthesis of this series of compounds. Up to now, only one method had been reported for the synthesis of **5** by Sato. The compound was prepared in 34% overall yield in 9 steps starting from an optically active (*R*)-ethyl-3-hydroxy-4-chlorobutyrate.[6] To improve the synthetic efficiency, we herein wish to report a much more concise and efficient synthetic route to this compound by modifying Schreiber's method.[7] This

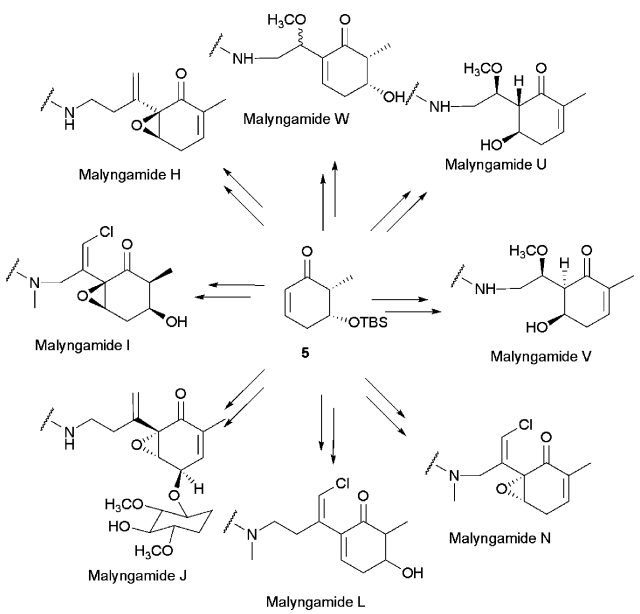

Fig. 1 Structure of malyngamides H, I, J, L, N, U, V, and W, potentially accessible from intermediate **5**.

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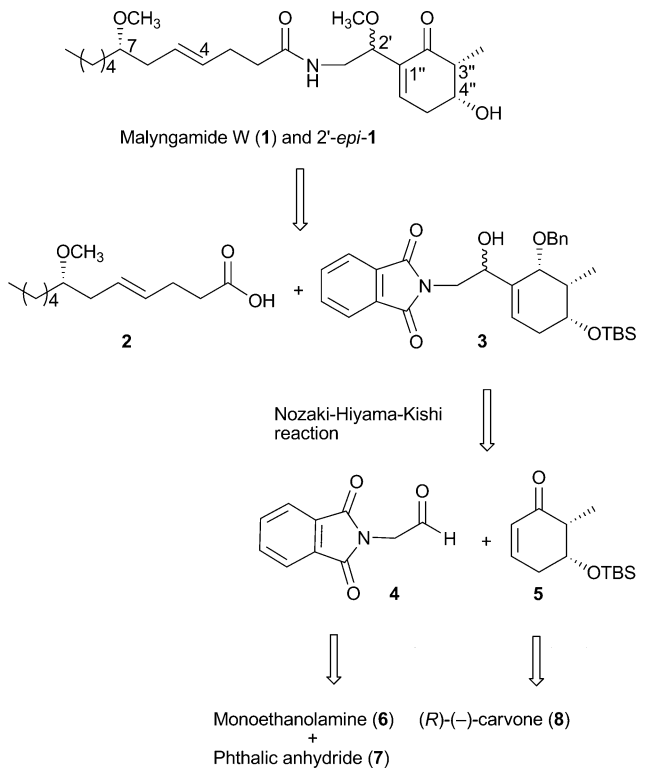
† Electronic supplementary information (ESI) available: Experimental procedures for **9**, **10**, **15**, **17**, **20**, 2′-*epi*-**19**, **22**, and 2′-*epi*-**20**; NMR spectra for all synthetic compounds. CCDC reference numbers 784532. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob01118e

new methodology should also allow the rapid synthesis of the other structurally related malyngamides.

In a search for convenient methods for the construction of the C(2′)–C(1″) bond of malyngamide W (**1**) and 2′-*epi*-**1**, we became aware of a few methods that may be of use in this project such as the Baylis–Hillman reaction,[8] Nozaki–Hiyama–Kishi reaction,[9] Weinreb ketone synthesis,[10] and rely on the addition of allyl or vinyl lithium reagents to an aldehyde or ketone. After much experimentation, we found that only the Nozaki–Hiyama–Kishi reaction offered a successful entry to construct the C(2′)–C(1″) bond efficiently. Herein we report a concise synthesis of **1** and 2′-*epi*-**1** *via* Nozaki–Hiyama–Kishi reaction as a key reaction capable of providing a high enough quantity of the product for further biological investigations, as well as clarifying its absolute configuration. This newly developed procedure is more succinct and practical, and should offer a convenient entry to other structurally related malyngamides.

Results and Discussion

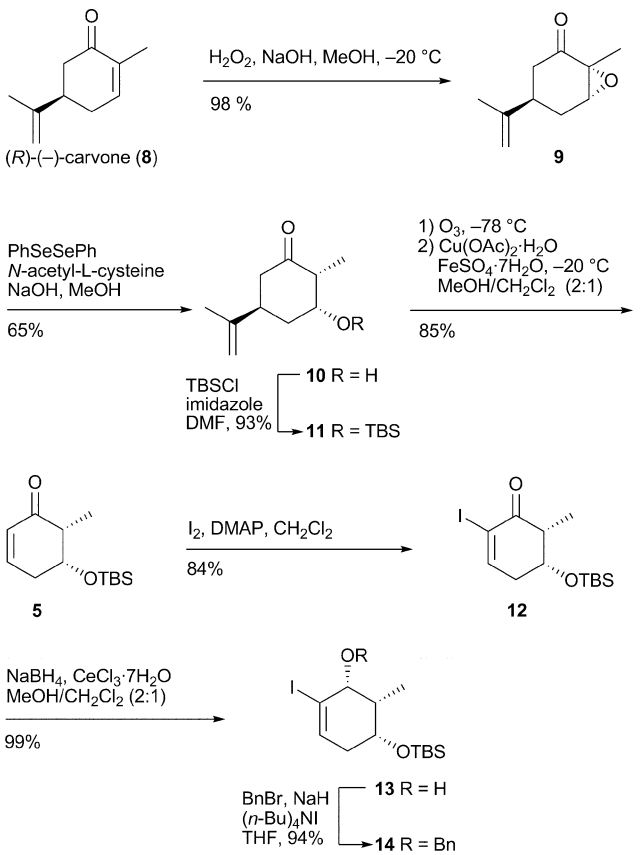
The structure of malyngamide W (**1**) consists of a chiral 12-carbon fatty acid portion containing a 4*E* double bond and a 7*S* chiral center, connecting to a highly oxygenated α,β-unsaturated cyclohexane moiety. The retrosynthetic analysis for **1** and 2′-*epi*-**1** is shown in Scheme 1. As the absolute stereochemistry of 2′-methoxyl carbon center in malyngamide W was not confirmed in the literature,[2] it seemed well advised to synthesize both the two 2′-position diastereoisomers. The diastereomer could be synthesized directly by amidation of acid **2** and an unmasked amine derived from phathalimide **3**, while the other diasteroisomer **1** could be prepared by stereoselective epimerization of the 2′-carbon center.



Scheme 1 Retrosynthetic analysis of malyngamide W (**1**) and 2′-*epi*-**1**.

The chiral fatty acid **2**, (4*E*,7*S*)-7-methoxydodec-4-enoic acid, had been synthesized earlier by us in six steps *via* a Johnson–Claisen rearrangement starting from hexanal in 43% overall yield.[4c] For the key intermediate **3**, it could be readily obtained by a stereoselective Nozaki–Hiyama–Kishi reaction[9e] between an aldehyde **4** and a chiral α,β-unsaturated cyclohexanone **5**. In turn, the aldehyde **4** could be generated from monoethanolamine (**6**) and phthalic anhydride (**7**), and the enone **5** could be synthesized from the commercially available (*R*)-(–)-carvone (**8**).

The preparation of the key intermediate **5** was started from (*R*)-(–)-carvone **8** (Scheme 2). Thus, base-catalyzed stereoselective epoxidation of **8** using hydrogen peroxide in methanol at –20 °C provided the α,β-epoxy ketone **9** in 98% yield.[11] Reductive ring opening of the epoxide **9** by *N*-acetyl-L-cysteine and a catalytic amount of diphenyl diselenide in methanol led to the *syn*-3α-hydroxyl ketone **10** in 65% yield.[12] This was followed by protection of the hydroxy group using *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole in *N*,*N*-dimethylformamide (DMF) to provide its TBS-ether **11** in 93% yield. Ozonolysis of **11** in methanol–dichloromethane (2 : 1) at −78 °C and subsequent treatment with copper(II) acetate monohydrate/iron sulfate heptahydrate at −20 °C to furnish the enone **5** in 85% yield.[7] Therefore the preparation of the optically pure enone **5** was accomplished in 4 steps and 50% overall yield from (*R*)-(–)-carvone (**8**).



Scheme 2 Preparation of **5** and **14**.

With the enone **5** in hand, we began the synthesis of the intermediate **14**. Iodination of **5** in the presence of 4-dimethylaminopyridine (DMAP) in dichloromethane gave an α-iodo-α,β-unsaturated cyclohexone **12** in 84% yield.[13] Subsequent

reduction of enone **12** under Luche's conditions (sodium borohydrite and cerium(III) chloride heptahydrate) generated stereoselectively the enol **13** in nearly quantitative yield.[14] The stereochemistry of **13** was unambiguously established to be 1*R*,5*R*,6*S* by X-ray crystallographic analysis (Fig. 2). Finally, the hydroxyl group in compound **13** was protected as its benzyl ether by alkylation with benzyl bromide (BnBr) in the presence of sodium hydride and a catalytic amount of tetrabutylammonium iodide [$(n\text{-Bu})_4$NI] to give the key iodide **14** in 94% yield.[15]

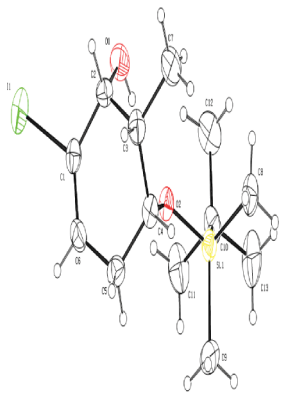
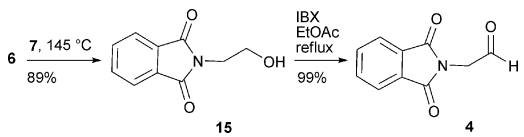


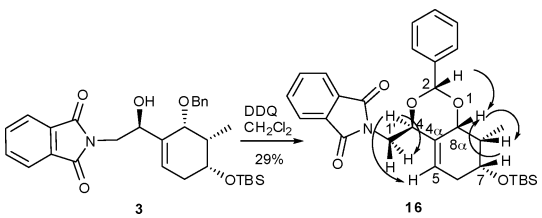
Fig. 2 ORTEP diagram of **13**.

Synthesis of aldehyde fragment **4** began with monoethanolamine **6**. The amino group was first protected by treatment with phthalic anhydride **7** at 145 °C in the absence of solvent to give compound **15** in 89% yield.[16] Subsequent oxidation of **15** with *o*-iodoxybenzoic acid (IBX) in ethyl acetate under refluxing temperature provided the aldehyde **4** in 99% yield (Scheme 3).[17]



Scheme 3 Preparation of aldehyde **4**.

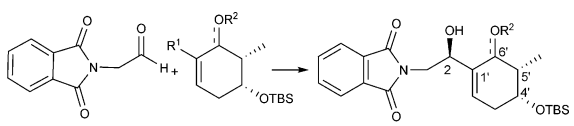
In order to construct the C(2)–C(1′) bond framework of **3** for the formation of the amine portion in malyngamides W (**1**) and 2′-*epi*-**1**, several methods and reaction conditions were explored (Table 1). Initially, we sought to couple aldehyde **4** with α,β-unsaturated cyclohexanone **5** under Baylis–Hillman conditions in the presence of 1.2 equiv. of titanium tetrachloride ($TiCl_4$) in dichloromethane at 0 °C.[8b] This protocol failed to give the desired products despite many attempts. We then resorted to reacting the α-iodo enone **12** with aldehyde **4** under the Nozaki–Hiyama–Kishi conditions [chromium(II) chloride ($CrCl_2$) and nickel(II) chloride ($NiCl_2$)], but again no desirable product could be obtained.[9d] However, when the Nozaki–Hiyama–Kishi conditions was applied to the iodinated benzyl ether **14** and aldehyde **4** in the presence of 6 equiv. of $CrCl_2$ and 0.06 equiv. of $NiCl_2$ in dry dimethyl sulfoxide (DMSO),[9e] the desired adduct **3** was obtained in 40% yield, together with a substantial amount (50%) of the deiodinated compound. When the reaction was run in DMF, the coupling product **3** as a single isomer was obtained in slightly high yield (53%) along with a smaller amount (40%) of the deiodinated compound. Our next challenge was how to confirm the stereochemistry of C(2) in **3**. After some aborted efforts to obtain crystals for X-ray diffraction analysis and the failure of employing the Mosher's method to define the stereochemistry of **3** (see ESI†),[18] the unambiguous stereochemistry assignment of compound **3** was confirmed by NOE experiment of its derivative **16** (see Scheme 4 and ESI†). Hence, selective irradiations of H-4 of **16** resulted in signal enhancements of H-1′a, H-1′b, and H-5, H-8α resulted in signal enhancements of H-2, H-7, and H-8, and H-1′a resulted in signal enhancements of H-2, H-8α, H-4, and H-1′b. Therefore the new chiral center at C-2 in compound **3** has an *S* configuration.



Scheme 4 Determination of absolute configuration of **3**.

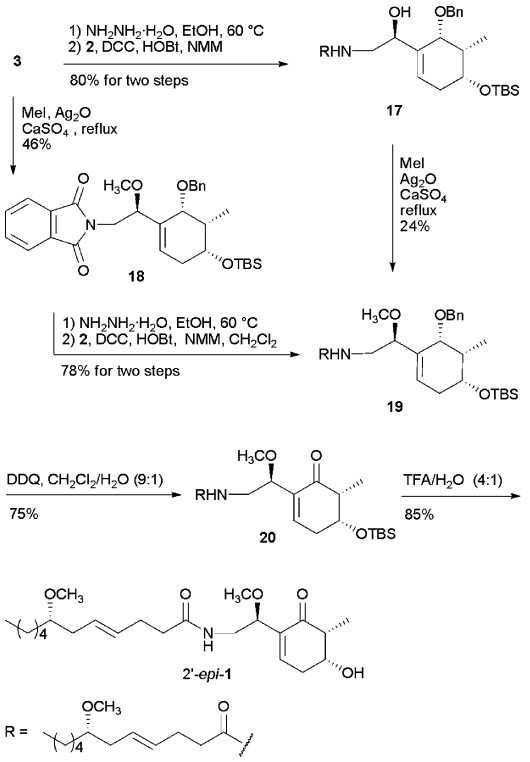
With the chiral fatty acid **2** and amine **3** in hand, we focused our efforts on the formation of the skeleton of malyngamide W (**1**) by an amidation reaction (Scheme 5). Thus, deprotection of compound **3** with hydrazine hydrate ($NH_2NH_2{\cdot}H_2O$) in ethanol

Table 1 Optimization for the coupling reaction of **4** with **5**, **12**, and **14**

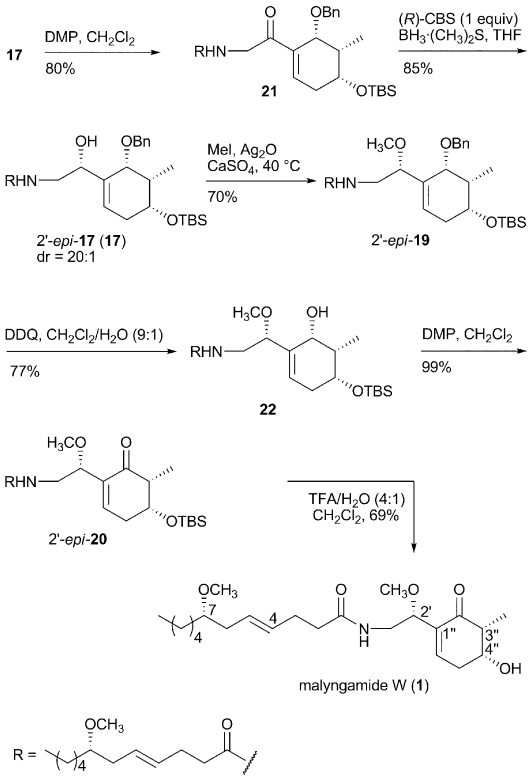


entry	substrates	R^1, R^2	conditions	% yield	product
1	**5**	R^1 = H	$TiCl_4$, CH_2Cl_2, 0 °C for 10 min and then stirred for another 12 h at room temperature.	no reaction	
2	**12**	R^1 = I	$CrCl_2$, $NiCl_2$ (1%), DMSO.[a]	no reaction	
3	**14**	R^1 = I R^2 = Bn	$CrCl_2$, $NiCl_2$ (1%), DMSO.[a]	40%	**3**
4	**14**	R^1 = I R^2 = Bn	$CrCl_2$, $NiCl_2$ (1%), DMF.[a]	53%	**3**

[a] 6 equiv. of $CrCl_2$ and 0.06 equiv. of $NiCl_2$ dissolved in dry DMSO or DMF vortexed for about 10 min, then aldehyde **4** and iodide **12** or **14** were added to the mixture respectively, the reaction stirred for 36 h at 28 °C.



Scheme 5 Synthesis of 2′-*epi*-**1**.



Scheme 6 Synthesis of malyngamide W (**1**).

at 60 °C,[19] followed by amidation of the resulting crude amine with the chiral fatty acid **2** in the presence of dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole (HOBt), and 4-methylmorpholine (NMM) in dichloromethane, afforded the amide **17** in 80% yield over two steps.[4b] However, *O*-methylation of compound **17** with calcium sulfate ($CaSO_4$) and silver oxide (Ag_2O) in neat methyl iodide (MeI) at 40 °C gave compound **19** in a very poor yield (24%), and a mixture was obtained if the reaction was warmed to reflux. On the other hand, *O*-methylation of **3** with MeI in the presence of $CaSO_4$ and Ag_2O under refluxing temperature gave amide **18** in 46% yield (89% yield, BORSM).[4c,20] Subsequent removal of the phthalimide group in compound **18** with $NH_2NH_2{\cdot}H_2O$ in ethanol at 60 °C, followed by amidation with the acid **2** in the presence of DCC, HOBt, and NMM afforded the target amide **19** in 78% yield for two steps. Then removal of the Bn protecting group in amide **19** and concomitant oxidation of the hydroxyl group in the presence of 4 equiv. of dichlorodicyano benzoquinone (DDQ) in a cosolvent of dicloromethane–water (9 : 1) produced the amide **20** in 75% yield.[4b,21] Finally, removal of the TBS moiety by trifluoroacetic acid (TFA) in wet dichloromethane afforded the desired product in 85% yield. However, both the ^1H and ^{13}C NMR data of synthetic product disagreed with the reported data for the isolated malyngamide W. As the absolute configuration of compound 2′-*epi*-**1** had been unambiguously confirmed by the crystal structure of compound **13** and the NOE experiments of compound **16**, the structure of malyngamide W should be **1**, with the absolute configuration at the C-2′ being opposite to that of 2′-*epi*-**1** (*i.e.*, *R* instead of *S*). Hence, our next goal was to prepare the 2′*R*-epimer.

In order to secure the desired absolute configuration at 2′, a redox strategy was performed. The synthesis of **1** started from compound **17** (Scheme 6). Thus, oxidation of **17** with Dess–Martin periodinane (DMP) in dichloromethane afforded amide **21** in 80% yield.[22] After several unsuccessful trials, the Corey–Bakshi–Shibata oxazaborolidine (CBS catalyst) mediated reduction[23] was used to reduce the α,β-unsaturated ketone **21** to give the diastereomeric amides 2′-*epi*-**17** and **17** (20 : 1) in 85% yield. Subsequent *O*-methylation of the hydroxyl group in 2′-*epi*-**17** in neat MeI by treatment with $CaSO_4$ and Ag_2O at 40 °C afforded the amide 2′-*epi*-**19** in 70% yield. It was interesting to note that when amide 2′-*epi*-**19** was treated with DDQ, only the alcohol **22** was obtained despite using a large excess of DDQ (8 equiv). This result could be due to a large difference in steric hindrance around the vicinity of the epimeric alcohol functionality in compounds **19** and 2′-*epi*-**19**.[24] In the end, oxidation of compound **22** could be realized with DMP to afford amide 2′-*epi*-**20** in nearly quantitative yield. Finally, removal of the TBS moiety in 2′-*epi*-**20** by TFA gave malyngamide W (**1**) in 69% yield. The NMR data of **1** were identical to the data reported for the isolated malyngamide W. The specific rotation of **1** was found to be $[\alpha]_D^{20}$ −19 (*c* 0.06 in $CHCl_3$), which was consistent with the reported value of $[\alpha]_D^{20}$ −15 (*c* 0.06 in $CHCl_3$). To conclude, we have completed the synthesis of malyngamide W (**1**) and 2′-*epi*-**1** in 4.1% and 3.6% yield, respectively. In addition, we clarified the absolute configuration of malyngamide W (**1**), which can now be assigned as 7*S*, 2′*R*, 3″*R*, and 4″*R*.

Conclusions

In summary, we reported the first enantioselective synthesis of malyngamide W (**1**) and its 2′-epimer. The absolute configuration of the C-2′ position on the amine portion of malyngamide W

was also confirmed. The stereochemistry of the amine part was secured by a stereoselective Nozaki–Hiyama–Kishi reaction and an asymmetric (*R*)-CBS reduction. The key intermediate **5** was prepared from relatively inexpensive (*R*)-(−)-carvone in 4 steps with 50% overall yield. This new synthetic protocol not only offers a concise entry to malyngamide W, but also to other structurally related malyngamides. Further synthesis work is currently under progress and will be presented in due course.

Experimental

General

All reactions that required anhydrous conditions were carried by standard procedures under argon atmosphere. Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying reagents. Petroleum ether used had a bp range of 60–90 °C. Reactions were monitored by TLC on silica gel plates. Column chromatography was generally performed through silica gel (200–300 mesh). IR spectra were reported in wave numbers (cm^{-1}). ^1H and ^{13}C NMR, DEPT 135, ^1H–^1H COSY and NOE experiments were recorded on an 400 MHz or 600 MHz spectrometer. Chemical shifts (δ) were reported in ppm relative to TMS (δ_H 0.00) for the ^1H NMR and to chloroform (δ_C 77.0) for the ^{13}C NMR measurements. High resolution mass spectra (HRMS) and mass spectra (MS) were obtained on the mass spectrometer.

(2*R*,3*R*,5*R*)-3-*tert*-Butyldimethylsilyloxy-2-methyl-5-(1-methylethenyl)-cyclohexanone (11). To a stirred solution of ketone **10** (2.00 g, 11.89 mmol) in dry *N*,*N*-dimethylformamide (2.5 mL), imidazole (2.43 g, 35.67 mmol) and TBSCl (3.60 g, 23.78 mmol) was added at 0 °C and the stirring was continued at room temperature for 24 h. Then the solution was poured into water (10 mL) and extracted with petroleum ether (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, 100 : 1) afforded ketone **11** (3.12 g, 93%) as a colorless oil: $[\alpha]_D^{20}$ −22 (*c* 1.0 in $CHCl_3$); IR (KBr, ν_{max}/cm^{-1}: 2932, 2858, 1718, 1254, 1069, 835; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.05 (s, 6H, 2 × CH_3), 0.87 (s, 9H, 3 × CH_3), 1.06 (d, *J* 6.8, 3H, CH_3), 1.70–1.80 (m, 4H, 4b-H and CH_3), 1.99–2.05 (m, 1H, 6b-H), 2.25 (dt, *J* 13.2, 13.6, 1H, 4a-H), 2.45–2.49 (m, 2H, 2-H and 6a-H), 2.84–2.92 (m, 1H, 5-H), 4.26 (br, 1H, 3-H), 4.72 (d, *J* 11, 1H, 2′b-H), 4.80 (d, *J* 11, 1H, 2′a-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) −5.0 (CH_3), −4.5 (CH_3), 11.4 (CH_3), 18.1 (C), 20.6 (CH_3), 25.7 (3 × CH_3), 38.7 (CH_2), 39.9 (CH, 2-C), 46.5 (CH_2), 49.9 (CH, 5-C), 74.2 (CH, 3-C), 109.7 (CH_2, 2′-C), 147.5 (C, 1′-C), 210.7 (CO); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{31}O_2Si$ $[M + H]^+$ 283.2088, found 283.2083.

(5*R*,6*R*)-5-*tert*-Butyldimethylsilyloxy-6-methyl-2-cyclohexenone (5)[7]. To a stirred solution of **11** (3.00 g, 10.60 mmol) in methanol and dichlormethane (60 mL, MeOH–CH_2Cl_2, 2 : 1), the mixture was bubbled with ozone at −78 °C. After consumption of **11** (monitored by TLC), argon was purged and the reaction mixture was allowed to warm up to −20 °C and copper(II) acetate monohydrate (4.23 g, 21.19 mmol) was then added. After stirring for 20 min at the same temperature, ferrous sulfate heptahydrate (3.53 g, 12.70 mmol) was added in small portions. The suspension was stirred at −20 °C for 7 h and then warmed up to ambient temperature. The stirring was continued for an additional 3 h, then water (20 mL) was added and extracted with dichloromethane (60 mL × 6). The combined organic layer was washed with saturated sodium bicarbonate solution, brine, and then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel (petroleum ether–EtOAc, 50 : 1) afforded α,β-unsaturated cyclohexenone **5** (2.17 g, 85%) as a colorless oil. $[\alpha]_D^{20}$ −41 (*c* 1.0 in $CHCl_3$); IR (KBr, ν_{max}/cm^{-1}: 3038, 2932, 2858, 1684, 1254, 1109, 777; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.02 (s, 6H, 2 × CH_3), 0.82 (s, 9H, 3 × CH_3), 1.10 (d, *J* 6.8, 3H, CH_3), 2.38–2.55 (m, 3H, 4-H and 6-H), 4.19 (dd, *J* 4.0 4.8, 1H, 5-H), 5.98 (d, *J* 10.0, 1H, 2-H), 6.71–6.75 (m, 1H, 3-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) −5.0 (CH_3), −4.8 (CH_3), 10.6 (CH_3), 17.9 (C), 25.6 (CH_3), 33.6 (CH_2, 4-C), 48.3 (CH, 6-C), 71.0 (CH, 5-C), 129.2 (CH, 2-C), 144.9 (CH, 3-C), 201.5 (CO); HRMS (ESI) *m*/*z* calcd for $C_{13}H_{25}O_2Si$ $[M + H]^+$ 241.1618, found 241.1615.

(5*R*,6*R*)-5-*tert*-Butyldimethylsilyloxy-2-iodo-6-methylcyclohex-2-enone (12). To a solution of α,β-unsaturated cyclohexenone **5** (2.05 g, 8.53 mmol) and DMAP (2.10 g, 17.1 mmol) in dichloromethane (20 mL), a solution of I_2 (2.59 g, 10.24 mmol) in dichloromethane (120 mL) was added dropwise over 20 min at room temperature. After stirring for 10 h at the same temperature, the reaction mixture was quenched by the addition of water and extracted with dichloromethane. The organic layer was washed with 1 M hydrochloric acid aqueous solution, water, 10% sodium thiosulfate aqueous solution, water and brine. Then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel (petroleum ether–EtOAc, 100 : 1) afforded ketone **12** (2.62 g, 84%) as a yellow oil: $[\alpha]_D^{20}$ +2 (*c* 1.0 in $CHCl_3$); IR (KBr, ν_{max}/cm^{-1}: 2953, 2857, 2708, 1692, 1252, 839; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.02 (s, 6H, 2 × CH_3), 0.83 (s, 9H, 3 × CH_3), 1.17 (d, *J* 6.8, 3H, CH_3), 2.45–2.52 (m, 1H, 4b-H), 2.59–2.66 (m, 1H, 4a-H), 2.73–2.77 (m, 1H, 6-H), 4.23 (dt, *J* 3.6, 4, 1H, 5-H), 7.51 (t, *J* 4.4, 1H, H-3); δ_C (100 MHz; $CDCl_3$; Me_4Si) −5.0 (CH_3), −4.8 (CH_3), 11.5 (CH_3), 17.9 (C), 25.6 (3 × CH_3), 37.7 (CH_2, 4-C), 48.1 (CH, 6-C), 70.9 (CH, 5-C), 103.0 (C, 2-C), 153.3 (CH, 3-C), 194.1 (CO); HRMS (ESI) *m*/*z* calcd for $C_{13}H_{24}IO_2Si$ $[M + H]^+$ 367.0585, found 367.0579.

(1*R*,5*R*,6*S*)-5-*tert*-Butyldimethylsilyloxy-2-iodo-6-methylcyclohex-2-enol (13). To a stirred solution of **12** (2.10 g, 5.73 mmol) in methanol and dichloromethane (60 mL, MeOH–CH_2Cl_2 2 : 1), cerium(III) chloride heptahydrate (2.35 g, 6.30 mmol) was added, followed by several portions of sodium borohydride (0.25 g, 96%, 6.30 mmol) at 0 °C. After stirring for 30 min, the reaction was quenched by saturated ammonium chloride solution. The aqueous phase was extracted with dichloromethane (40 mL × 3). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel (petroleum ether–EtOAc, 100 : 1) afforded alcohol **13** (2.09 g, 99%) as a white solid: mp 58–60 °C; $[\alpha]_D^{20}$ −10 (*c* 2.0 in $CHCl_3$); IR (KBr, ν_{max}/cm^{-1}: 3497, 2931, 2875, 1420, 1256, 1005, 949; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.05 (s, 3H, CH_3), 0.07 (s, 3H, CH_3), 0.86 (s, 9H, 3 × CH_3), 1.17 (d, *J* 7.2, 3H, CH_3), 1.95–2.01 (m, 1H, 6-H), 2.20–2.34 (m, 2H, H-4), 3.28 (d, *J* 11.2, 1H), 3.86–3.90 (m, 1H, 5-H), 4.03 (br, 1H, 1-H), 6.26 (dd, *J* 1.6, 3.0, 1H, 3-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) −5.1 (CH_3), −4.8 (CH_3), 14.7 (CH_3), 17.7 (C), 25.6 (CH_3), 25.7 (CH_3), 38.1 (CH_2, 4-C), 38.6 (CH,

6-C), 70.1 (CH, 5-C), 76.8 (CH, 1-C), 102.9 (C, 2-C), 133.6 (CH, 3-C); HRMS (ESI) m/z calcd for $C_{13}H_{26}IO_2Si$ $[M + H]^+$ 369.0741, found 369.0744; Crystal data for **13**: $C_{13}H_{25}IO_2Si$, M = 368.32, orthorhombic, a = 11.5224(12), b = 11.6757(14), c = 12.5624(15) Å, U = 1690.0(3) Å^3, T = 296(2) K, space group $P2_12_12_1$, Z = 4, Dx = 1.448 g cm^{-3}, Mo-Kα radiation, 10387 reflections measured, 3682 unique (R_{int} = 0.0416), final R indices $[I > 2\sigma(I)]$: R_1 = 0.0295, wR_2 = 0.0669, R indices (all data): R_1 = 0.0368, wR_2 = 0.0702.

[(1*R*,5*R*,6*S*)-5-Benzyloxy-4-iodo-6-methylcyclohex-3-enyloxy]-*tert*-butyldimethylsilane (14). To a suspension of sodium hydride (0.28 g, 6.52 mmol) in dry THF (50 mL), a solution of alcohol **13** (2.00 g, 5.43 mmol) in dry THF (10 mL) was added at 0 °C under an argon atmosphere. After being stirred for 30 min at the same temperature, benzyl bromide (0.77 mL, 6.52 mmol) and tetra-*n*-butylammunium iodide (18 mg, 0.05 mmol) were added to the mixture. After being stirred for 12 h at room temperature, the reaction mixture was diluted with ether and poured into water, then the aqueous phase was extracted with ether (40 mL × 4). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel (petroleum ether–EtOAc, 150 : 1) afforded iodide **14** (2.34 g, 94%) as a colorless oil: $[\alpha]_D^{20}$ −10 (c 1.0 in $CHCl_3$); IR (KBr, ν_{max}/cm^{-1}: 3040, 2929, 2856, 1254, 1116, 833; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.070 (s, 3H, CH_3), 0.074 (s, 3H, CH_3), 0.92 (s, 9H, 3 × CH_3), 0.99 (d, J 7.2, 3H, CH_3), 2.05–2.11 (m, 1H, 2b-H), 2.12–2.22 (m, 1H, 2a-H), 2.28–2.36 (m, 1H, 6-H), 3.94–4.00 (m, 1H, 1-H), 4.01–4.03 (m, 1H, 5-H), 4.67 (dd, J 11.6, 15.6, 2H, $ArCH_2$), 6.37–6.40 (m, 1H, 3-H), 7.31–7.41 (m, 3H, 3 × ArH), 7.51 (d, J 6.8, 2H, 2 × ArH); δ_C NMR ($CDCl_3$, 100 MHz) –4.9 (CH_3), –4.7 (CH_3), 5.8 (CH_3), 18.0 (C), 25.7 (3 × CH_3), 34.5 (CH_2, 2-C), 39.1 (CH, 6-C), 68.2 (CH, 1-C), 71.6 (CH_2), 79.7 (CH, 5-C), 102.5 (C, 4-C), 127.6 (ArCH), 128.0 (2 × ArCH), 128.3 (2 × ArCH), 136.5 (CH, 3-C), 137.9 (ArC); HRMS (ESI) m/z calcd for $C_{20}H_{32}IO_2Si$ $[M + H]^+$ 459.1211, found 459.1216.

2-(1,3-Dioxoisoindolin-2-yl)acetaldehyde (4). To a solution of amide alcohol **15** (3.00 g, 15.69 mmol) in dry ethyl acetate (60 mL), IBX (8.79 g, 31.38 mmol) was added. The resulting suspension was immersed in an oil bath which was set to 78 °C and stirred vigorously under an argon atmosphere for 10 h. The reaction was cooled to room temperature and filtered through a medium glass frit. The filter cake was washed with ethyl acetate (150 mL). The filtrate was concentrated *in vacuo* which afforded aldehyde **4** (2.94 g, 99%) as a white solid: mp 114–115 °C; IR (KBr, ν_{max}/cm^{-1}: 3059, 2933, 1708, 1610, 1014, 872, 714; δ_H (400 MHz; $CDCl_3$; Me_4Si) 4.55 (s, 2H, 2-H), 7.74–7.76 (m, 2H, 2 × ArH), 7.85–7.88 (m, 2H, 2 × ArH), 9.65 (s, 1H, 1-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 47.3 (CH_2, 2-C), 123.6 (2 × CH), 131.9 (C), 134.3 (2 × CH), 167.5 (CO), 193.5 (CO, 1-C); HRMS (ESI) m/z calcd for $C_{10}H_{11}N_2O_3$ $[M + NH_4]^+$ 207.0764, found 207.0768.

***N*-2*S*-{[(4*R*,5*S*,6*R*)-6-Benzyloxy-4-*tert*-butyldimethylsilyoxy)-5-methyl-1-cyclohexenyl]-2-hydroxyethyl}-isoindolin-1,3-dione (3).** To a mixture of 1% anhydrous nickelous chloride (w/w 4 mg, 0.03 mmol) of chromium chloride (3.54 g, 28.80 mmol) in *N*,*N*-dimethylformamide (2 mL) at 28 °C, a mixture of the vinyl iodide **14** (2.2 g, 4.80 mmol) and aldehyde **4** (2.72 g, 14.38 mmol) in *N*,*N*-dimethylformamide (20 mL) was added. The reaction mixture was deep green in color and was stirred continuously at this temperature for 36 h. The reaction mixture was diluted with ether and poured into water, then the aqueous phase was extracted with ether (40 mL × 4). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel (petroleum ether–EtOAc, 6 : 1) afforded **3** (1.33 g, 53%) as a colorless oil: $[\alpha]_D^{20}$ −15 (c 1.0 in $CHCl_3$); IR (KBr, ν_{max}/cm^{-1}: 3412, 3004, 2920, 1714, 1362, 1222, 1092, 902, 748; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.04 (s, 3H, CH_3), 0.06 (s, 3H, CH_3), 0.90 (s, 9H, 3 × CH_3), 0.95 (d, J 6.8, 3H, CH_3), 1.97–2.14 (m, 2H, 3′-H), 2.44–2.48 (m, 1H, 5′-H), 3.75–3.81 (m, 1H, 4′-H), 3.82–3.87 (m, 1H, 1b-H), 3.91 (d, J 11.2, 1H, 6′-H), 3.93–3.98 (m, 1H, 1a-H), 4.31–4.37 (m, 1H, 2-H), 4.66 (br, 1H, OH), 4.68 (d, J 10.8, 1H, ArCH), 4.75 (d, J 10.8, 1H, ArCH), 5.61 (dt, J 2.4, 2.8, 1H, 2′-H), 7.32–7.36 (m, 1H, ArH), 7.39–7.42 (m, 2H, 2 × ArH), 7.52 (d, J 7.2, 2H, 2 × ArH), 7.71–7.73 (m, 2H, 2 × ArH), 7.84–7.86 (m, 2H, 2 × ArH); δ_C (100 MHz; $CDCl_3$; Me_4Si) –4.9 (CH_3), –4.7 (CH_3), 5.4 (CH_3), 17.9 (C), 25.7 (3 × CH_3), 30.8 (CH_2, 3′-C), 36.5 (CH, 5′-C), 42.8 (CH_2, 1-C), 68.2 (CH, 4′-C), 70.3 (CH_2), 74.4 (CH, 2-C), 78.4 (CH, 6′-C), 123.1 (2 × ArCH), 126.8 (CH, 2′-C), 128.0 (CH), 128.5 (2 × ArCH), 128.6 (2 × ArCH), 132.0 (2 × ArC), 133.8 (2 × ArCH), 134.6 (C, 1′-C), 137.1 (ArC), 168.3 (2 × CO); HRMS (ESI) m/z $C_{30}H_{39}NO_5SiNa$ $[M + Na]^+$ 544.2490, found 544.2492.

1-{[(2*S*,4*R*,7*R*,8*S*,8α*R*)-7-*tert*-Butyldimethylsilyloxy-8-methyl-2-phenyl-6,7,8,8α-tetrahydro-4*H*-benzo[d][1,3] dioxin-4-yl]-methyl}-isoindoline-1,3-dione (16). To a stirred solution of **3** (63 mg, 0.12 mmol) in dichloromethane (1.8 mL) and water (0.2 mL), DDQ (217 mg, 0.96 mmol) was added and the mixture was stirred for a further 12 h. Then the reaction mixture was concentrated *in vacuo*. Flash chromatography of the residue over silica gel (petroleum ether–EtOAc, 8 : 1) afforded amide **16** (18 mg, 29%) as a colorless oil: $[\alpha]_D^{20}$ +3 (c 1.0 in $CHCl_3$); IR (KBr, ν_{max}/cm^{-1}: 2949, 2929, 1715, 1396, 1095, 1032, 864, 716; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.080 (s, 3H, CH_3), 0.084 (s, 3H, CH_3), 0.91 (s, 9H, 3 × CH_3), 1.04 (d, J 6.8, 3H, CH_3), 2.08–2.23 (m, 2H, 6-H), 2.41–2.45 (m, 1H, 8-H), 3.69 (dd, J 2.2, 5.2, 1H, 1′b-H), 3.90–3.95 (m, 1H, 7-H), 4.46–4.53 (m, 1H, 1′a-H), 4.77–4.80 (m, 1H, 4-H), 4.83 (br, 1H, 8α-H), 5.58 (br, 1H, 5-H), 6.18 (s, 1H, 2-H), 7.31–7.34 (m, 3H, 3 × ArH), 7.49–7.51 (m, 2H, 2 × ArH), 7.70–7.73 (m, 2H, 2 × ArH), 7.83–7.85 (m, 2H, 2 × ArH); δ_C (100 MHz; $CDCl_3$; Me_4Si) –4.8 (CH_3), –4.7 (CH_3), 5.9 (CH_3), 18.1 (C), 25.8 (3 × CH_3), 31.1 (CH_2, 6-C), 38.5 (CH, 8-C), 39.1 (CH_2, 1′-C), 68.3 (CH, 7-C), 74.0 (CH, 4-C), 74.3 (CH, 8α-C), 94.7 (CH, 2-C), 123.1 (CH, 5-C), 123.3 (2 × ArCH), 126.5 (2 × ArCH), 128.2 (2 × ArCH), 128.8 (CH), 128.6 (ArC), 132.1 (2 × ArC), 134.0 (2 × ArCH), 138.3 (C, 4α-C), 168.2 (2 × CO); HRMS (ESI-TOF) m/z calcd for $C_{30}H_{37}NO_5SiNa$ $[M + Na]^+$ 542.2333, found 542.2354.

2-{(2*S*)-[(4*R*,5*S*,6*R*)-6-Benzyloxy-4-*tert*-butyldimethylsilyoxy-5-methyl-1-cylohexenyl]-2-methoxyethyl}-isoindoline-1,3-dione (18). To a stirred solution of alcohol **3** (486 mg, 0.93 mmol) in MeI (10.0 mL), dry calcium sulfate (1.64 g, 12.09 mmol) was added, followed by silver oxide (1.08 g, 4.65 mmol) in one portion. The reaction mixture was stirred for 24 h at 55 °C, then filtered through celite. The filter cake was washed with EtOAc (20 mL × 4), dried over $MgSO_4$ and the filtrate was concentrated *in vacuo*. Flash chromatography of the residue over silica gel (petroleum ether–EtOAc, 7 : 1) afforded amide **18** (230 mg, 46%) as a colorless oil: $[\alpha]_D^{20}$ +40 (c 0.8 in $CHCl_3$); IR (KBr, ν_{max}/cm^{-1}: 2930, 1717, 1394,

1106, 838, 718; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.02 (d, *J* 10.8, 6H, 2 × CH_3), 0.77 (d, *J* 6.8, 3H, CH_3), 0.89 (s, 9H, 3 × CH_3), 2.12–2.16 (m, 2H, 3′-H), 2.26–2.30 (m, 1H, 5′-H), 3.12 (s, 3H, OCH_3), 3.76–3.82 (m, 1H, 1b-H), 3.83–3.85 (m, 1H, 4′-H), 3.92–3.97 (m, 1H, 1a-H), 4.07 (br, 1H, 6′-H), 4.21 (t, *J* 6.8, 1H, 2-H), 4.44 (d, *J* 11.6, 1H, ArCH), 4.53 (d, *J* 11.6, 1H, ArCH), 5.87 (t, *J* 2.4, 1H, 2′-H), 7.29–7.38 (m, 3H, 3 × ArH), 7.44 (d, *J* 7.2, 2H, 2 × ArH), 7.67–7.69 (m, 2H, 2 × ArH), 7.79–7.81 (m, 2H, 2 × ArH); δ_C (100 MHz; $CDCl_3$; Me_4Si) –4.8 (CH_3), –4.6 (CH_3), 5.5 (CH_3), 18.0 (C), 25.8 (3 × CH_3), 30.8 (CH_2, 3′-C), 37.0 (CH, 5′-C), 42.8 (CH_2, 2-C), 56.4 (OCH_3), 68.9 (CH, 4′-C), 70.4 (CH_2), 76.5 (CH, 2-C), 77.8 (CH, 6′-C), 123.0 (2 × CH), 124.0 (CH, 2′-C), 127.6 (ArCH), 128.3 (2 × ArCH), 128.4 (2 × ArCH), 132.4 (2 × C), 133.5 (2 × CH), 135.6 (C, 1′-C), 138.2 (C), 168.4 (2 × CO); HRMS (ESI) *m*/*z* calcd for $C_{31}H_{45}N_2O_5Si$ $[M + NH_4]^+$ 553.3092, found 553.3087.

(4*E*,7*S*)-*N*-{(2*S*)-[(4*R*,5*S*,6*R*)-6-Benzyloxyl-4-*tert*-butyldimethylsilyoxy-5-methyl-1-cyclohexenyl]-2-methoxyethyl}-7-methoxydodec-4-enamide (19). To a stirred solution of compound **18** (182 mg, 0.34 mmol) in ethanol (4 mL), hydrazine monohydrate (0.99 mL, 2.04 mmol) was added and the resulting mixture was stirred for 2 h at 60 °C. The precipitate formed was filtered off and the filtrate was evaporated to give crude amine, which was immediately used in the next step without further purification. To the crude amine, a solution of acid **2** (84 mg, 0.37 mmol) in dichloromethane (10 mL), DCC (85 mg, 0.41 mmol), HOBt (46 mg, 0.34 mmol) and NMM (34 mg, 0.34 mmol) were added at 0 °C. After being stirred for 30 min at the same temperature, the reaction was warmed to room temperature and stirred for 8 h. Then the reaction mixture was concentrated *in vacuo* and flash chromatography of the residue over silica gel (petroleum ether–EtOAc, 2 : 1) afforded amide **19** as a colorless oil. (163 mg, 78%): $[\alpha]_D^{20}$ +20 (*c* 0.2 in $CHCl_3$); IR (KBr, ν_{max}/cm^{-1}: 2985, 2938, 1742, 1374, 1242, 1047, 937; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.05 (s, 3H, CH_3), 0.06 (s, 3H, CH_3), 0.87 (m, 6H, 2 × CH_3), 0.90 (s, 9H, 3 × CH_3), 1.26–1.43 (m, 8H, 8-H, 9-H, 10-H, and 11-H), 2.00–2.38 (m, 8H, 2-H, 3″-H, 3-H, and 6-H), 2.39–2.42 (m, 1H, 5″-H), 3.12–3.15 (m, 1H, 7-H), 3.20 (s, 3H, OCH_3), 3.26–3.31 (m, 1H, 1′a-H), 3.32 (s, 3H, OCH_3), 3.48–3.52 (m, 1H, 1′b-H), 3.81–3.84 (m, 1H, 2′-H), 3.85–3.89 (m, 1H, 4″-H), 4.17 (br, 1H, 6″-H), 4.41 (d, *J* 11.6, 1H, ArCH), 4.68 (d, *J* 11.6, 1H, ArCH), 5.39–5.42 (m, 2H, 4-H and 5-H), 5.71 (t, *J* 2.4, 2″-H), 6.09 (br, 1H, NH), 7.29–7.36 (m, 5H, 5 × ArH); δ_C (100 MHz; $CDCl_3$; Me_4Si) –4.8 (CH_3), –4.6 (CH_3), 5.7 (CH_3), 14.0 (CH_3, 12-C), 18.0 (C), 22.6 (CH_2, 11-C), 24.9 (CH_2, 9-C), 25.7 (3 × CH_3), 28.7 (CH_2, 3-C), 30.7 (CH_2, 10-C), 32.0 (CH_2, 8-C), 33.3 (CH_2, 3″-C), 36.3 (CH_2), 36.4 (CH_2, 2-C), 37.0 (CH, 5″-C), 44.1 (CH_2, 1′-C), 56.2 (OCH_3), 56.5 (OCH_3), 68.7 (CH, 4″-C), 70.6 (CH_2), 77.8 (CH, 2′-C), 78.7 (CH, 6″-C), 80.8 (CH, 7-C), 123.4 (CH, 2″-C), 127.1 (CH, 5-C), 127.8 (CH), 127.9 (2 × CH), 128.5 (2 × CH), 131.0 (CH, 4-C), 135.5 (C, 1″-C), 137.9 (C), 172.1 (CO); HRMS (ESI) *m*/*z* calcd for $C_{36}H_{62}NO_5Si$ $[M + H^+]$ 616.4392, found 616.4380.

(4*E*,7*S*)-*N*-{(2*S*)-[(3*R*,4*R*)-4-Hydroxy-3-methyl-2-oxocyclohex-1-enyl]-2-methoxyethyl}-7-methoxydodec-4-enamide (2′-*epi*-1). To a stirred solution of **20** (15 mg, 0.03 mmol) in dichloromethane (7.5 mL), TFA (0.6 mL) and water (0.15 mL) was added at 0 °C and the stirring was continued at this temperature for 20 h. Then the reaction mixture was poured into brine (8 mL) and extracted with dichloromethane (10 mL × 6). The organic layer was washed with saturated ammonium chloride solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel (petroleum ether–EtOAc, 1 : 1) afforded amide 2′-*epi*-**1** (9 mg, 85%) as a colorless oil: $[\alpha]_D^{20}$ −52 (*c* 0.5 in $CHCl_3$); IR (KBr, ν_{max}/cm^{-1}: 3411, 2928, 1711, 1363, 1219, 1142, 974; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.89 (dt, *J* 6.4, 7.2, 3H, CH_3 and 12-H), 1.28–1.30 (m, 9H, 9-H, 10-H, 11-H and CH_3), 1.41–1.45 (m, 2H, 8-H), 2.18–2.31 (m, 6H, 2-H, 3-H, and 6-H), 2.59–2.75 (m, 4H, 3″-H, 5″-H, and OH), 3.14–3.25 (m, 2H, 1′b-H and 7-H), 3.27 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.74–3.80 (m, 1H, 1′a-H), 4.14 (br, 1H, 4″-H), 4.28 (br, 1H, 2′-H), 5.44–5.47 (m, 2H, 4-H and 5-H), 5.90 (br, 1H, NH), 6.66 (br, 1H, 6″-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 11.6 (CH_3), 14.4 (CH_3, 12-C), 23.0 (CH_2, 11-C), 25.4 (CH_2, 9-C), 28.8 (CH_2, 3-C), 32.4 (CH_2, 10-C), 33.6 (CH_2, 8-C), 34.9 (CH_2, 5″-C), 36.7 (CH_2, 6-C), 36.9 (CH_2, 2-C), 43.0 (CH_2, 1′-C), 48.4 (CH, 3″-C), 56.8 (OCH_3), 57.4 (OCH_3), 71.9 (CH, 4″-C), 76.4 (CH, 2′-C), 81.1 (CH, 7-C), 128.0 (CH, 5-C), 131.1 (CH, 4-C), 136.1 (C, 1″-C), 140.3 (CH, 6″-C), 174.8 (CO, 1-C), 199.7 (CO, 2″-C); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{40}NO_5$ $[M + H]^+$ 410.2901, found 410.2905.

(4*E*,7*S*)-*N*-{[(4*R*,5*S*,6*R*)-6-Benzyloxy-4-*tert*-butyldimethylsilyoxy-5-methyl-1-cyclohexenyl]-2-oxoethyl}-7-methoxydodec-4-enamide (21). To a stirred solution of amide **17** (150 mg, 0.25 mmol) in dichloromethane (8 mL), Dess–Martin periodinane (127 mg, 0.30 mmol) was added at room temperature. The reaction mixture was stirred for 1 h at this temperature and was then concentrated *in vacuo*. Flash chromatography of the residue over silica gel (petroleum ether–EtOAc, 3 : 1) afforded amide **21** (120 mg, 80%) as colorless oil: $[\alpha]_D^{20}$ +8 (*c* 1.0 in $CHCl_3$); IR (KBr, ν_{max}/cm^{-1}: 2930, 2860, 1653, 1459, 1254, 1095, 838, 77; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.05 (s, 6H, 2 × CH_3), 0.88 (br, 12H, 4 × CH_3), 0.96 (d, *J* 6.8, 3H, CH_3), 1.27–1.43 (m, 8H, 8-H, 9-H, 10-H, and 11-H), 2.18–2.36 (m, 9H, 2-H, 3-H, 6-H, and 3″-H, 5″-H), 3.13–3.15 (m, 1H, 7-H), 3.31 (s, 3H, OCH_3), 3.81–3.85 (m, 1H, 4″-H), 4.11–4.17 (m, 1H, 1′b-H), 4.49–4.54 (m, 2H, 1′a-H and 2″-H), 4.57 (d, *J* 11.0, 1H, ArCH), 4.64 (d, *J* 11.0, 1H, ArCH), 5.47–5.48 (m, 2H, 4-H and 5-H), 6.40 (br, 1H, NH), 6.60 (br, 1H, 6″-H), 7.26–7.37 (m, 5H, ArH); δ_C (100 MHz; $CDCl_3$; Me_4Si) –4.9 (CH_3), –4.8 (CH_3), 6.6 (CH_3), 14.0 (CH_3, 12-C), 17.9 (C), 22.7 (CH_2, 11-C), 24.8 (CH_2, 9-C), 25.7 (3 × CH_3), 28.5 (CH_2, 3-C), 31.4 (CH_2, 10-C), 31.9 (CH_2, 8-C), 33.2 (CH_2, 6-C), 36.16 (CH_2), 36.24 (CH_2), 37.0 (CH, 3″-C), 46.9 (CH_2, 1′-C), 56.4 (OCH_3), 67.9 (CH, 4″-C), 71.6 (CH_2), 75.1 (CH, 6″-C), 80.6 (CH, 7-C), 127.5 (CH, 5-C), 127.6 (ArCH), 128.1 (2 × ArCH), 128.3 (2 × ArCH), 130.6 (CH, 4-C), 136.5 (CH, 2″-C), 137.8 (C), 138.2 (C), 172.3 (CO), 196.2 (CO); HRMS (ESI) *m*/*z* calcd for $C_{35}H_{61}N_2O_5Si$ $[M + NH_4]^+$ 617.4344, found 617.4333.

(4*E*,7*S*)-*N*-{(2*R*)-[(4*R*,5*S*,6*R*)-6-Benzyloxy-4-*tert*-butyldimethylsilyloxy-5-methyl-1-cyclohexenyl]-2-hydroxyethyl}-7-methoxydodec-4-enamide (2′-*epi*-17). To a stirred solution of (*R*)-CBS oxazaborolidine catalyst (47 mg, 0.17 mmol) in THF (6 mL), $BH_3{\cdot}(CH_3)_2S$ (2 M in THF, 0.17 mL) was added at 0 °C. The reaction was stirred for 15 min and a solution of amide **21** (100 mg, 0.17 mmol) in THF was then added. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 3 h. It was then re-cooled to 0 °C, another equivalent of $BH_3{\cdot}(CH_3)_2S$ (2 M in THF, 0.17 mL) was added and the reaction stirred for an additional 2 h. The reaction was quenched with methanol and

residue partitioned between dichloromethane (10 mL) and water (5 mL). 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 amide 2′-*epi*-**17** (85 mg, 85%) as a colorless oil: $[\alpha]_D^{20}$ −22 (*c* 0.5 in $CHCl_3$); IR (KBr, ν_{max}/cm^{-1}: 3375, 2928, 1561, 1383, 1068, 837, 636; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.05 (s, 3H, CH_3), 0.06 (s, 3H, CH_3), 0.90 (s, 9H, 3 × CH_3), 0.87–0.92 (m, 3H, CH_3), 1.24–1.45 (m, 8H, 8-H, 9-H, 10-H, and 11-H), 2.09–2.12 (m, 2H, 3-H), 2.17–2.23 (m, 4H, 2-H and 6-H), 2.30–2.34 (m, 2H, 3″-H), 2.41–2.42 (m, 1H, 5″-H), 3.14–3.16 (m, 1H, 7-H), 3.22–3.28 (m, 1H, 1′b-H), 3.31 (s, 3H, OCH_3), 3.50–3.55 (m, 1H, 1′a-H), 3.82–3.84 (m, 1H, 4″-H), 4.28 (d, *J* 2.0, 1H, 2′-H), 4.34 (d, *J* 6.8, 1H, 6″-H), 4.41(d, *J* 11.0, 1H, $ArCH_2$), 4.68 (d, *J* 11.0, 1H, $ArCH_2$), 5.46–5.48 (m, 2H, 4-H and 5-H), 5.62 (br, 1H, NH), 5.94–5.97 (m, 1H, 2″-H), 7.31–7.37 (m, 5H, 5 × ArH); δ_C (100 MHz; $CDCl_3$; Me_4Si) –4.8 (CH_3), –4.6 (CH_3), 5.5 (CH_3), 14.1 (CH_3, 12-C), 18.1 (C), 22.7 (CH_2, 11-C), 25.0 (CH_2, 9-C), 25.8 (3 × CH_3), 28.8 (CH_2, 3-C), 30.7 (CH_2, 3″-C), 32.0 (CH_2, 10-C), 33.3 (CH_2, 8-C), 36.3 (CH_2, 6-C), 36.5 (CH_2, 2-C), 36.8 (CH, 5″-C), 44.1 (CH_2, 1′-C), 56.4 (OCH_3), 68.5 (CH, 7-C), 70.4 (CH_2), 70.9 (CH, 4″-C), 78.6 (CH, 2′-C), 80.7 (CH, 6″-C), 121.8 (CH, 2″-C), 127.5 (CH, 5-C), 127.9 (ArCH), 128.0 (2 × ArCH), 128.6 (2 × ArCH), 130.8 (CH, 4-C), 136.5 (C, 1″-C), 137.8 (ArC), 172.9 (CO, 1-C); HRMS (ESI) *m*/*z* calcd for $C_{35}H_{60}NO_5Si$ $[M + H]^+$ 602.4235, found 602.4237.

(4*E*,7*S*)-*N*-{(2*R*)-[(3*R*,4*R*)-4-Hydroxy-3-methyl-2-oxocyclohex-1-enyl]-2-methoxyethyl}-7-methoxydodec-4-enamide (1). According to the preceding procedure for 2′-*epi*-**1**, amide 2′-*epi*-**20** (15 mg, 0.03 mmol), TFA (0.6 mL) and water (0.15 mL), afforded **1** (8 mg, 69%) as a colorless oil: $[\alpha]_D^{20}$ −19 (*c* 0.06 in $CHCl_3$); IR (KBr, ν_{max}/cm^{-1}: 3411, 2828, 1677, 1142, 1093, 974; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.89 (t, *J* 6.8, 3H, 12-H), 1.21 (d, *J* 7.2, 3H, CH_3), 1.26–1.32 (m, 6H, 9-H, 10-H, and 11-H), 1.34–1.46 (m, 2H, 8-H), 2.18–2.31 (m, 6H, 2-H, 3-H, and 6-H), 2.64–2.72 (m, 3H, 3″-H and 5″-H), 3.14–3.17 (m, 1H, 7-H), 3.28 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.40 (t, *J* 5.2, 2H, 1′-H), 4.26–4.32 (m, 2H, 2′-H and 4″-H), 5.46–5.49 (m, 2H, 4-H and 5-H), 5.80 (br, 1H, NH), 6.67 (t, *J* 7.2, 1H, 6″-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 11.1 (CH_3), 14.5 (CH_3, 12-C), 23.0 (CH_2, 11-C), 25.4 (CH_2, 9-C), 29.1 (CH_2, 3-C), 32.4 (CH_2, 10-C), 33.70 (CH_2, 8-C), 33.78 (CH_2, 5″-C), 36.8 (CH_2, 6-C), 36.9 (CH_2, 2-C), 43.0 (CH_2, 1′-C), 48.0 (CH, 3″-C), 56.9 (OCH_3), 57.4 (OCH_3), 71.6 (CH, 4″-C), 77.0 (CH, 2′-C), 81.1 (CH, 7-C), 127.9 (CH, 5-C), 131.2 (CH, 4-C), 136.3 (C, 1″-C), 140.4 (CH, 6″-C), 172.8 (CO, 1-C), 200.0 (CO, 2″-C); HRMS (ESI) *m*/*z* calcd for/$C_{23}H_{40}NO_5$ $[M + H]^+$ 410.2901, found 410.2908.

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