Tetrahedron 66 (2010) 3499–3507

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of malyngamide M and isomalyngamide M

Jie Chen, Zi-Fa Shi, Ling Zhou, An-Le Xie, Xiao-Ping Cao *

State Key Laboratory of Applied Organic Chemistry and College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, PR China

ARTICLE INFO

Article history:
Received 17 September 2009
Received in revised form 26 February 2010
Accepted 2 March 2010
Available online 12 March 2010

Keywords:
Malyngamide
Lyngbic acid
Amine
Amidation
Isomerization
Total synthesis

ABSTRACT

The stereoselective synthesis of malyngamide M (**1**) was accomplished in nine steps from *o*-cresol in 12% overall yield. The key steps involved the Wittig reaction of an α-NHBoc aryl ketone **4** for the introduction of vinyl chloride functionality, an amidation of lyngbic acid **3** with a secondary amine **2** for the framework of target molecule, and an isomerization of a (*Z*)-vinyl chloride to the (*E*)-configuration using benzophenone as a photosensitizer. The isomalyngamide M (*Z*-**1**) was also synthesized.

1. Introduction

Cyanobacteria of the genus *Lyngbya majuscula* are a rich source of a wide variety of biologically active secondary metabolites. The malyngamides, common metabolites of *L. majuscula*, are *N*-substituted amides of long chain fatty acids. The amine portion of them often possesses a wide structural variety. It can be a heavily oxygenated six-membered ring, a heterocycle, an aromatic ring, a tripeptide, or a unit containing a vinylic chloride moiety. Since 1978, 30 different malyngamides have been isolated. These natural products were found to possess a wide range of biological activities.[1]

The total syntheses of malyngamide X,[2] malyngamide U,[1b,3] 2′-*epi*-malyngamide U,[3] and serinol-derived malyngamides[4] have been reported. A convergent route for the total syntheses of malyngamides O, P, Q, and R has been accomplished by us recently.[5] We are also interested in a subclass of malyngamides that bears a communal and

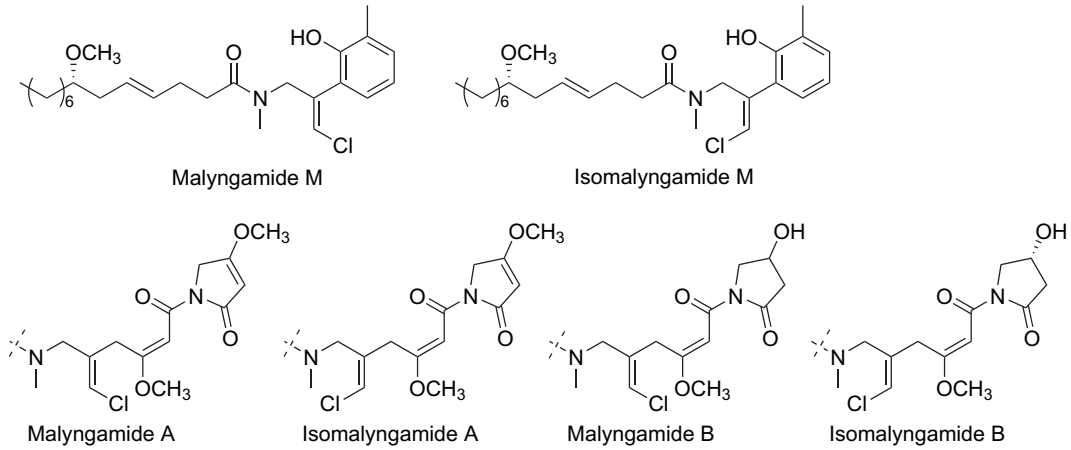


Figure 1. Structure of malyngamides M, *iso*-M, A, *iso*-A, B and *iso*-B.

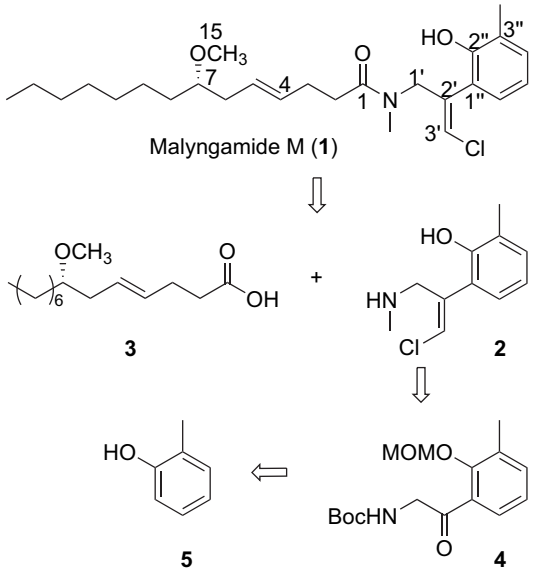
* Corresponding author. Tel.: +86 931 3911268; fax: +86 931 8912582; e-mail address: caoxplzu@163.com.

0040-4020/$ – see front matter
doi:10.1016/j.tet.2010.03.004

interesting terminal vinyl chloride functionality, such as malyngamides A, B, M, and isomalyngamides A, B, M (Fig. 1). Malyngamide M (**1**) was isolated from the Hawaiian red alga *Gracilaria coronopifolia* by Nagai's group.[6] It was the first example of a natural aromatized malyngamide, which possesses a special terminal vinyl chloride substructure. The compound also shows weak cytotoxicity to NB cells (IC_{50}>20 μM). However, only 0.6 mg of malyngamide M (**1**) was obtained from 4.8 kg of sample, and the synthesis of **1** had not been reported so far. Herein we wish to disclose efficient stereoselective synthesis of malyngamide M (**1**) and its geometrical isomer, isomalyngamide M (*Z*-**1**), which provide us with enough samples for a thorough examination of their biological activities.

2. Results and discussion

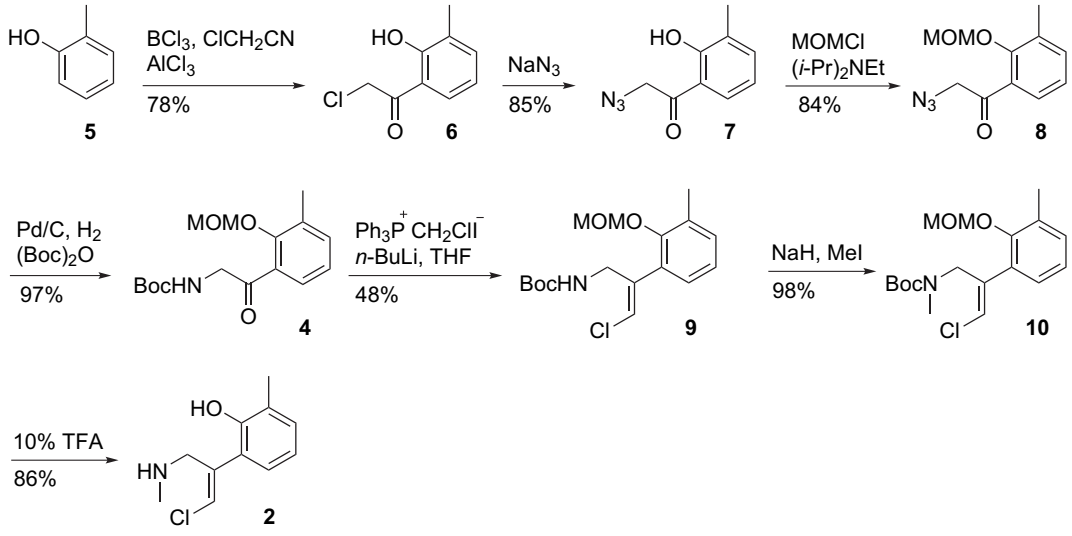
Malyngamide M (**1**) can be retrosynthetically divided into two parts: a lyngbic acid **3**[1,2,3] containing a 4*E* double bond and a 7*S* chiral center, and an amino phenol moiety (Scheme 1). According to our earlier works, the preparation of the lyngbic acid **3** could be achieved by two routes. One was based on a reduction strategy by using Na/*l*-NH_3,[7] while the other strategy employed a Johnson–Claisen rearrangement as the key step.[3] The vinyl chloride functionality of the other key intermediate **2** could be introduced via a Wittig reaction of the ketone **4**, which in turn could be obtained from *o*-cresol (**5**) by a Friedel–Crafts acetylation reaction followed by a series of functional group transformations.



Scheme 1. Retrosynthetic analysis.

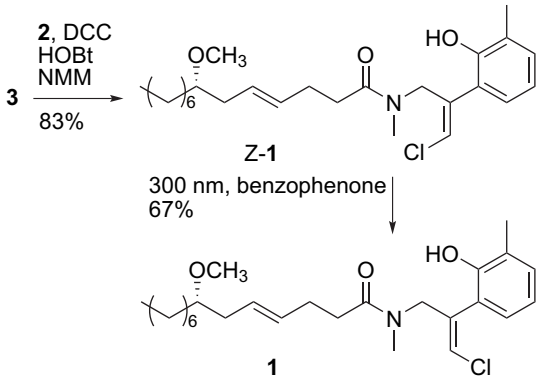
The preparation of amine segment **2** began with *o*-cresol (**5**) (Scheme 2). Thus, Friedel–Crafts acetylation of **5** with chloroacetonitrile in the presence of boron trichloride and aluminum trichloride gave phenol **6** in 78% yield (based on recovered starting material 95%).[8] Then reaction of **6** with sodium azide provided phenol **7** in 85% yield.[9] Protection of phenol **7** with methoxymethyl chloride (MOMCl) was conducted in the presence of *i*-Pr_2NEt to provide MOM ether **8** in 84% yield.[10] Subsequent hydrogenation of **8** by 10% Pd/C in EtOAc and in situ protection with di-*tert*-butyl dicarbonate (Boc_2O) afforded the Boc-protected amine **4** in 97% yield.[11] Compound **4** was then subjected directly to a Wittig olefination with chloromethyltriphenylphosphonium iodide ($Ph_3P^+CH_2ClI^-$) in the presence of *n*-BuLi in THF (−78 to −30 °C) to afford (*Z*)-vinyl chloride **9** in 48% yield (vide infra). The predominant formation of the *Z*-isomer with α-amino ketone **4** was similar to reported precedents[12] involved structurally similar α-alkoxy substituted ketones. In order to improve the yield of **9**, other reaction conditions were tested by varying the bases used (KHMDS, LiHMDS, *n*-BuLi) and the reaction temperature. In cases where KHMDS or LiHMDS was used as the base, no product was obtained. Using Mg/$TiCl_4$/$CHCl_3$ to prepare vinyl chloride **9** from ketone **4** also met with limited success.[5] No product could be obtained when the Wittig reaction was operated in the presence of *n*-BuLi at −78 °C, while a complex mixture was formed when the temperature was raised to 0 °C. Finally, it was found that the optimal temperature was between −78 and −30 °C. Subsequently, *N*-methylation of compound **9** gave the corresponding methyl derivative **10** in 98% yield.[13] The (*Z*)-configuration of the vinyl chloride functionality in **10** was confirmed by NOE experiment. Hence selective irradiation of H-3 of **10** resulted in signal enhancement of H-6′. Finally, simultaneous removal of both the MOM and Boc groups in **10** by trifluoroacetic acid (TFA) afforded the amine portion **2** in 86% yield.

Preparation of the lyngbic acid segment **3** was achieved according to our earlier work for the syntheses of other Malyngamide homologs.[7] As shown in Scheme 3, octanal (**11**) was reacted with allyltributyltin in the presence of a catalytic amount of bis{[(*R*)-binaphthoxy](isopropoxy)titanium} oxide [bis(*R*)-Ti(IV) oxide] afforded chiral alcohol **12** in 88% yield.[14] Alcohol **12** was treated with CH_3I in the presence of NaH to give the corresponding methyl ether **13** in 96% yield. The double bond of **13** was then cleaved with OsO_4/

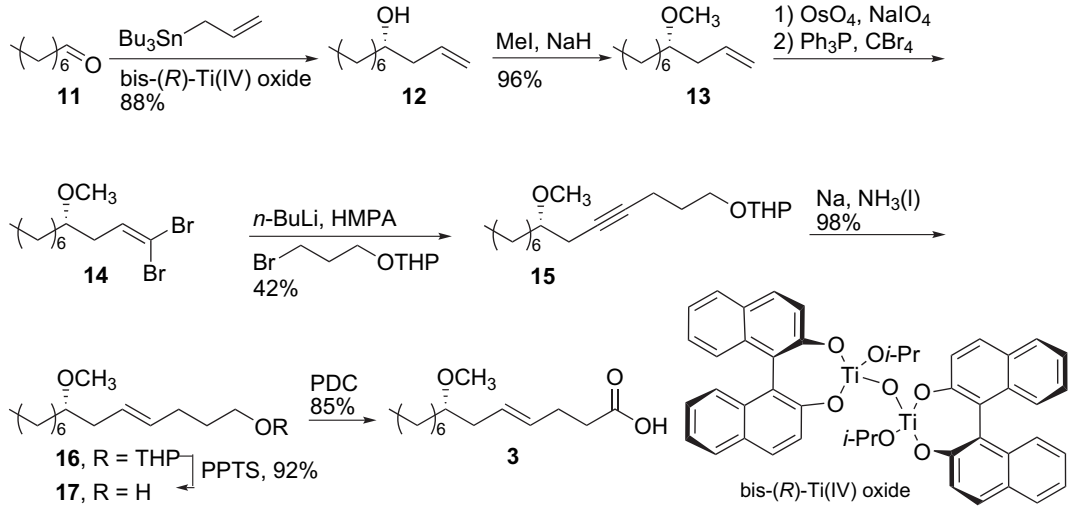


Scheme 2. Preparation of methyl amine **2**.

$NaIO_4$ using 4-methylmorpholine *N*-oxide (NMO) as a co-oxidant, and followed by reaction with PPh_3/CBr_4 to produce unstable vinylic dibromide **14**.[15] Compound **14** was then immediately reacted with 3-bromo-1-tetrahydropyranyloxypropane in the presence of *n*-BuLi to furnish alkyne **15** in 42% yield.[7] Subsequent stereocontrolled reduction of **15** with sodium in liquid ammonia in the presence of *t*-BuOH produced alkene **16** in 98% yield with *E*-configuration.[16] Then removal of tetrahydro-2*H*-pyran (THP) group in compound **16** by a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in EtOH afforded primary alcohol **17** in 92% yield, and subsequent oxidation of **17** with pyridinium dichromate (PDC) gave lyngbic acid **3** in 85% yield. The configuration and diastereomeric purity of lyngbic acid segment **3** were identical to those described for the natural lyngbic acid.[1a] On the other hand, lyngbic acid **3** could been also synthesized in six steps using a Johnson–Claisen rearrangement as a key step in 50% overall yield using the intermediate **13**.[3] The second strategy gave more satisfactory overall yield in large scale preparation and is more convenient to handle.



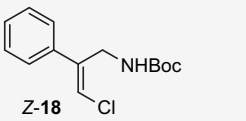
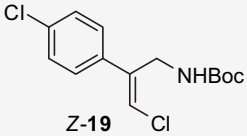
Scheme 4. Preparation of malyngamide M (**1**) and isomalyngamide M (*Z*-**1**).

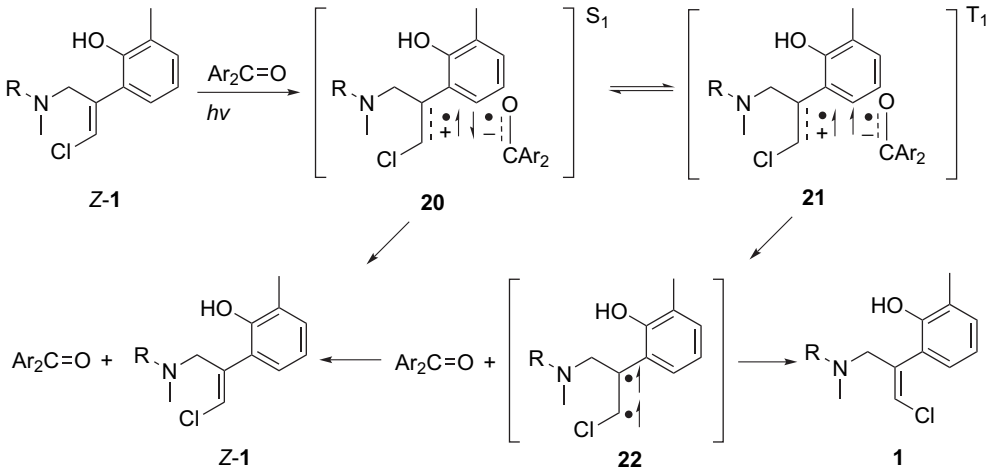


Scheme 3. Preparation of lyngbic acid **3**.

With the secondary amine **2** and lyngbic acid **3** in hand, their coupling was run in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole (HOBt), and 4-methylmorpholine (NMM) to afford isomalyngamide (*Z*-**1**) in 83% yield (Scheme 4).[1b] As expected, the ^1H NMR, ^{13}C NMR data, and specific rotation $[\alpha]_D^{20}$ −9 (*c* 0.2, MeOH) of synthetic isomalyngamide disagreed with the data of reported for the natural malyngamide M due to the difference in the double bond geometry. These results further confirmed the *Z*-configuration of vinyl chloride of the intermediate **9**. Hence, at this stage, we were faced with the task of transforming *Z*-vinyl chloride to *E*-vinyl chloride in order to complete the synthesis of the natural product. According to the literature,[12] *Z*-vinyl chloride could be converted to *E*-vinyl chloride by irradiation with UV light in the presence of catalytic amounts of I_2, but no expected product was obtained in our case. When *Z*-**1** was exposed to visible light in the presence of the same catalyst, the reaction was very messy. Then we tried to conduct the isomerization of the intermediates **9** and **10** (Table 1). Compound **9** was found to decompose under light of different wavelengths (254 nm–780 nm) in the presence of I_2, while compound **10** remained unaltered under the same conditions. All the experiments tested on **9**, **10**, and *Z*-**1** in the presence of I_2 were unsuccessful. Finally, it was found that *Z*-**1** could be converted to a mixture of **1**/*Z*-**1** (2.5:1) when exposed to UV-light ($\lambda \geq 300$ nm) in the presence of benzophenone in CH_2Cl_2 for 8 h at rt.[17] Fortunately, the two isomers could be separated by flash chromatography over silica gel easily, and pure **1** was obtained in 67% yield. While under the same condition in the absence of benzophenone,

Table 1
Optimization for transforming *Z*-isomers to *E*-isomers

Substrate	Wavelength of UV light (nm)	Photosensitizer	Results
9	254	I_2	Complex
9	≥300	I_2	Complex
9	380–780	I_2	Complex
9	≥300	Benzophenone	Complex
9	254	—	No reaction
10	254	I_2	No reaction
10	≥300	I_2	No reaction
10	≥300	Benzophenone	Complex
10	≥300	—	No reaction
Z-**1**	254–380	I_2	Complex
Z-**1**	≥300	Benzophenone	67% yield *E*-**1**
Z-**1**	≥300	—	20% yield *E*-**1**
		I_2	44% yield *E*-**18**
		Benzophenone	45% yield *E*-**18**
 *Z*-**18**	≥300		
 *Z*-**19**	≥300	I_2	Complex
		Benzophenone	43% yield *E*-**19**



Scheme 5. The possible mechanism of photochemical isomerization of *Z*-**1** to **1**.

compound **1** was obtained only in 20% yield. The spectral data (^{1}H NMR, ^{13}C NMR, IR, MS) and specific rotation $[\alpha]_D^{20}$ −31 (*c* 0.1, MeOH) of synthetic malyngamide M (**1**) were identical with those of the natural product.[6] While comparing the NMR data of *Z*-**1** with those of isolated malyngamide M, the obvious differences of chemical shift were observed in the vicinity of the vinyl chloride functionality, such as H-1′, H-3′, H-NCH$_3$, C-1′, C-3′ and C-1″ position. The maximum discrepancy of chemical shift was 0.23 ppm for ^{1}H NMR at H-1′ position, and 2.9 ppm for ^{13}C NMR at C-1′ and C-1″ positions. It should be noted that, some of the ^{1}H NMR signals of synthetic **1** and *Z*-**1** appeared as pairs of peaks due to the presence of two *tert*-amide isomers, but ^{13}C NMR signals did not appear as pairs of peaks, but this is a fairly common phenomenon observed among the malyngamides.[1a,6,18]

The benzophenone-sensitized photochemical *Z*-*E* isomerization reaction of vinyl chloride was also applied to other substrates. In the above conditions, compound **9** and **10** were both decomposed maybe due to the existence of the MOM group in their skeletons. *E*-**18** and *E*-**19** were obtained from *Z*-**18** and *Z*-**19** in 45% and 43% yields, respectively. The possible mechanism (Scheme 5) of photochemical *Z*-*E* isomerization of vinyl chloride (*Z*-**1** to **1**), sensitized by benzophenone, involves electron transfer pathway[19] from the vinyl chloride π-bond to the excited singlet acceptors-benzophenone, generating a radical cation as part of a singlet pair **20**. The triplet radical ion pair **21** formed by intersystem crossing, on the other hand, undergoes electron transfer to produce the triplet vinyl chloride of orthogonal geometry, capable therefore of partitioning to either the *Z*-**1** or **1**.

3. Conclusion

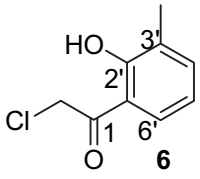
In summary, the first concise and efficient stereoselective total syntheses of malyngamide M and isomalyngamide M has been achieved using the Wittig reaction, amidation, and isomerization reaction as key steps. Both the stereo- and geometric-isomerisms were established in a facile manner with high selectivity. The synthesis of malyngamide M consisted of nine steps starting from commercially available *o*-cresol in 12% overall yield. Further application of this strategy toward the synthesis of the structurally related malyngamides with a vinylic chloride functionality, such as A, B, *iso*-A, *iso*-B, I, K, F, and G is currently in progress and will be presented in due course.

4. Experimental section

4.1. General

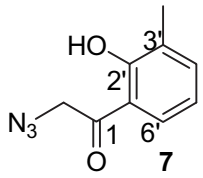
All reactions that required anhydrous condition were carried by standard procedures under argon atmosphere. Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying reagents. Petroleum ether used had a bp range of 60–90 °C. Reactions were monitored by TLC on silica gel GF 254 plates. Column chromatography was generally performed through silica gel (200–300 mesh). IR spectra were recorded on a Nicolet NEXUS 670 FT-IR spectrophotometer and reported in wavenumbers (cm^{-1}). Melting points were determined by use of a Reichert Microscope apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra, DEPT 135, and NOE experiments were recorded on a Mercury Plus-400 spectrometer or a Mercury Plus-300 spectrometer. Chemical shifts (δ) are reported in ppm relative to TMS (δ 0.00) or chloroform (δ 7.26) or acetone (δ 2.05) for the ^{1}H NMR, and to chloroform (δ 77.0) or acetone (δ 30.6) for the ^{13}C NMR measurements. High resolution mass spectra (HRMS) and mass spectra (MS) were obtained on a Bruker Daltonics APEX II 47e and a Finnegan LCQ mass spectrometer, respectively. The photochemical reaction was irradiated at $\lambda \geq 300$ nm with a high-pressure mercury lamp (500 W).

4.2. 2-Chloro-1-(2-hydroxy-3-methylphenyl)ethanone (6)[8]



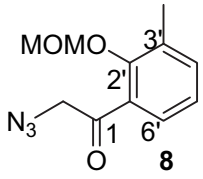
To a stirred solution of BCl_3 (15 mL, 30 mmol) in CH_2Cl_2 (15 mL) was added *o*-cresol (2.70 g, 25 mmol) in CH_2Cl_2 (25 mL), $ClCH_2CN$ (1.9 mL, 30 mmol), and $AlCl_3$ (1.67 g, 12.5 mmol) at 0 °C. The reaction mixture was stirred at rt for 40 h, then, ice and 2 N HCl (20 mL) were added and the reaction mixture was stirred for 2 h to hydrolyze the corresponding ketimine. The mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were washed with brine (60 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc, 40:1) afforded ketone **6** (3.60 g, 78% yield) as a white solid. Mp 65.5–66.5 °C; IR (KBr): 3418, 1653, 1428, 1263, 1244, 1072, 767, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 3H, CH_3), 4.73 (s, 2H, CH_2, H-2), 6.83 (t, 1H, *J*=8.0 Hz, ArH), 7.38 (d, 1H, *J*=8.0 Hz, ArH), 7.53 (d, 1H, *J*=8.0 Hz, ArH), 11.98 (br, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5 (CH_3), 45.4 (CH_2, C-2), 116.4 (C, C-1′), 118.7 (ArCH), 127.0 (ArCH), 128.0 (ArC, C-3′), 138.0 (ArCH), 161.2 (ArC, C-2′), 196.6 (C, C-1); MS (ESI) *m*/*z*: 185.1 ([M+H]$^+$).

4.3. 2-Azido-1-(2-hydroxy-3-methylphenyl)ethanone (7)



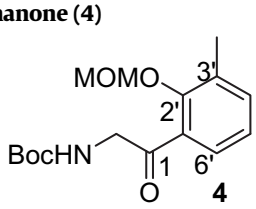
To a stirred solution of compound **6** (590 mg, 3.20 mmol) in acetone and H_2O (40 mL, acetone/H_2O, 1:1) was added NaN_3 (2.08 g, 32.00 mmol). The reaction mixture was stirred at rt for 6 h. After removal of acetone, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3×35 mL). The organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc, 35:1) afforded phenol **7** (520 mg, 85% yield) as a white solid. Mp 67–68 °C; IR (KBr): 3391, 2119, 1645, 1423, 1270, 761, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.25 (s, 3H, CH_3), 4.56 (d, 2H, J=1.8 Hz, NCH_2, H-2), 6.79–6.85 (m, 1H, ArH), 7.36–7.39 (m, 2H, 2×ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.4 (CH_3), 54.1 (NCH_2, C-2), 116.4 (C, C-1′), 118.7 (ArCH), 126.0 (ArCH), 128.0 (ArC, C-3′), 137.9 (ArCH), 160.8 (ArC, C-2′), 198.6 (C, C-1); MS (EI) m/z (%): 191 (M^+, 20), 135 (83), 77 (91), 51 (82), 39 (100). Various attempts to further characterize **7** by high resolution mass spectrometry, including RSI and FAB as ionization techniques were unsuccessful.

4.4. 2-Azido-1-[2-(methoxymethoxy)-3-methylphenyl]-ethanone (8)



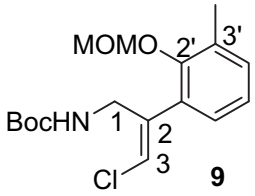
To a stirred solution of compound **7** (501 mg, 2.62 mmol) in CH_2Cl_2 (18 mL) was added MOMCl (2.00 mL, 26.2 mmol) and i-Pr_2NEt (1.36 mL, 7.86 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and continued for 4 h. Then the reaction mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc, 30:1) afforded MOM ether **8** (517 mg, 84% yield) as a pale yellow oil. IR (KBr): 2830, 2050, 1719, 1603, 1511, 1249, 1177, 832, 790, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H, CH_3), 3.46 (s, 3H, OCH_3), 4.51 (s, 2H, NCH_2, H-2), 4.97 (s, 2H, OCH_2), 7.14 (t, 1H, J=7.8 Hz, ArH), 7.40 (t, 2H, J=8.0 Hz, 2×ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.6 (CH_3), 57.9 (OCH_3 and NCH_2), 100.4 (OCH_2), 124.7 (ArH), 127.1 (ArH), 131.8 (ArC), 132.3 (ArC), 135.5 (ArCH), 154.3 (ArC, C-2′), 196.9 (C, C-1); HRMS (ESI) m/z $C_{11}H_{13}N_3O_3Na$ $[M+Na]^+$ calcd for 258.0849, found 258.0855.

4.5. 2-[(*tert*-Butoxycarbonyl)amino]-1-[2-(methoxymethoxy)-3-methylpheny]-ethanone (4)



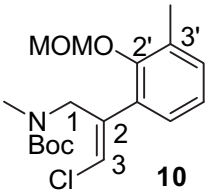
To a stirred mixture of azide **8** (400 mg, 1.70 mmol) and $(Boc)_2O$ (742 mg, 3.40 mmol) in EtOAc (15 mL) was added 10% Pd/C (40 mg). The reaction mixture was stirred for 1.5 h under H_2 (1 atm) atmosphere at rt, then filtered, and the filtrate was concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc, 10:1) afforded ketone **4** (510 mg, 97% yield) as a pale yellow oil. IR (KBr): 3373, 2977, 1699, 1502, 1245, 1160, 1073, 957, 783, 598 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9H, 3×CH_3), 2.34 (s, 3H, CH_3), 3.48 (s, 3H, OCH_3), 4.53 (d, 2H, J=4.8 Hz, NCH_2, H-2), 4.97 (s, 2H, OCH_2), 5.49 (br, 1H, NH), 7.10 (t, 1H, J=7.6 Hz, ArH), 7.36 (d, 1H, J=7.6 Hz, ArH), 7.42 (d, 1H, J=7.6 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.6 (CH_3), 28.2 (CH_3), 50.4 (NCH_2), 57.6 (OCH_3), 79.5 (C), 100.5 (OCH_2), 124.3 (ArCH), 126.9 (ArCH), 131.6 (ArC), 132.4 (ArC), 135.1 (ArCH), 154.3 (ArC, C-2′), 155.6 (C), 198.1 (C, C-1); HRMS (ESI) m/z $C_{16}H_{23}NO_5Na$ $[M+Na]^+$ calcd for 332.1468, found 332.1462.

4.6. (*Z*)-*N*-(*tert*-Butoxycarbonyl)-3-chloro-2-[2-(methoxymethoxy)-3-methylphenyl]-prop-2-en-amine (9)



To a stirred suspension of (choromethyl)triphenylphosphonium iodide (999 mg, 2.28 mmol) in dry THF (15 mL) under Ar atmosphere was added n-BuLi (0.68 mL, 1.71 mmol, 2.5 M in hexane) slowly at −78 °C. The stirring was continued at this temperature for 1 h and allowed to warm to −10 °C over 50 min. The resulting red solution was cooled again to −78 °C, and the ketone **4** (176 mg, 0.57 mmol) was added in THF dropwise (2 mL). The mixture was stirred for 20 min at −78 °C and allowed to warm to −30 °C over 30 min, and then quenched with saturated NH_4Cl solution (25 mL), and extracted with EtOAc (3×25 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc, 20:1) afforded vinyl chloride **9** (93 mg, 48% yield) as a pale yellow oil. IR (KBr): 3367, 2976, 1714, 1506, 1249, 1162, 1071, 969, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (s, 9H, 3×CH_3), 2.31 (s, 3H, CH_3), 3.53 (s, 3H, OCH_3), 4.31 (d, 2H, J=5.7 Hz, NCH_2), 4.90 (s, 2H, OCH_2), 4.97 (br, 1H, NH), 6.21 (s, 1H, H-3), 6.99–7.10 (m, 2H, 2×ArH), 7.14–7.17 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.7 (CH_3), 28.2 (CH_3), 40.7 (NCH_2), 57.5 (OCH_3), 79.0 (C), 99.2 (OCH_2), 118.4 (CH, C-3), 124.5 (ArCH), 128.2 (ArCH), 131.4 (2×ArC), 131.6 (ArCH), 138.9 (C, C-2), 153.4 (ArC), 155.8 (C); HRMS (ESI) m/z $C_{17}H_{24}ClNO_4Na$ $[M+Na]^+$ calcd for 364.1286, found 364.1286.

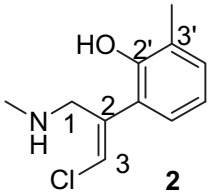
4.7. (*Z*)-*N*-(*tert*-Butoxycarbonyl)-3-chloro-2-[2-(methoxymethoxy)-3-methylphenyl]-*N*′-methyl-prop-2-en-amine (10)



To a stirred solution of compound **9** (89 mg, 0.26 mmol) in THF (3 mL) was added NaH (23 mg, 0.52 mmol, 55% in oil) at 0 °C. The reaction mixture was stirred for 10 min and CH_3I (0.05 mL, 0.78 mmol) was then added. The reaction mixture was allowed to warm to rt and stirred for 10 h, then quenched with saturated NH_4Cl solution (10 mL), and extracted with EtOAc (3×15 mL). The combined organic layers were washed with saturated brine (40 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc, 30:1) afforded Boc-protected amine **10** (91 mg, 98% yield) as a pale yellow oil. IR (KBr): 2974, 1698, 1394, 1247, 1152, 970,

771 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23/1.30 (s, 9H, 3×CH_3), 2.30 (s, 3H, CH_3), 2.65/2.75 (s, 3H, NCH_3), 3.52 (s, 3H, OCH_3), 4. 48 (s, 2H, NCH_2, H-1), 4.91 (s, 2H, OCH_2), 6.22/6.27 (s, 1H, CH, H-3), 6.87–6.99 (m, 2H, 2×ArH), 7.13–7.16 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.6 (CH_3), 27.9 (CH_3), 33.5 (NCH_3), 47.4 (NCH_2, C-1), 57.3 (OCH_3), 79.1 (C), 99.1 (OCH_2), 118.7 (CH, C-3), 124.2 (ArCH), 128.6 (ArCH), 131.2 (ArC), 131.4 (ArC), 131.7 (ArCH), 138.6 (C, C-2), 153.5 (ArC), 155.3 (ArC); HRMS (ESI) *m/z* $C_{18}H_{26}ClNO_4Na$ $[M+Na]^+$ calcd for 378.1443, found 378.1442. The ^1H NMR signals of compound **10** appeared as pairs of peaks due to the presence of two interconverting *tert*-amide isomers.

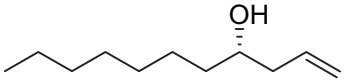
4.8. (*Z*)-3-Chloro-2-[2-hydroxy-3-methylphenyl]-*N*-methylprop-2-en-amine (2)



2

To a stirred solution of compound **10** (64 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was added TFA (0.2 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1 h, followed by the addition of saturated $NaHCO_3$ solution (5 mL), and extracted with EtOAc (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc/triethylamine, 96:12:1) afforded the secondary amine **2** (33 mg, 86% yield) as a pale yellow oil. IR (KBr): 3312, 2920, 1462, 1422, 1253, 1097, 769, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.24 (s, 3H, CH_3), 2.59 (s, 3H, NCH_3), 3.62 (s, 2H, NCH_2), 6.35 (s, 1H, CH, H-3), 6.67 (t, 1H, *J*=5.5 Hz, ArH), 6.88 (d, 1H, *J*=5.5 Hz, ArH), 7.09 (d, 1H, *J*=5.5 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.7 (CH_3), 35.2 (NCH_3), 49.8 (NCH_2, H-1), 118.3 (CH, C-3), 120.8 (ArCH), 125.4 (ArC), 126.2 (ArC), 127.1 (ArCH), 131.1 (ArCH), 139.4 (C, C-2), 154.5 (ArC); HRMS (ESI) *m/z* $[M+H]^+$ $C_{11}H_{15}ClNO$ calcd for 212.0837, found 212.0843.

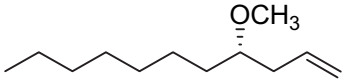
4.9. (*S*)-Undec-1-en-4-ol (12)[3,14]



12

On the similar method of the Reference,[3,14] to a stirred solution of $TiCl_4$ (66 μL, 0.60 mmol) in CH_2Cl_2 (6 mL) was added Ti(*i*-PrO)$_4$ (0.53 mL, 1.80 mmol) at 0 °C under argon atmosphere. The solution was allowed to warm to rt. After 3 h, Ag_2O (278 mg, 1.20 mmol) was added, and the reaction mixture was stirred for 5 h under exclusion of direct light. The mixture was diluted with CH_2Cl_2 (16 mL), and treated with (*R*)-binaphthol (687 mg, 2.40 mmol) at rt for 2 h to furnish chiral bis-Ti(IV) oxide. The in situ generated chiral bis-Ti(IV) oxide in CH_2Cl_2 (6 mL) was cooled to −15 °C and treated sequentially with aldehyde **11** (1.54 g, 12.00 mmol) in CH_2Cl_2 (4 mL) and allyltributyltin (4.05 mL, 13.20 mmol) in this temperature. The reaction was allowed to 0 °C and stirred for 20 h, then quenched with saturated $NaHCO_3$ solution (10 mL), and extracted with ether (3×40 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc, 40:1) afforded alcohol **12** (1798 mg, 88% yield, 98% ee) as a pale yellow oil. $[\alpha]_D^{20}$ −9 (*c* 1.0, $CHCl_3$) [Ref. 3 $[\alpha]_D^{20}$ −9 (*c* 1.0, $CHCl_3$)]; IR (KBr): 3350, 2927, 2856, 1641, 1463, 995, 913 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, 3H, *J*=6.6 Hz, CH_3), 1.21–1.49 (m, 12H, 6×CH_2, H-5, H-6, H-7, H-8, H-9, and H-10), 1.71 (br, 1H, OH), 2.07–2.31 (m, 2H, H-3), 3.60–3.64 (m, 1H, H-4), 5.09–5.14 (m, 2H, H-1), 5.75–5.87 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (CH_3), 22.6 (CH_2), 25.6 (CH_2), 29.2 (CH_2), 29.6 (CH_2), 31.8 (CH_2), 36.8 (CH_2), 41.9 (CH_2), 70.7 (CH, C-4), 117.9 (CH_2, C-1), 134.9 (CH, C-2); MS (EI) *m/z* (%): 152 ($[M-H_2O]^+$, 1), 69 (100), 55 (60), 41 (84).

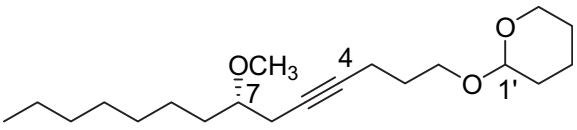
4.10. (*S*)-4-Methoxy-1-undecene (13)[3]



13

To a stirred solution of compound **12** (952 mg, 5.59 mmol) in THF (15 mL) was added NaH (488 mg, 11.18 mmol, 55% in oil) at 0 °C. The reaction mixture was stirred for 10 min and CH_3I (1.04 mL, 16.77 mmol) was then added. The reaction mixture was allowed to warm to rt and stirred for 12 h, then quenched with saturated NH_4Cl solution (20 mL), and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (55 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc, 50:1) afforded **13** (988 mg, 96% yield) as a pale yellow oil. $[\alpha]_D^{20}$ −12 (*c* 1.0, $CHCl_3$) [Ref. 3 $[\alpha]_D^{20}$ −11 (*c* 1.0, $CHCl_3$)]; IR (KBr): 2928, 2856, 1641, 1100, 912 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, 3H, *J*=6.6 Hz, CH_3), 1.22–1.48 (m, 12H, 6×CH_2, H-5, H-6, H-7, H-8, H-9, and H-10), 2.24–2.28 (m, 2H, H-3), 3.18–3.22 (m, 1H, H-4), 3.34 (s, 3H, OCH_3), 5.03–5.10 (m, 2H, H-1), 5.77–5.86 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3), 22.6 (CH_2), 25.2 (CH_2), 29.3 (CH_2), 29.7 (CH_2), 31.8 (CH_2), 33.3 (CH_2), 37.7 (CH_2), 56.5 (OCH_3), 80.5 (CH, C-4), 116.7 (CH_2, C-1), 135.0 (CH, C-2); MS (EI) *m/z* (%): 183 ($[M-H]^+$, 1), 143 (31), 111 (15), 69 (100).

4.11. (7*S*)-7-Methoxy-1-tetrahydropyranyloxy-4-tetradecyne (15)[2,20b,d]

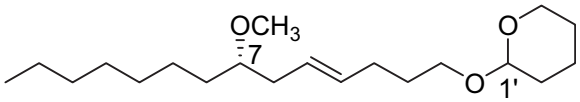


15

To a stirred solution of compound **13** (400 mg, 2.17 mmol) in THF and H_2O (16 mL, THF/H_2O, 3:1) was added NMO (305 mg, 2.60 mmol) and OsO_4 (20 mg). The reaction mixture was stirred at rt for two days. The reaction mixture was quenched with saturated Na_2SO_3 solution (20 mL) and extracted with EtOAc (3×30 mL). The combined organic extracts were concentrated in vacuo to give the diol. The crude diol was dissolved in THF and H_2O (18 mL, THF/H_2O, 1.25:1), then $NaIO_4$ (650 mg, 3.04 mmol) was added. The reaction mixture was stirred at rt for 2 h, then quenched with saturated $Na_2S_2O_3$ solution (20 mL) and extracted with ether (3×25 mL). The organic layers were washed with water (70 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was passed through a short silica gel column to afford the aldehyde. This aldehyde in CH_2Cl_2 (2 mL) was added to a stirred solution of CBr_4 (1307 mg, 3.94 mmol), and PPh_3 (2067 mg, 7.88 mmol) in CH_2Cl_2 (5 mL) at 0 °C, the reaction mixture was stirred for 1 h, then the solvent was concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc, 80:1) afforded dibromide **14** (624 mg, 84% yield) as a pale yellow oil. To a stirred solution of **14** (526 mg, 1.54 mmol) in THF (10 mL) was added *n*-BuLi (2.5 M in hexane, 1.23 mL, 3.08 mmol) at −78 °C under an argon atmosphere. Stirring was continued at this temperature for 1 h and then the reaction mixture was allowed to warm to −10 °C over 1 h. Then the solution was cooled to −78 °C, HMPA (2 mL) followed by bromide

(344 mg, 1.54 mmol) in THF (2 mL) was added. The reaction mixture was allowed to warm to rt for 5 h. Work-up as above preparation of **13** afforded **15** (210 mg, 42% yield) as a colorless oil. $[\alpha]_D^{20}$ −22 (*c* 1.0, $CHCl_3$) [Ref. 20d $[\alpha]_D^{22}$ −3.7 (*c* 1.47, $CHCl_3$)]; IR (KBr): 2929, 2857, 2214, 1736, 1461, 1169, 1100, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, 3H, *J*=6.6 Hz, CH_3), 1.22–1.50 (m, 12H, 6×CH_2), 1.52–1.62 (m, 4H, 2×CH_2), 1.67–1.84 (m, 4H, 2×CH_2), 2.26–2.43 (m, 4H, 2×CH_2), 3.20–3.26 (m, 1H, H-7), 3.37 (s, 3H, OCH_3), 3.43–3.54 (m, 2H, OCH_2), 3.78–3.90 (m, 2H, OCH_2), 4.59 (t, 1H, *J*=3.2 Hz, H-1′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3), 15.7 (CH_2), 19.5 (CH_2), 22.6 (CH_2), 23.4 (CH_2), 25.2 (CH_2), 25.4 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.6 (CH_2), 30.6 (CH_2), 31.8 (CH_2), 33.6 (CH_2), 56.9 (OCH_3), 62.1 (OCH_2), 66.0 (OCH_2), 76.9 (C), 79.8 (CH, C-7), 81.0 (C), 98.7 (CH, C-1′); MS (EI) *m*/*z* (%): 187 (59), 181 (36), 167 (45), 157 (47), 143 (26), 137 (1), 88 (1), 69 (67), 43 (100).

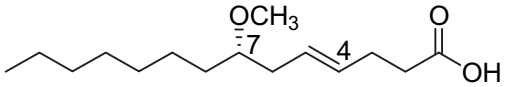
4.12. *E*,(7*S*)-7-Methoxy-1-tetrahydropyranyloxy-4-tetradecene (16)[2,20b,d]



16

To a dry liquid ammonia (approximate 24 mL) was added sodium metal (190 mg, 8.26 mmol), followed by THF (4 mL) and *t*-BuOH (2 mL). Then a solution of **15** (354 mg, 1.09 mmol) in THF (4 mL) was added immediately. The reaction mixture was held under ammonia reflux for 1.5 h, quenched by NH_4Cl (200 mg), after the ammonia evaporation, water (20 mL) was added. The mixture was extracted with EtOAc (3×15 mL). The organic layers were washed with brine (40 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc, 30:1) afforded alkene **16** (348 mg, 98% yield) as a colorless oil. $[\alpha]_D^{20}$ −14 (*c* 1.0, $CHCl_3$) [Ref. 2 $[\alpha]_D^{28}$ −10.34 (*c* 0.5, $CHCl_3$)]; IR (KBr): 2928, 1735, 1461, 1357, 1120, 1079, 1032, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, 3H, *J*=6.6 Hz, CH_3), 1.27–1.88 (m, 20H, 10×CH_2), 2.06–2.21 (m, 4H, H-6, and H-3), 3.10–3.16 (m, 1H, H-7), 3.33 (s, 3H, OCH_3), 3.34–3.51 (m, 2H, OCH_2), 3.70–3.89 (m, 2H, OCH_2), 4.58 (t, 1H, *J*=3.9 Hz, H-1′), 5.37 (dt, 1H, *J*=15.9, 6.0 Hz, H-4 or H-5), 5.54 (dt, 1H, *J*=15.9, 6.0 Hz, H-5 or H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (CH_3), 19.6 (CH_2), 22.6 (CH_2), 25.2 (CH_2), 25.5 (CH_2), 29.2 (2×CH_2), 29.5 (CH_2), 29.7 (CH_2), 30.7 (CH_2), 31.8 (CH_2), 33.3 (CH_2), 36.3 (CH_2), 56.4 (OCH_3), 62.2 (OCH_2), 66.9 (OCH_2), 80.8 (CH, C-7), 98.8 (CH, C-1′), 126.5 (CH), 132.0 (CH); MS (EI) *m*/*z* (%): 326 (M^+, 2), 281 (11), 239 (21), 69 (86), 45 (63), 41 (100).

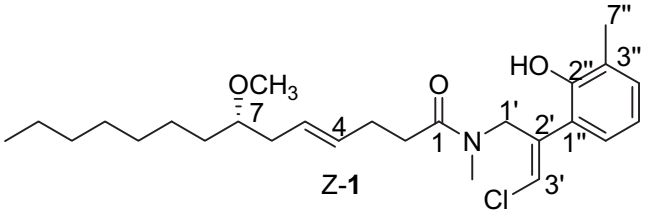
4.13. *E*,(7*S*)-7-Methoxytetradec-4-enoic acid [lyngbic acid (3)][1–3,20]



3

To a stirred solution of compound **16** (320 mg, 0.98 mmol) in ethanol (5 mL) was added PPTS (cat.), then the reaction was stirred at 65 °C for 5 h. The solvent was then concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc, 5:1) afforded the primary alcohol **17** (219 mg, 92% yield) as a colorless oil. To a stirred solution of **17** (191 mg, 0.79 mmol) in DMF (6 mL) was added PDC (2.08 g, 5.53 mmol). After 12 h, the mixture was quenched with cold water (10 mL), and extracted with EtOAc (3×15 mL). The combined organic layers were washed with $KHSO_4$ (40 mL, 1 mol/L), water (40 mL), and brine (40 mL), respectively, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (CH_2Cl_2/MeOH, 20:1) afforded acid **3** as a colorless oil (172 mg, 85% yield). $[\alpha]_D^{20}$ −13.8 (*c* 0.2, $CHCl_3$) [Ref. 1a $[\alpha]_D^{20}$ −8.3 (*c* 0.18, $CHCl_3$)]; IR (KBr): 3126, 2928, 2856, 1737, 1712, 1440, 1098, 971 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, 3H, *J*=6.8 Hz, CH_3, H-14), 1.27–1.45 (m, 12H, 6×CH_2, H-8, H-9, H-10, H-11, H-12, and H-13), 2.19–2.45 (m, 6H, H-2, H-3, and H-6), 3.12–3.20 (m, 1H, H-7), 3.33 (s, 3H, OCH_3), 5.43–5.56 (m, 2H, H-4, and H-5), 11.25 (br, 1H, CO_2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3), 22.6 (CH_2), 25.2 (CH_2), 27.6 (CH_2), 29.3 (CH_2), 29.7 (CH_2), 31.8 (CH_2), 33.3 (CH_2), 33.9 (CH_2), 36.3 (CH_2), 56.5 (OCH_3), 80.8 (CH, C-7), 127.7 (CH), 130.1 (CH), 179.2 (C, C-1); HRMS (ESI) *m*/*z* $C_{15}H_{32}NO_3$ $[M+NH_4]^+$ calcd for 274.2377, found 274.2373.

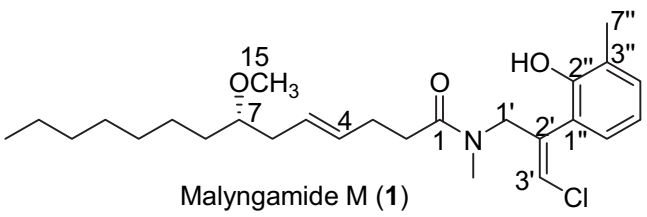
4.14. *E*,(7*S*)-*N*-[(*Z*)-3-Chloro-2-(2-hydroxy-3-methylphenyl)-allyl]-7-methoxy-*N*-methyl-tetradec-4-enamide [isomalyngamide (*Z*-1)]



Z-**1**

To a stirred solution of amine **2** (27 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was added a solution of acid **3** (33 mg, 0.13 mmol) in CH_2Cl_2 (2 mL), DCC (27 mg, 0.13 mmol), HOBt (22 mg, 0.16 mmol), and a solution of NMM (13 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The stirring was allowed to warm to rt and continued for 10 h, and then solvent was concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc, 10:1) afforded amide isomalyngamide M (*Z*-**1**) (49 mg, 83% yield) as a pale yellow oil. $[\alpha]_D^{20}$ −9 (*c* 0.2, MeOH); IR (KBr): 3293, 2927, 2855, 1628, 1462, 1213, 1096, 972, 767 cm^{-1}; ^1H NMR (Me_2CO-d_6, 400 MHz) δ 0.88 (t, 3H, *J*=6.4 Hz, H-14), 1.23–1.36 (m, 10H, 5×CH_2, H-9, H-10, H-11, H-12, and H-13), 1.37–1.43 (m, 2H, CH_2, H-8), 2.12–2.40 (m, 7H, H-3, H-6, and H-7″), 2.38 (t, 2H, *J*=7.2 Hz, H-2), 3.07–3.18 (m, 4H, NCH_3, and H-7), 3.27 (s, 3H, OCH_3, H-15), 4.33 (s, 2H, H-1′), 5.40–5.52 (m, 2H, H-4, and H-5), 6.23 (s, 1H, H-3′), 6.69 (t, 1H, *J*=7.6 Hz, H-5″), 6.85 (d, 1H, *J*=7.6 Hz, H-6″), 7.08 (d, 1H, *J*=7.6 Hz, H-4″), 9.33 (br, 1H, ArOH); ^{13}C NMR (Me_2CO-d_6, 100 MHz) δ 14.4 (CH_3, C-14), 16.6 (CH_3, C-7″), 23.3 (CH_2, C-13), 26.0 (CH_2, C-9), 28.7 (CH_2, C-3), 30.0 (2×CH_2, C-10, and C-11), 32.8 (CH_2, C-12), 33.5 (CH_2, C-2), 34.2 (CH_2, C-8), 37.2 (CH_2, C-6), 38.0 (NCH_3), 51.0 (CH_2, C-1′), 56.5 (OCH_3, C-15), 81.4 (CH, C-7), 118.2 (CH, C-3′), 119.9 (CH, C-5″), 126.0 (C, C-1″), 126.6 (C, C-3″), 128.1 (CH, C-5), 129.0 (CH, C-6″), 131.8 (CH, C-4″), 132.0 (CH, C-4), 138.9 (C, C-2′), 154.1 (C, C-2″), 174.1 (C, C-1); HRMS (ESI) *m*/*z* $C_{26}H_{41}ClNO_3$ $[M+H]^+$ calcd for 450.2769, found 450.2763.

4.15. *E*,(7*S*)-*N*-[(*E*)-3-Chloro-2-(2-hydroxy-3-methylphenyl)-allyl]-7-methoxy-*N*-methyl-tetradec-4-enamide [malyngamide M (1)][6]

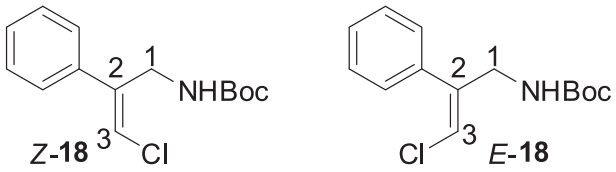


Malyngamide M (**1**)

To a solution of isomalyngamide M (27 mg, 0.06 mmol) in CH_2Cl_2 (20 mL) was added benzophenone (4 mg, 0.02 mmol). The reaction mixture was irradiated with UV-light ($\lambda \geq 300$ nm) for 8 h, then the

solvent was concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc, 2:1) afforded amide malyngamide M (**1**) (18 mg, 67% yield) as a pale yellow oil. $[\alpha]_D^{20}$ −31 (*c* 0.1, MeOH) [Ref. 6 $[\alpha]_D^{20}$ −35 (*c* 0.06, MeOH)]; IR (KBr): 3275, 2927, 2855, 1629, 1463, 1209, 1095, 972, 746 cm^{-1}; ^1H NMR (Me_2CO-d_6, 400 MHz) δ 0.88 (t, 3H, *J*=6.2 Hz, H-14), 1.20–1.39 (m, 10H, 5×CH_2, H-9, H-10, H-11, H-12, and H-13), 1.40–1.45 (m, 2H, CH_2, H-8), 2.12–2.20 (m, 2H, H-6), 2.21 (s, 3H, H-7″), 2.28–2.33 (q, 2H, *J*=7.4 Hz, H-3), 2.52 (t, 2H, *J*=7.4 Hz, H-2), 3.12–3.16 (m, 1H, H-7), 3.27 (s, 3H, OCH_3, H-15), 3.29 (s, 3H, NCH_3), 4.10 (s, 2H, H-1′), 5.50–5.54 (m, 2H, H-4 and H-5), 6.39 (s, 1H, H-3′), 6.73 (t, 1H, *J*=7.4 Hz, H-5″), 6.85 (d, 1H, *J*=7.4 Hz, H-6″), 7.07 (d, 1H, *J*=7.4 Hz, H-4″), 8.95 (br, 1H, ArOH); ^{13}C NMR (Me_2CO-d_6, 100 MHz) δ 14.3 (CH_3, C-14), 16.4 (CH_3, C-7″), 23.3 (CH_2, C-13), 25.9 (CH_2, C-9), 28.6 (CH_2, C-3), 29.9 (CH_2, C-10), 30.1 (CH_2, C-11), 32.5 (CH_2, C-12), 33.6 (CH_2, C-2), 34.1 (CH_2, C-8), 37.2 (CH_2, C-6), 38.0 (NCH_3), 53.8 (CH_2, C-1′), 56.5 (OCH_3, C-15), 81.3 (CH, C-7), 116.8 (CH, C-3′), 119.6 (CH, C-5″), 123.1 (C, C-1″), 126.1 (C, C-3″), 128.1 (CH, C-5), 128.2 (CH, C-6″), 131.5 (CH, C-4″), 131.9 (CH, C-4), 138.6 (C, C-2′), 153.5 (C, C-2″), 174.2 (C, C-1); HRMS (ESI) *m*/*z* $C_{26}H_{41}ClNO_3$ $[M+H]^+$ calcd for 450.2769, found 450.2763.

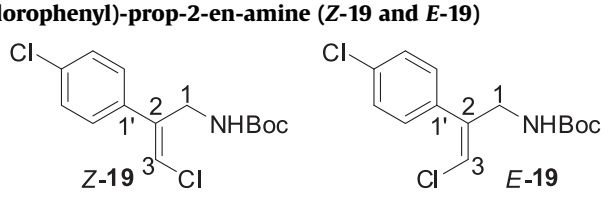
4.16. (*Z*)/(*E*)-*N*-(*tert*-Butoxycarbonyl)-3-chloro-2-phenyl-prop-2-en-amine (*Z*-18 and *E*-18)



As above described procedure for the preparation of **9**, 2-*N*-(*tert*-butoxycarbonyl)amino-1-phenylethanone[21] (235 mg, 1.00 mmol) afforded vinyl chloride *Z*-**18** (*Z*-**18**/*E*-**18**=1:1) (116 mg, 43% yield) as a white solid. Mp 157–158 °C; IR (KBr): 3422, 3005, 2970, 1715, 1421, 1363, 1221, 1092, 902, 786 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 9H, 3×CH_3), 4.40 (d, *J*=5.6 Hz, 2H, NCH_2), 4.64 (br, 1H, NH), 6.38 (s, 1H, H-3), 7.26–7.36 (m, 5H, 5×ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3 (CH_3), 39.6 (NCH_2), 79.5 (C), 118.3 (CH, C-3), 126.5 (ArCH), 128.2 (ArCH), 128.6 (ArCH), 137.2 (C, C-2), 140.1 (ArC), 155.6 (ArC); HRMS (ESI) *m*/*z* $C_{14}H_{18}ClNO_2Na$ $[M+Na]^+$ calcd for 290.0918, found 290.0921. The *Z*-configuration of *Z*-**18** was confirmed by its NOE experiment. Selective irradiation of H-3 of **18** resulted in signal enhancement of H-6′. However, there is no signal enhancement of H-3 when irradiated H-1.

According to the preceding procedure for the preparation of malyngamide M (**1**), *Z*-**18** (20 mg, 0.07 mmol) afforded *E*-**18** (9 mg, 45% yield) as a white solid. Mp 74.0–75.0 °C; IR (KBr): 3390, 2979, 1702, 1490, 1367, 1250, 1166, 1092, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H, 3×CH_3), 4.08 (d, *J*=5.2 Hz, 2H, NCH_2), 4.61 (br, 1H, NH), 6.34 (s, 1H, H-3), 7.27–7.43 (m, 5H, 5×ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3 (CH_3), 45.7 (NCH_2), 79.7 (C), 116.2 (CH, C-3), 128.1 (ArCH), 128.3 (ArCH), 128.4 (ArCH), 135.6 (C, C-2), 139.7 (ArC), 155.5 (ArC); HRMS (ESI) *m*/*z* $C_{14}H_{18}ClNO_2Na$ $[M+Na]^+$ calcd for 290.0918, found 290.0921.

4.17. (*Z*)/(*E*)-*N*-(*tert*-Butoxycarbonyl)-3-chloro-2-(4-chlorophenyl)-prop-2-en-amine (*Z*-19 and *E*-19)



As above described procedure for the preparation of **9**, 2-*N*-(*tert*-butoxycarbonyl)amino-1-(4-chlorophenyl) ethanone[22] (270 mg, 1.00 mmol) afforded vinyl chloride *Z*-**19** (*Z*-**19**/*E*-**19**=1:1) (160 mg, 53% yield) as a white solid. Mp 142.0–143.0 °C; IR (KBr): 3413, 3005, 2925, 1715, 1422, 1363, 1221, 1093, 902, 786 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H, 3×CH_3), 4.37 (d, *J*=5.2 Hz, 2H, NCH_2), 4.64 (br, 1H, NH), 6.38 (s, 1H, H-3), 7.27–7.31 (m, 4H, 4×ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3 (CH_3), 39.5 (NCH_2), 79.7 (C), 118.8 (CH, C-3), 128.0 (ArCH), 128.8 (ArCH), 134.2 (ArC), 135.7 (ArC), 139.4 (C-2), 155.6 (ArC); HRMS (ESI) *m*/*z* $C_{14}H_{21}Cl_2N_2O_2$ $[M+NH_4]^+$ calcd for 319.0975, found 317.0983. The *Z*-configuration of *Z*-**19** was confirmed by its NOE experiment. Selective irradiation of H-3 of **19** resulted in signal enhancement of H-6′. However, there is no signal enhancement of H-3 when irradiated H-1.

According to the preceding procedure for the preparation of malyngamide M (**1**), *Z*-**19** (50 mg, 0.16 mmol) afforded *E*-**19** (26 mg, 43% yield) as a white solid. Mp 62.0–63.0 °C; IR (KBr): 3369, 2919, 1716, 1366, 1217, 1168, 1026, 786 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H, 3×CH_3), 4.04 (d, *J*=4.8 Hz, 2H, NCH_2), 4.63 (br, 1H, NH), 6.33 (s, 1H, H-3), 7.26–7.28 (m, 2H, 2×ArH), 7.35–7.38 (m, 2H, 2×ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3 (CH_3), 45.5 (NCH_2), 79.9 (C), 116.7 (CH, C-3), 128.6 (ArCH), 129.8 (ArCH), 133.9 (ArC), 134.0 (ArC), 138.7 (C-2), 155.4 (ArC); HRMS (ESI) *m*/*z* $C_{14}H_{21}Cl_2N_2O_2$ $[M+NH_4]^+$ calcd for 319.0975, found 317.0983.

Acknowledgements

The authors are grateful to the National Basic Research Program of China (973 Program) (Grant No. 2010CB833203), the National Natural Science Foundation of China (Grant Nos. 20872055 and 20972060), Specialized Research Fund for the Doctoral Program of Higher Education, and the 111 Project for continuing financial support. We also gratefully acknowledge Professor Hak-Fun Chow, The Chinese University of Hong Kong, for his helpful guidance in revising the manuscript.

References and notes

1. (a) Cardellina, J. H., II; Dalietos, D.; Marner, F. J.; Mynderse, J. S.; Moore, R. E. *Phytochemistry* **1978**, *17*, 2091; (b) Li, Y.; Feng, J. P.; Wang, W. H.; Chen, J.; Cao, X. P. *J. Org. Chem.* **2007**, *72*, 2344 and reference therein.
2. Suntornchashwej, S.; Suwanborirux, K.; Isobe, M. *Tetrahedron* **2007**, *63*, 3217.
3. Feng, J. P.; Shi, Z. F.; Li, Y.; Zhang, J. T.; Qi, X. L.; Chen, J.; Cao, X. P. *J. Org. Chem.* **2008**, *73*, 6873.
4. Chen, J.; Li, Y.; Cao, X. P. *Tetrahedron: Asymmetry* **2006**, *17*, 933.
5. Chen, J.; Fu, X. G.; Zhou, L.; Zhang, J. T.; Qi, X. L.; Cao, X. P. *J. Org. Chem.* **2009**, *74*, 4149 and reference therein.
6. Kan, Y.; Fujita, T.; Nagai, H.; Sakamoto, B.; Hokama, Y. *J. Nat. Prod.* **1998**, *61*, 152.
7. Li, Y.; Chen, J.; Cao, X. P. *Synth.* **2006**, 320.
8. Toyoda, T.; Sasakura, K.; Sugasawa, T. *J. Org. Chem.* **1981**, *46*, 189.
9. (a) Peese, K. M.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 8734; (b) Ursini, C. V.; Mazzeo, F.; Rodrigues, J. A. R. *Tetrahedron: Asymmetry* **2006**, *17*, 3335; (c) Peach, P.; Cross, D. J.; Kenny, J. A.; Mann, I.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron* **2006**, *62*, 1864.
10. (a) Chrovian, C. C.; Knapp-Reed, B.; Montgomery, J. *Org. Lett.* **2008**, *10*, 811; (b) Jin, Y. L.; Kim, S.; Kim, Y. S.; Kim, S. A.; Kim, H. S. *Tetrahedron Lett.* **2008**, *49*, 6835.
11. (a) Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2006**, *8*, 2839; (b) Vallinayagam, R.; Schmitt, F.; Barge, J.; Wagnieres, G.; Wenger, V.; Neier, R.; Juillerat-Jeanneret, L. *Bioconjugate Chem.* **2008**, *19*, 821.
12. (a) Kahnberg, P.; Lee, C. W.; Grubbs, R. H.; Sterner, O. *Tetrahedron* **2002**, *58*, 5203; (b) Kahnberg, P.; Sterner, O. *Tetrahedron* **2001**, *57*, 7181; (c) Gruijters, B. W. T.; Veldhuizen, A. V.; Weijers, C. A. G. M.; Wijnberg, J. B. P. A. *J. Nat. Prod.* **2002**, *65*, 558.
13. Ardá, A.; Soengas, R. G.; Nieto, M. I.; Jiménez, C.; Rodríguez, J. *Org. Lett.* **2008**, *10*, 2175.
14. Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708.
15. (a) Paterson, I.; Razzak, M.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 3295; (b) Corey, E. J.; Fuch, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
16. (a) Dryden, H. L., Jr.; Webber, G. M.; Burtner, R. R.; Cella, J. A. *J. Org. Chem.* **1961**, *26*, 3237; (b) Guo, Z.; Schultz, A. G. *J. Org. Chem.* **2001**, *66*, 2154.
17. Xu, L. B.; Jin, J.; Lal, M.; Daublain, P.; Newcomb, M. *Org. Lett.* **2007**, *9*, 1837.
18. (a) Todd, J. S.; Gerwick, W. H. *Tetrahedron Lett.* **1995**, *36*, 7837; (b) Wu, M.; Milligan, K. E.; Gerwick, W. H. *Tetrahedron* **1997**, *53*, 15983; (c) Gallimore, W. A.; Scheuer, P. J. *J. Nat. Prod.* **2000**, *63*, 1422; (d) Milligan, K. E.; Márquez, B.; Williamson, R. T.; Davies-Coleman, M.; Gerwick, W. H. *J. Nat. Prod.* **2000**, *63*, 965; (e) Kan, Y.; Sakamoto, B.; Fujita, T.; Nagai, H. *J. Nat. Prod.* **2000**, *63*, 1599.

19. (a) Saltiel, J.; Neuberger, K. R.; Wrighton, M. *J. Am. Chem. Soc.* **1969**, *91*, 3658; (b) Arai, T.; Wakabayashi, T.; Sakuragi, H.; Tokumaru, K. *Chem. Lett.* **1985**, 279.
20. (a) Virolleaud, M. A.; Menant, C.; Fenet, B.; Piva, O. *Tetrahedron Lett.* **2006**, *47*, 5127; (b) Fryhle, C. B.; Williard, P. G.; Rybak, C. M. *Tetrahedron Lett.* **1992**, *33*, 2327; (c) Müller, C.; Voss, G.; Gerlach, H. *Liebigs Ann.* **1995**, 673; (d) Sankaranarayanan, S.; Sharma, A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **1996**, *7*, 2639; (e) Mesguiche, V.; Valls, R.; Piovetti, L.; Peiffer, G. *Tetrahedron Lett.* **1999**, *40*, 7473; (f) Braddock, D. C.; Matsuno, A. *Synlett* **2004**, 2521.
21. Gilmore, N. J.; Jones, S.; Muldowney, M. P. *Org. Lett.* **2004**, *6*, 2805.
22. Cho, B. T.; Shin, S. H. *Bull. Korean Chem. Soc.* **2004**, *25*, 747.