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First stereoselective synthesis of serinol-derived malyngamides and their 1′-*epi*-isomers

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Received 23 January 2006; accepted 28 February 2006
Available online 4 April 2006

Abstract—A stereoselective synthesis of **1a** {*N*-[(1*R*)-2-hydroxy-1-methoxy-methyl ethyl]-(4*E*,7*S*)-7-methoxy-4-eicosenamide} has been accomplished in 10 steps from 1-tetradecanol for the first time in 28% overall yield. The key steps involved the coupling reaction of a chiral alkyne with a protected bromide in the presence of *t*-BuLi, as well as the amidation reaction of (4*E*,7*S*)-7-methoxyeicos-4-enoic acid with (*R*)-methoxyamino alcohol. Acetylation of **1a** finished the preparation of **1b** {*N*-[(1*S*)-2-acetyloxy-1-methoxy-methyl ethyl]-(4*E*,7*S*)-7-methoxy-4-eicosenamide}. Their 1′-*epi*-isomers have also been synthesized with a similar strategy.

1. Introduction

Cyanobacteria of the genus *Lyngbya* is 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 bears a heteroatom or a vinylic chloride functional group. Since 1978, 29 malyngamides have been isolated.[1] Compounds **1a** {*N*-[(1*R*)-2-hydroxy-1-methoxy-methyl ethyl]-(4*E*,7*S*)-7-methoxy-4-eicosenamide} and **1b** {*N*-[(1*S*)-2-acetyloxy-1-methoxy-methyl ethyl]-(4*E*,7*S*)-7-methoxy-4-eicosenamide} belong to the malyngamides family because their fatty acid component **6** contains a *trans*-double bond and a 7*S* stereogenic center as its homologues (Fig. 1). All of the malyngamides possess similar fatty acid portion **3** [(4*E*,7*S*)-7-methoxydodec-4-enoic acid],[1j] **4** [(4*E*,7*S*)-7-methoxytetradec-4-enoic acid],[2a] **5** [(4*E*,7*S*)-7-methoxy-9-methylheptadec-4-enoic acid],[2b] and **6** [(4*E*,7*S*)-7-methoxyeicos-4-enoic acid].[3] Malyngamides **1a** and **1b** were isolated from a blue-green alga collected at the mouth of the King George River in northwestern Australia by Erickson et al. in 1999, which display weak anti-HIV activity.[3] The amount of these in Nature, which can only be obtained by preparative TLC was very limited, and the synthesis of **1a** and **1b** had not been reported. Attracted by their potential activity, and to provide material for more extensive biological evaluation, along with access to a promising general procedure for these analogues, we have undertaken the first synthesis of the serinol-derived malyngamides.

The structure of target molecule **1a** can be divided into two parts by retrosynthetic analysis (Scheme 1). One was regarded as the long fatty acid **6** with a stereogenic center and the other belonged to the derivative of serinol. The earlier synthesis of homologous fatty acids not only had some drawbacks such as low yield, multi-steps, rather inaccessible synthons, but also the resulting product was frequently a racemic mixture.[4] Moreover, the route for the synthesis of (±)-**3** led to the geometric isomers (*Z*:*E*, 3:1).[4d] Recently, the stereoselective synthesis of fatty acid **3** had been accomplished by us.[5] The stereogenic center was constructed by catalytic asymmetric allylation reaction and the *trans*-double bond was evolved (only *E*-configuration) using sodium in ammonia (l) reduction successfully. This result promoted us to follow a similar method on the aliphatic chain counterpart with the aim of obtaining direct access to these homologous fatty acids. Hence, the preparation of acid **6** would be achieved through the above two key reactions. Simultaneously, the other part of **1a** would be synthesized from chiral starting material D-serine by the method of Meyers et al.[6] Having secured a convenient entry to the stereochemically pure acid and methoxyamino alcohol, the target molecule **1a** would be constructed easily by the

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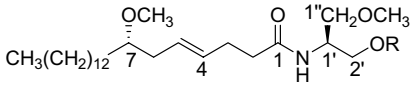
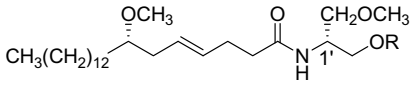
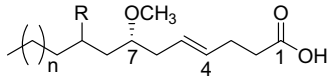
doi:10.1016/j.tetasy.2006.02.027



1a, R = H, *N*-[(1*R*)-2-hydroxy-1-methoxy-methyl ethyl]-(4*E*,7*S*)-7-methoxy-4-eicosenamide
1b, R = $COCH_3$, *N*-[(1*S*)-2-acetyloxy-1-methoxy-methyl ethyl]-(4*E*,7*S*)-7-methoxy-4-eicosenamide

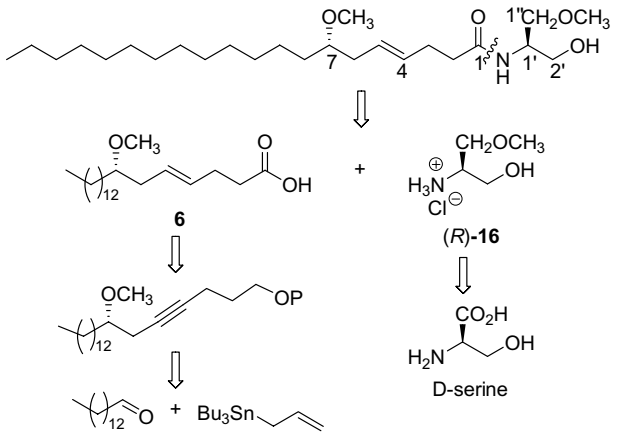


2a, (1'-*epi* **1a**), R = H
2b, (1'-*epi* **1b**), R = $COCH_3$



	n	R	
3,	1	H	(4*E*,7S)-7-methoxydodec-4-enoic acid
4,	3	H	(4*E*,7*S*)-7-methoxytetradec-4-enoic acid
5,	5	CH_3	(4*E*,7*S*)-7-methoxy-9-methylheptadec-4-enoic acid
6,	9	H	(4*E*,7*S*)-7-methoxyeicos-4-enoic acid

Figure 1. Structure of **1a**, **1b**, **2a**, **2b**, and **3**–**6**.



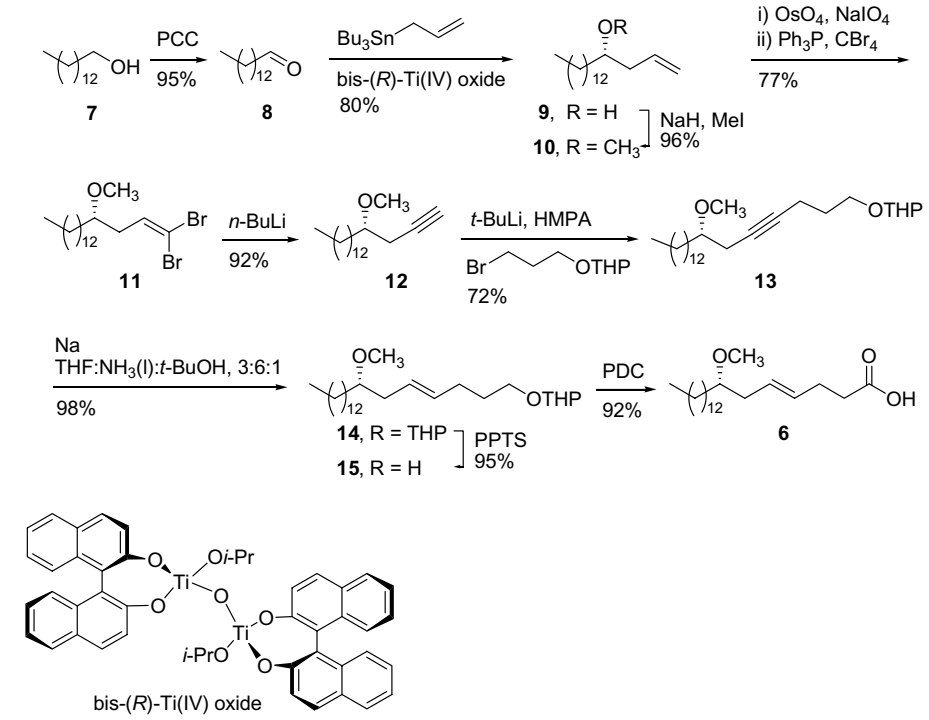
Scheme 1. Retrosynthetic analysis of **1a**.

amidation reaction of acid **6** with (*R*)-**16**. Acetylation of **1a** could generate **1b**. Compound **2a** (1′-*epi* **1a**) and **2b** (1′-*epi* **1b**) could also be synthesized via a similar strategy in order to study the activity–stereochemistry relationship.

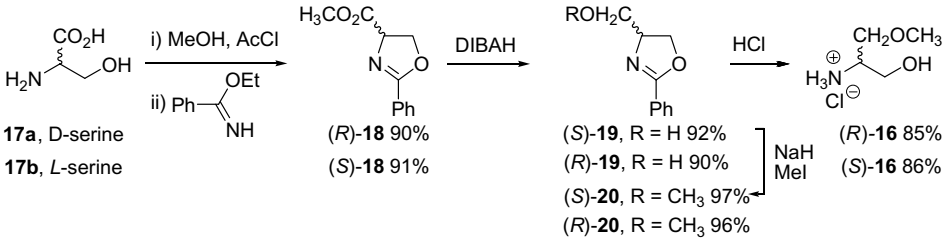
2. Results and discussion

As shown in Scheme 2, 1-tetradecanol **7** was chosen as the starting material, which was then oxidized by pyridinium chlorochromate (PCC) in CH_2Cl_2 at room temperature to give aldehyde **8** in 95% yield.[7] The reaction of compound **8** with allyltributyltin in the presence of a catalytic amount of bis-(*R*)-Ti(IV) oxide (bis{[(*R*)-binaphthoxy](isopropoxy)titanium}oxide) afforded chiral alcohol **9** in 80% yield (98% ee for its 4-nitrobenzoate).[5,8] Alcohol **9** was treated with CH_3I in the presence of NaH to give its methyl derivative **10** in 96% yield. The double bond of **10** was dihydroxylated with OsO_4 using 4-methylmorpholine *N*-oxide (NMO) as a co-oxidant, followed by treatment with $NaIO_4$ to afford the corresponding aldehyde. This aldehyde was then reacted with PPh_3/CBr_4 to produce dibromide **11** in 77% yield for the two steps. Dibromide **11** was treated with 2.2 equiv *n*-BuLi to afford alkyne **12** in 92% yield. When using the literature procedure,[9] only the elimination by-product was obtained. Here, it was important that the reaction temperature had to be kept below −10 °C for the whole reaction. The coupling reaction of compound **12** with 3-bromo-1-tetrahydropyranyloxypropane[10] in the presence of *t*-BuLi gave the key intermediate **13** in 72% yield.[5] Stereocontrolled reduction of **13** with sodium in ammonia (l) in the presence of *t*-BuOH produced compound **14** in near quantitative yield with *E*-configuration.[11] At first, conversion was incomplete. Research showed that alkene **14** and alkyne **13** could not be separated due to the long chain. Hence the reduction of **13** must be thoroughly completed. After many trials, the appropriate ratio of solvents (THF/ammonia (l)/*t*-BuOH, 3:6:1) was found to carry out this reducing procedure smoothly. Sequentially, the deprotection of the tetrahydro-2*H*-pyran (THP) group of **14** by a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) afforded alcohol **15** in 95% yield.[12] Finally, the hydroxyl group of **15** was oxidized with pyridinium dichromate (PDC) to give acid **6** in 92% yield. The configuration and diastereomeric purity of compound **6** was determined by comparing the spectral data of NMR and specific rotation value within the literature. It was observed that the maximum error in chemical shifts were all less than 0.1 ppm in ^1H NMR and ^{13}C NMR spectra, and its specific rotation value matched that reported $\{[\alpha]_D^{16} = -10$ (*c* 0.2, $CHCl_3$), Ref. 3 $[\alpha]_D^{20} = -8.3$ (*c* 0.18, $CHCl_3$)$\}$.[3] These facts not only confirmed that acid **6** was the 7*S* isomer, but also indicated the good stereoselectivity of this method.

In a parallel sequence, using the Meyers' method,[6] D-serine **17a** or L-serine **17b** was chosen as the starting material for



Scheme 2. Synthesis of **6**.



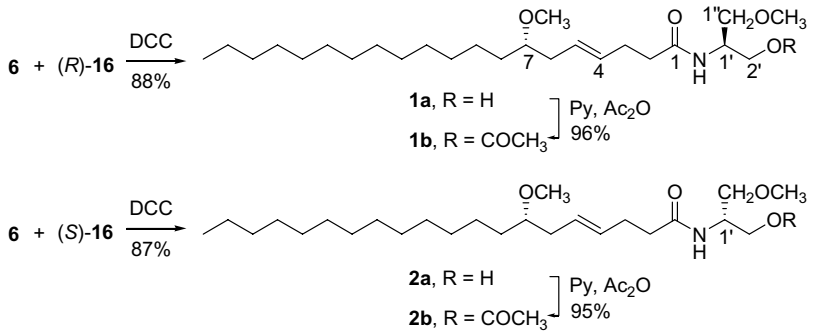
Scheme 3. Preparation of **16**.

synthesis of the serinol-derived synthon (Scheme 3). Thus, the esterification of **17a** or **17b** and the reaction with ethyl benzimidate gave either oxazoline (*R*)-**18** or (*S*)-**18** in 90% or 91% yield over two steps, respectively. The reduction of oxazoline **18** with diisobutylaluminum hydride (DIBAL) produced alcohol (*S*)-**19** or (*R*)-**19** in 92% or 90% yield. Alkylation of alcohol **19** with CH_3I in the presence of NaH afforded its methoxy derivative (*S*)-**20** or (*R*)-**20** in 97% or 96% yield. The methoxy oxazoline **20** was cleaved by heating in 4 M hydrochloric acid to produce (*R*)-2-amino-3-methoxypropan-1-ol hydrochloride (*R*)-**16** or (*S*)-2-amino-3-methoxypropan-1-ol hydrochloride (*S*)-**16** in 85% or 86% yield.

It should be noted that the (*R*)-**16** displayed an $[\alpha]_D^{16} = -2$ (*c* 1.8, EtOH) while the (*S*)-**16** displayed an $[\alpha]_D^{16} = +4$ (*c* 2.8, EtOH), while Meyers only reported an $[\alpha]_D^{20} = -1.9$ (*c* 1.8, EtOH) for the (*S*)-**16** and no data for (*R*)-**16**.[6] This outcome was identical with Erickson's views.[3] The NMR spectra of these compounds were recorded in D_2O due to their poor solubility in $CDCl_3$ (the data of NMR were recorded in $CDCl_3$ in the literature). Hence the spectral data (^1H and ^{13}C NMR) of **16** were slightly different from the reported data.[6] The maximum chemical shift error was 1.6 ppm in ^{13}C NMR.

Sequentially, the reaction of acid **6** with (*R*)-**16** in the presence of 1,3-dicyclohexylcarbodiimide (DCC) in pyridine produced the target molecule **1a** in 88% yield (Scheme 4). The reaction of **1a** with Ac_2O in pyridine gave **1b** in 96% yield.[3] On the other hand, the reaction of acid **6** with (*S*)-**16** produced **2a** in 87% yield under the same conditions. Acetylation of **2a** gave **2b** in 95% yield.

In the literature,[3] the absolute configuration at C-7 of **1a** had been determined by comparison of the specific rotation value of 7-methoxyeicos-4(*E*)-enoic acid {obtained by hydrolyzation of **1a,** $[\alpha]_D^{20} = -8.3$ (*c* 0.18, $CHCl_3$)} with its analogue **4** {$[\alpha]_D^{20} = -11.1$ (*c* 0.2, $CHCl_3$) and $[\alpha]_D^{20} = -11.3$ (*c* 0.2, $CHCl_3$)}. In our synthesis, the C-7 stereogenic center of **1a** was successfully constructed and confirmed by a classical and credible asymmetric allylation reaction, and intermediate **6** displayed an $[\alpha]_D^{16} = -10$ (*c* 0.2, $CHCl_3$), which was in agreement with the hydrolysis

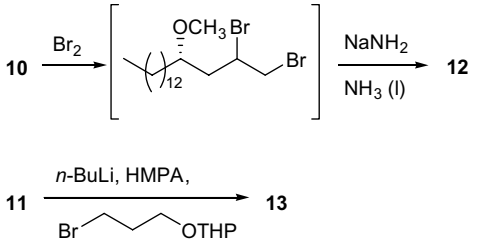


Scheme 4. Synthesis of **1a**, **1b**, **2a**, and **2b**.

product of **1a** reported in the literature. The C-1′ stereogenic center of **1a** was established from D-serine in our synthetic strategy. All of the data (MS, NMR) measured on the synthetic samples of **1a** and **1b** were in good agreement with the reported data,[3] especially when comparing the NMR data of target molecules **1a** and **1b** with those of natural products; it was observed that the maximum error of chemical shift was less than 0.04 ppm for ^{1}H NMR and 0.3 ppm for ^{13}C NMR. The specific rotation values of **1a** $\{[\alpha]_D^{16} = -4$ (c 0.35, $CHCl_3$), Ref. 3 $[\alpha]_D^{20} = -3$ (c 0.33, $CHCl_3$)$\}$ and **1b** $\{[\alpha]_D^{16} = -8$ (c 0.35, $CHCl_3$), Ref. 3 $[\alpha]_D^{20} = -6.1$ (c 0.33, $CHCl_3$)$\}$ were consistent with the natural products. These facts not only confirmed the structures of target molecules further, but also indicated the good stereoselectivity of our synthetic route.

In the assignments of the NMR spectra, we found that the data of **1a** and its *epi*-isomer **2a**, as well as **1b** and its *epi*-isomer **2b** only differed slightly. The reason was due to the large distance between the two stereogenic carbons in the carbon chain.

Alkyne **12** can be constructed in a shorter procedure to that shown in Scheme 5. Bromination of **10** followed by dehydrobromination with $NaNH_2$ also produced **12**.[13] However reaction was difficult to manipulate and the intermediate was unstable. It was hard to separate the pure compound **12** by chromatography from the reaction mixture. In addition, the yield of the two steps was too low. All attempts at trying to improve the product yield by varying the reaction conditions such as the temperature, the reaction time, the amount of Na and the solvent fail to produce any positive results. So the strategy in Scheme 2 was adopted to synthesize **12**.



Scheme 5. One-pot reaction.

Dibromide **11** was then used to directly obtain compound **13**, thus reducing the number of the reaction steps in the synthetic route (Scheme 5).[14] Thus, treatment of dibromide **11** with *n*-BuLi, followed by HMPA and 3-bromo-1-tetrahydropyranyloxypropane, gave compound **13** in 20% yield. Although compound **12** did not need separation, we still gave up this route due to its too low yield.

3. Conclusion

Serinol-derived malyngamides **1a** and **1b** and its *epi*-isomers have been synthesized stereoselectively for the first time. A convenient and rapid synthetic method was presented. The synthetic transformation utilized readily available starting materials. The synthetic routes were facile and the yields satisfactory, hence all of the reactions can be performed on a large scale. Moreover, the absolute configuration of **1a** at C-7 position was further confirmed by synthesis. The method was also general to the synthesis of the malyngamide family. The investigation of biological activity of these compounds is in progress.

4. Experimental

4.1. General

Melting points were measured on a XT-4 mp apparatus. The optical rotation was measured with a TE 342 polarimeter. Nuclear magnetic resonance (NMR) spectra were recorded on a Mercury Plus-300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) and Mercury Plus-400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) referenced to TMS or residual $CHCl_3$. Chemical shifts (δ) are reported in parts per million and coupling constants (J) in Hertz. Infrared spectra (IR) were recorded on a Nicolet AVATAR 360 FT-IR spectrophotometer and reported in wave numbers (cm^{-1}). Mass spectra (MS) data were obtained on a HP-5988A and high resolution mass spectra (HRMS) data were obtained on a Bruker Daltonics APEX II 47e mass spectrometers. All materials were used directly as commercially available analytic purity. Anhydrous reactions were carried out under argon atmosphere using freshly dried solvents. Column chromatography was generally performed on silica gel (200–300 mesh) and TLC inspection on silica gel GF_{254} plates.

4.2. Tetradecanal, 8[8a]

Following a literature precedent,[7] alcohol **7** (200 mg, 0.93 mmol) in CH_2Cl_2 (4.8 mL) was oxidized with PCC (400 mg, 1.80 mmol) to afford compound **8** as a ceraceous white solid (187 mg, 95% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $J = 6.6$ Hz, 3H, CH_3), 1.26–1.29 (m, 20H, $10 \times CH_2$), 1.60–1.65 (m, 2H, CH_2), 2.40–2.50 (m, 2H, CH_2), 9.77 (t, $J = 1.8$ Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 22.0, 22.7, 29.1, 29.3, 29.6 (overlapping signals), 31.9, 43.9, 202.9; MS (EI) m/z (%): 212 (M^+, 2), 194 (10), 168 (20), 109 (40), 57 (100).

4.3. (*S*)-4-Hydroxy-1-heptadecene, 9

Following a similar method to the reference,[5,8] to a stirred solution of $TiCl_4$ (22 μL, 0.20 mmol) in CH_2Cl_2 (2 mL) was added Ti(*i*-PrO)$_4$ (0.18 mL, 0.60 mmol) at 0 °C under an argon atmosphere. The solution was allowed to warm to room temperature. After 3 h, Ag_2O (92 mg, 0.40 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 (4 mL), and treated with (*R*)-binaphthol (286 mg, 0.80 mmol) at room temperature for 2 h to furnish the 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 compound **8** (848 mg, 4.00 mmol) in CH_2Cl_2 (2 mL) and allyltributyltin (1.38 mL, 4.40 mmol) at this temperature. The reaction was allowed to warm to 0 °C and stirred for 20 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL), and extracted with ether (3×20 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel column (petroleum ether/ethyl acetate, 30:1) afforded **9** as a ceraceous white solid (813 mg, 80% yield). The enantioselectivity of the asymmetric allylation product **9** has been determined as 98% ee by conversion to its 4-nitrobenzoate. For the measurement of enantiomeric excess, the alcohol was converted into its 4-nitrobenzoate because the HPLC apparatus used a UV detector,[15] followed by analysis with a Waters HPLC {Chiralcel OJ, *i*-PrOH/hexane = 1:99, flow rate = 0.4 mL/min, $t_R = 10.432$ min [(*R*)-isomer], $t_R = 10.974$ min [(*S*)-isomer]} in comparison with the racemic sample. $[\alpha]_D^{17} = -5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $J = 6.6$ Hz, 3H, CH_3), 1.05–1.46 (m, 24H, $12 \times CH_2$), 1.67 (br, 1H, OH), 2.09–2.34 (m, 2H, H-3), 3.60–3.65 (m, 1H, H-4), 5.11 (d, $J = 12.9$ Hz, 1H, H-1), 5.15 (d, $J = 15.9$ Hz, 1H, H-1), 5.77–5.90 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 22.7, 25.6, 29.3, 29.6 (overlapping signals), 31.9, 36.8, 41.9, 70.6 (t, C-4), 118.0 (s, C-1), 134.9 (t, C-2); MS (EI) m/z (%): 236 ($M-H_2O$, 1), 213 (45), 125 (21), 111 (50), 97 (95), 83 (100). Various attempts to further characterize **9** by high resolution mass spectrometry, including RSI and FAB as ionization techniques, were unsuccessful.

4.4. (*S*)-4-Methoxy-1-heptadecene, 10

To a stirred solution of **9** (320 mg, 1.26 mmol) in THF (5 mL) was added NaH (61 mg, 2.54 mmol) and CH_3I (0.24 mL, 3.85 mmol). The reation mixture was stirred at room temperature for 10 h, then quenched with saturated NH_4Cl solution (5 mL), and extracted with ethyl acetate (3×15 mL). The combined organic layer was washed with saturated brine (40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel column (petroleum ether/ethyl acetate, 90:1) afforded **10** as a pale yellow oil (324 mg, 96% yield). $[\alpha]_D^{17} = -8$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, $J = 6.4$ Hz, 3H, CH_3), 1.26–1.29 (m, 24H, $12 \times CH_2$), 2.24–2.27 (m, 2H, H-3), 3.17–3.23 (m, 1H, H-4), 3.34 (s, 3H, OCH_3), 5.04 (d, $J = 10.4$ Hz, 1H, H-1), 5.08 (d, $J = 15.2$ Hz, 1H, H-1), 5.76–5.87 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 22.7, 25.3, 29.3, 29.7 (overlapping signals), 29.8, 31.9, 33.4, 37.8, 56.5 (p, OCH_3), 80.5 (t, C-4), 116.7 (s, C-1), 135.0 (t, C-2); IR (KBr): ν 3435, 2925, 2854, 1738, 1462, 1099, 913 cm^{-1}; HRMS (ESI) $C_{18}H_{40}NO$ $[M+NH_4]^+$ calcd 286.3104, found 286.3109.

4.5. (*S*)-1,1-Dibromo-4-methoxyheptadec-1-ene, 11

Using a similar method to the Corey–Fuchs' reaction,[9] to a stirred solution of **10** (210 mg, 0.78 mmol) in THF and H_2O (3 mL, THF/H_2O, 3:1) was added NMO (92 mg, 0.79 mmol) and OsO_4 (4 mg). The reaction mixture was stirred at room temperature for 2 days. The reaction mixture was quenched with saturated Na_2SO_3 solution (10 mL) and extracted with ethyl acetate (3×20 mL). The combined organic extracts were concentrated in vacuo to give the diol. The crude diol was dissolved in THF and H_2O (10 mL, THF/H_2O, 1.25:1), then $NaIO_4$ (260 mg, 1.17 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, then quenched with saturated $Na_2S_2O_3$ solution (10 mL) and extracted with ether (3×20 mL). The organic layer was washed with water, dried over $MgSO_4$, 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 (4 mL) was added to a stirred solution of CBr_4 (520 mg, 1.58 mmol) and PPh_3 (870 mg, 3.32 mmol) in CH_2Cl_2 (20 mL) at 0 °C, the reaction was stirred for 1 h, then was concentrated in vacuo. Flash chromatography of the residue over silica gel column (petroleum ether/ethyl acetate, 90:1) afforded **11** as a pale yellow oil (255 mg, 77% yield). $[\alpha]_D^{17} = -10$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $J = 6.6$ Hz, 3H, CH_3), 2.19–2.38 (m, 24H, $12 \times CH_2$), 2.26–2.34 (m, 2H, H-3), 3.26–3.34 (m, 1H, H-4), 3.34 (s, 3H, OCH_3), 6.48 (t, $J = 6.9$ Hz, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 22.7, 25.3, 29.4, 29.6 (overlapping signals), 29.7, 31.9, 33.6, 36.8 (s, C-3), 56.7 (p, OCH_3), 79.2 (t, C-4), 89.7 (q, C-1), 135.1 (t, C-2); IR (KBr): ν 3406, 2923, 2852, 1462, 1092, 966 cm^{-1}; MS (ESI) m/z (%): 447 ($[M+Na]^+$ 100), 425 ($[M+H]^+$ 49). Various attempts to further characterize **11** by high resolution mass spectrometry, including RSI and FAB as ionization techniques were unsuccessful.

4.6. (*S*)-4-Methoxy-1-heptadecyne, 12

To a stirred solution of dibromide **11** (160 mg, 0.38 mmol) in THF (12 mL) was added *n*-BuLi (0.34 mL, 0.85 mmol, 2.5 M in hexane) at −78 °C under an argon atmosphere. Stirring was continued at this temperature for 1 h and the

temperature then warmed to −10 °C slowly. The reaction was quenched with water (10 mL), and extracted with ethyl acetate (3 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/ethyl acetate, 80:1) afford **12** as a pale yellow oil (93 mg, 92% yield). $[\alpha]_D^{16} = -20$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $J = 6.6$ Hz, 3H, CH_3), 1.26–1.61 (m, 24H, 12 × CH_2), 2.00 (t, $J = 2.1$ Hz, 1H, H-1), 2.39 (dd, $J = 4.8$ and 3.0 Hz, 2H, H-3), 3.28–3.32 (m, 1H, H-4), 3.38 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 22.7, 23.0, 25.2, 29.4, 29.6 (overlapping signals), 31.9, 33.5, 57.0 (p, OCH_3), 69.7 (t, C-1), 79.2 (t, C-4), 81.1 (q, C-2); IR (KBr): *v* 3312, 2925, 2854, 2120, 1462, 1106, 631 cm^{-1}; HRMS (ESI) $C_{18}H_{38}NO$ $[M+NH_4]^+$ calcd 284.2948, found 284.2952.

4.7. (*S*)-7-Methoxy-1-tetrahydropyranyloxy-4-icosyne, 13

Using a similar method,[5] to a stirred solution of **12** (80 mg, 0.30 mmol) in THF (4 mL) was added *t*-BuLi (0.2 mL, 0.30 mmol, 1.5 mol/L in pentane) at 0 °C under argon atmosphere. Stirring was continued at this temperature for 45 min, then HMPA (0.7 mL) was added to this solution and followed by 3-bromo-1-tetrahydropyranyloxypropane (70 mg, 0.30 mmol, in THF 1 mL), which was prepared according to the reference.[10] The reaction mixture was allowed to warm to room temperature and stirred there for 2 h, then quenched by saturated NH_4Cl solution (5 mL), and extracted with ethyl acetate (3 × 10 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel column (petroleum ether/ethyl acetate, 40:1) afforded **13** as a colorless oil (88 mg, 72% yield). $[\alpha]_D^{16} = -18$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $J = 6.6$ Hz, 3H, CH_3), 1.26–1.85 (m, 32H, 16 × CH_2), 2.26–2.37 (m, 4H, H-3 and 6), 3.22–3.26 (m, 1H, H-7), 3.37 (s, 3H, OCH_3), 3.43–3.54 (m, 2H, OCH_2), 3.76–3.90 (m, 2H, OCH_2), 4.59 (t, $J = 3.5$ Hz, 1H, H-1′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 15.7, 19.5, 22.6, 23.4, 25.2, 25.4, 29.1, 29.3, 29.6 (overlapping signals), 30.6, 31.9, 33.6, 56.9 (p, OCH_3), 62.1, 66.0, 76.9 (q, C≡), 79.8 (t, C-7), 81.0 (q, C≡), 98.7 (t, C-1′); IR (KBr): *v* 3434, 2925, 2854, 1640, 1461, 1114, 1033, 991 cm^{-1}; HRMS (ESI) $C_{26}H_{52}NO_3$ $[M+NH_4]^+$ calcd 426.3942, found 426.3948.

4.8. (4*E*,7*S*)-7-Methoxy-1-tetrahydropyranyloxy-4-icosene, 14

To dry liquid ammonia (approximate 12 mL) was added sodium metal (80 mg, 3.48 mmol), followed by THF (4 mL) and *t*-BuOH (2 mL, 22.4 mmol). Then a solution of **13** (45 mg, 0.11 mmol) in THF (2 mL) was added immediately. The reaction mixture was held at ammonia reflux for 1 h, quenched by NH_4Cl (200 mg), after the ammonia evaporation, water (10 mL) was added. The mixture was extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel column (petroleum ether/ethyl acetate, 40:1) afforded **14** as a colorless oil (44 mg, 98% yield). $[\alpha]_D^{16} = -17$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $J = 6.3$ Hz, 3H, CH_3), 1.26–1.85 (m, 32H, 16 × CH_2), 2.06–2.21 (m, 4H, H-6 and 3), 3.12–3.16 (m, 1H, H-7), 3.33 (s, 3H, OCH_3), 3.34–3.51 (m, 2H, OCH_2), 3.70–3.90 (m, 2H, OCH_2), 4.58 (t, $J = 3.9$ Hz, 1H, H-1′), 5.36 (dt, $J = 15.9$ and 6 Hz, 1H, H-4 or 5), 5.52 (dt, $J = 15.9$ and 6 Hz, 1H, H-5 or 4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 19.6, 22.6, 25.2, 25.4, 29.3, 29.5, 29.6 (overlapping signals), 29.8, 30.7, 31.9, 33.3, 36.3, 56.4 (p, OCH_3), 62.2, 66.9, 80.8 (t, C-7), 98.7 (t, C-1′), 126.5 (t, CH=), 132.0 (t, CH=); IR (KBr): *v* 3416, 2925, 2854, 1461, 1354, 1120, 1099, 1031, 970 cm^{-1}; HRMS (ESI) $C_{26}H_{54}NO_3$ $[M+NH_4]^+$ calcd 428.4098, found 428.4092.

4.9. (4*E*,7*S*)-7-Methoxyicos-4-en-1-ol, 15

To a stirred solution of **14** (40 mg, 0.10 mmol) in ethanol (5 mL) was added PPTS (cat.), then the reaction mixture was stirred for 5 h at 62 °C. The reaction mixture was concentrated in vacuo. Flash chromatography of the residue over a silica gel column (petroleum ether/ethyl acetate, 10:1) afforded **15** as a colorless oil (31 mg, 95% yield). $[\alpha]_D^{16} = -11$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.86 (t, $J = 6.6$ Hz, 3H, CH_3), 1.23–1.64 (m, 26H, 13 × CH_2), 2.01 (br, 1H, OH), 2.08–2.19 (m, 4H, H-6 and 3), 3.12–3.16 (m, 1H, H-7), 3.30 (s, 3H, OCH_3), 3.63 (t, $J = 6.1$ Hz, 2H, H-1), 5.42 (dt, $J = 15.9$ and 5.1 Hz, 1H, H-4 or 5), 5.47 (dt, $J = 15.9$ and 5.1 Hz, 1H, H-5 or 4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 22.6, 25.2, 29.1, 29.3, 29.6 (overlapping signals), 29.8, 31.9, 32.2, 33.2, 36.3, 56.4 (p, OCH_3), 62.3 (s, C-1), 80.7 (t, C-7), 126.7 (t, CH=), 132.1 (t, CH=); IR (KBr): *v* 3429, 2924, 2853, 1635, 1460, 1102, 1062, 968, 719 cm^{-1}; HRMS (EI) $C_{20}H_{38}O$ $[M-CH_3OH]^+$ calcd 294.2917, found 294.2920.

4.10. (4*E*,7*S*)-7-Methoxyicos-4-enoic acid, 6[3]

To a stirred solution of **15** (29 mg, 0.09 mmol) in DMF (0.7 mL) was added PDC (173 mg, 0.46 mmol) at room temperature. After 10 h, the mixture was quenched with cold water (5 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with $KHSO_4$ (20 mL, 1 mol/L), water (20 mL), and brine (20 mL), respectively, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel column (CH_2Cl_2/MeOH, 40:1) afforded **6** as a colorless oil (28 mg, 92% yield). $[\alpha]_D^{16} = -10$ (*c* 0.2, $CHCl_3$) {Ref. 3 $[\alpha]_D^{20} = -8.3$ (*c* 0.18, $CHCl_3$)}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, $J = 6.6$ Hz, 3H, CH_3), 1.19–1.42 (m, 24H, 12 × CH_2), 2.19–2.45 (m, 6H, H-2, 3, and 6), 3.13–3.17 (m, 1H, H-7), 3.32 (s, 3H, OCH_3), 5.49 (m, 2H, H-4 and 5); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 22.7, 25.2, 27.6, 29.4, 29.6 (overlapping signals), 29.8, 31.9, 33.3, 33.9, 36.3, 56.5 (p, OCH_3), 80.8 (t, C-7), 127.8 (t, CH=), 130.1 (t, CH=), 179.2 (q, C-1); IR (KBr): *v* 3427, 2924, 2853, 1712, 1641, 1097, 1068, 617 cm^{-1}; HRMS (ESI) $C_{21}H_{39}O_3$ $[M-H]^-$ calcd 339.2905, found 339.2901.

4.11. *N*-[(1*R*)-2-Hydroxy-1-methoxy-methyl ethyl]-(4*E*,7*S*)-7-methoxy-4-eicosenamide, 1a[3]

A solution of acid **6** (14 mg, 0.04 mmol) in $CHCl_3$ (0.4 mL) was added dropwise to a solution of DCC (11 mg,

0.05 mmol) in $CHCl_3$ (0.7 mL) with stirring at 0 °C. The mixture was stirred for an additional 5 min, and then added over a period of 10 min to a cold solution of (*R*)-**16** (8 mg, 0.06 mmol) in pyridine (1.5 mL). Stirring was then continued for 8 h at 0 °C. After evaporation of the solvent, followed by addition of ether (5 mL), the precipitate of the dicyclohexylurea appeared, which was then filtered. The filtrate was concentrated in vacuo. Flash chromatography of the residue over silica gel column (petroleum ether/ethyl acetate, 3:1) afforded **1a** as a white solid (15 mg, 88% yield). Mp 31–32 °C; $[\alpha]_D^{16} = -4$ (*c* 0.35, $CHCl_3$) {Ref. 3 $[\alpha]_D^{20} = -3$ (*c* 0.33, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (t, $J = 6.6$ Hz, 3H, CH_3), 1.19–1.42 (m, 24H, $12 \times CH_2$), 2.18–2.34 (m, 6H, H-2, 3, and 6), 3.10 (br, 1H, OH), 3.14–3.16 (m, 1H, H-7), 3.31 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.52–3.56 (m, 2H, H-1″), 3.65 (dd, $J = 11.2$ and 4 Hz, 1H, H-2′a), 3.79 (dd, $J = 11.2$ and 4 Hz, 1H, H-2′b), 4.04–4.08 (m, 1H, H-1′), 5.45–5.47 (m, 2H, H-4 and 5), 6.20 (d, 1H, $J = 6.4$ Hz, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (p, C-20), 22.7 (s, C-19), 25.3 (s, C-9), 28.6 (s, C-3), 29.3 (s, C-17), 29.6 (s, overlapping signals), 29.8 (s, C-16), 31.9 (s, C-18), 33.3 (s, C-8), 36.3 (s, C-6), 36.5 (s, C-2), 50.6 (t, C-1′), 56.4 (p, OCH_3), 59.2 (p, OCH_3), 63.9 (s, C-2′), 73.0 (s, C-1″), 80.7 (t, C-7), 127.7 (t, C-5), 130.6 (t, C-4), 173.0 (q, C-1); IR (KBr): ν 3323, 2925, 2854, 1648, 1546, 1461, 1098, 971 cm^{-1}; MS (EI) *m*/*z* (%): 427 (M^+, 1), 408 (5), 394 (32), 227 (30), 182 (85), 129 (100).

4.12. *N*-[(1*S*)-2-Acetyloxy-1-methoxy-methyl ethyl]-(4*E*,7*S*)-7-methoxy-4-eicosenamide, 1b[3]

A mixture of **1a** (17 mg, 0.04 mmol) in dry pyridine (2 mL) and Ac_2O (4 mL) was stirred at room temperature for 2 days. The reaction mixture was dissolved in ether (20 mL) and washed with water (2×20 mL) until the pH was neutral, at which point it was saturated with $NaHCO_3$ solution (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel column (petroleum ether/ethyl acetate, 2:1) afforded **1b** as a white solid (18 mg, 96% yield). Mp 38–39.5 °C; $[\alpha]_D^{16} = -8$ (*c* 0.35, $CHCl_3$) [Ref. 3 $[\alpha]_D^{20} = -6.1$ (*c* 0.33, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $J = 6.0$ Hz, 3H, CH_3), 1.19–1.42 (m, 24H, $12 \times CH_2$), 2.07 (s, 3H, $COCH_3$), 2.19–2.35 (m, 6H, H-2, 3, and 6), 3.12–3.19 (m, 1H, H-7), 3.33 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.37 (dd, 1H, $J = 9.9$ and 3.5 Hz, H-1″a), 3.48 (dd, 1H, $J = 9.9$ and 3.5 Hz, H-1″b), 4.12 (dd, 1H, $J = 11.1$ and 6.0 Hz, H-2′a), 4.17 (dd, 1H, $J = 11.1$ and 6.0 Hz, H-2′b), 4.32–4.36 (m, 1H, H-1′), 5.46–5.50 (m, 2H, H-4 and 5), 6.17 (d, $J = 8.1$ Hz, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (p, C-20), 20.8 (p, $COCH_3$), 22.7 (s, C-19), 25.3 (s, C-9), 28.6 (s, C-3), 29.3 (s, C-17), 29.6 (s, overlapping signals), 29.8 (s, C-16), 31.9 (s, C-18), 33.3 (s, C-8), 36.3 (s, C-6), 36.5 (s, C-2), 47.7 (t, C-1′), 56.5 (p, OCH_3), 59.1 (p, OCH_3), 63.2 (s, C-2′), 71.0 (s, C-1″), 80.6 (t, C-7), 127.5 (t, C-5), 130.6 (t, C-4), 170.9 (q, C=O), 172.2 (q, C-1); MS (EI) *m*/*z* (%): 469 (M^+, 1), 243 (85), 189 (100).

4.13. *N*-[(1*S*)-2-Hydroxy-1-methoxy-methyl ethyl]-(4*E*,7*S*)-7-methoxy-4-eicosenamide, 2a (1′-*epi* 1a)

Similar to the preparation of **1a**, **2a** was obtained from acid **6** (22 mg, 0.06 mmol) and (*S*)-**16** (13 mg, 0.09 mmol) in 87% yield. Mp 31–32.5 °C; $[\alpha]_D^{13} = -8$ (*c* 0.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86 (t, $J = 6.6$ Hz, 3H, CH_3), 1.21–1.43 (m, 24H, $12 \times CH_2$), 2.18–2.35 (m, 6H, H-2, 3, and 6), 3.11 (br, 1H, OH), 3.13–3.17 (m, 1H, H-7), 3.31 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.50–3.59 (m, 2H, H-1″), 3.65 (dd, $J = 11.2$ and 4 Hz, 1H, H-2′a), 3.80 (dd, $J = 11.2$ and 4 Hz, 1H, H-2′b), 4.06–4.08 (m, 1H, H-1′), 5.46–5.49 (m, 2H, H-4 and 5), 6.10 (d, 1H, $J = 6.4$ Hz, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (p, C-20), 22.7 (s, C-19), 25.3 (s, C-9), 28.6 (s, C-3), 29.3 (s, C-17), 29.6 (s, overlapping signals), 29.8 (s, C-16), 31.9 (s, C-18), 33.3 (s, C-8), 36.2 (s, C-6), 36.4 (s, C-2), 50.4 (t, C-1′), 56.4 (p, OCH_3), 59.2 (p, OCH_3), 63.8 (s, C-2′), 73.0 (s, C-1″), 80.6 (t, C-7), 127.5 (t, C-5), 130.6 (t, C-4), 173.0 (q, C-1); IR (KBr): ν 3323, 2925, 2854, 1648, 1546, 1461, 1098, 971 cm^{-1}; HRMS (ESI) $C_{25}H_{50}NO_4$ $[M+H]^+$ calcd 428.3734, found 428.3739.

4.14. *N*-[(1*R*)-2-Acetyloxy-1-methoxy-methyl ethyl]-(4*E*,7*S*)-7-methoxy-4-eicosenamide, 2b (1′-*epi* 1b)

Similar to the preparation of **1b**, **2b** was obtained from **2a** (8 mg, 0.02 mmol) and Ac_2O (1 mL) in 95% yield. Mp 38–40 °C; $[\alpha]_D^{13} = -9$ (*c* 0.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $J = 6.9$ Hz, 3H, CH_3), 1.25–1.42 (m, 24H, $12 \times CH_2$), 2.07 (s, 3H, $COCH_3$), 2.17–2.37 (m, 6H, H-2, 3, and 6), 3.11–3.19 (m, 1H, H-7), 3.32 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.39 (dd, 1H, $J = 9.3$ and 4.5 Hz, H-1″a), 3.50 (dd, 1H, $J = 9.3$ and 4.5 Hz, H-1″b), 4.09 (dd, 1H, $J = 11.1$ and 6.0 Hz, H-2′a), 4.19 (dd, 1H, $J = 11.1$ and 6.0 Hz, H-2′b), 4.32–4.36 (m, 1H, H-1′), 5.46–5.50 (m, 2H, H-4 and 5), 6.17 (d, $J = 9.0$ Hz, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (p, C-20), 20.9 (p, $COCH_3$), 22.7 (s, C-19), 25.3 (s, C-9), 28.6 (s, C-3), 29.3 (s, C-17), 29.7 (s, overlapping signals), 29.8 (s, C-16), 31.9 (s, C-18), 33.3 (s, C-8), 36.3 (s, C-6), 36.5 (s, C-2), 47.7 (t, C-1′), 56.5 (p, OCH_3), 59.1 (p, OCH_3), 63.2 (s, C-2′), 71.0 (s, C-1″), 80.6 (t, C-7), 127.6 (t, C-5), 130.6 (t, C-4), 171.0 (q, C=O), 172.2 (q, C-1); HRMS (ESI) $C_{27}H_{52}NO_5$ $[M+H]^+$ calcd 470.3840, found 470.3844.

4.15. The preparation of compounds (*R*)-18, (*S*)-19, (*S*)-20, and (*R*)-16 followed a literature reference[6]

D-Serine **17a** (1.00 g, 9.52 mmol) was chosen as the starting material, esterification of **17a** with methanol (14 mL), followed by reaction with benzimido ethylether, which was prepared according to the reference, gave crude oxazoline (*R*)-**18** (1.76 g, 90%). Reduction of compound (*R*)-**18** (205 mg, 1.00 mmol) using DIBAH (3 mL, 3 mmol, 1 mol/L in pentane) gave alcohol (*S*)-**19** (163 mg, 92%). Alkylation of alcohol (*S*)-**19** (720 mg, 4.07 mmol) with CH_3I (0.76 mL, 12.21 mmol) in the presence of NaH (195 mg, 8.13 mmol) afforded methoxy derivative (*S*)-**20** (754 mg, 97%). Compound (*S*)-**20** (290 mg, 1.52 mmol) was cleaved by heating in hydrochloric acid (8.7 mL,

4 M) to produce methoxyamino alcohol (*R*)-**16** (183 mg, 85%).

4.15.1. (*R*)-4-Carbomethoxy-2-phenyl-oxazoline, (*R*)-18. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.79 (s, 3H, CH_3), 4.56 (dd, $J = 10.5$ and 8.9 Hz, 1H), 4.82 (dd, $J = 8.9$ and 8.1 Hz, 1H), 4.95 (dd, $J = 10.5$ and 8.1 Hz, 1H), 7.36–7.51 (m, 3H), 7.99 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.3, 68.1, 69.2, 126.5, 128.0, 128.2, 131.5, 165.9, 171.2; MS (EI) *m*/*z* (%): 205 (M^+, 1), 146 (100), 105 (30), 91 (90), 77 (35).

4.15.2. (*S*)-4-Hydroxymethyl-2-phenyl-oxazoline, (*S*)-19. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.52 (dd, $J = 11.7$ and 3.0 Hz, 1H), 4.03 (dd, $J = 11.7$ and 2.4 Hz, 1H), 4.34–4.48 (m, 3H), 4.97 (br, 1H, OH), 7.24–7.42 (m, 3H), 7.70–7.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 63.2, 67.9, 68.9, 126.8, 128.0, 128.1, 131.3, 165.4; MS (EI) *m*/*z* (%): 177 (M^+, 1), 146 (100), 118 (40), 105 (3), 91 (90), 77 (35).

4.15.3. (*S*)-4-Methoxymethyl-2-phenyl-oxazoline, (*S*)-20. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.40 (s, 3H, OCH_3), 3.48 (dd, $J = 9.3$ and 8.7 Hz, 1H), 3.64 (dd, $J = 9.3$ and 3.9 Hz, 1H), 4.28–4.29 (m, 1H), 4.47–4.48 (m, 2H), 7.36–7.46 (m, 3H), 7.94–7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 59.2, 66.1, 70.2, 74.5, 127.4, 128.1, 128.2, 131.3, 164.7; MS (EI) *m*/*z* (%): 191 (M^+, 1), 161 (40), 146 (100), 130 (3), 118 (50), 105 (30), 91 (95), 77 (40).

4.15.4. (*R*)-2-Amino-3-methoxy-propan-1-ol hydrochloride, (*R*)-16. $[\alpha]_D^{16} = -2$ (*c* 1.8, $CHCl_3$); ^{1}H NMR (D_2O, 300 MHz): δ 3.37 (s, 3H, OCH_3), 3.52–3.81 (m, 5H); ^{13}C NMR (D_2O, 75 MHz): δ 52.5, 59.0, 59.2, 69.3; (EI) *m*/*z* (%): 105 (M^+, 1), 74 (60), 60 (100), 45 (30), 42 (85).

4.16. Compounds (*S*)-18, (*R*)-19, (*R*)-20, and (*S*)-16 were prepared using the same method as in 4.15 and the data was identical to the samples proposed in 4.15 except for opposite specific rotations

4.17. One-pot reaction

To compound **10** (1.24 g, 4.88 mmol) was added bromine with stirring (0.23 mL, 4.88 mmol) dropwise at 0 °C and the stirring was continued at room temperature for 5 h. Allyl alcohol (two drops) was then added to quench the reaction until the bromide color disappeared. The reaction mixture was passed through a short silica gel column to give the dibromide. The resulting dibromide was added to a stirred suspension of sodium amide in liquid ammonia, which was prepared from Na (280 mg, 12.2 mmol), $FeNO_3{\cdot}9H_2O$ (3 mg) and ammoia (12 mL). The stirring was continued for 2 h and the reaction quenched by NH_4Cl (200 mg). After ammonia evaporation, water (15 mL) was added. The reaction mixture was then extracted with ether (3×15 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silia gel column (petroleum ether/ethyl acetate, 90:1) affored alkyne **12** (40%), along with alkene **10** (60%), which could not be seperated.

To a stirred solution of **11** (80 mg, 0.19 mmol) in THF (6 mL) was added *n*-BuLi (0.17 mL, 0.42 mmol, 2.5 M in hexane) at −78 °C under an argon atmosphere over 5 min. The stirring was continued at this temperature for 1 h and the mixture was warmed to −10 °C slowly. The mixture was then cooled to −78 °C again, HMPA (1.4 mL) followed by 3-bromo-1-tetrahydropyranyloxypropane (71 mg, 0.19 mmol) in THF (2 mL) was added. The reaction mixture was allowed to warm to room temperature for 3 h and then quenched with water (8 mL), extracted with ethyl acetate (3×10 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/ethyl acetate, 40:1) affored **13** as a pale yellow oil (14 mg, 20% yield).

Acknowledgements

Projects 20472025 and 20021001 supported by National Natural Science Foundation of China.

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