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Total Synthesis and Correct Absolute Configuration of Malyngamide U

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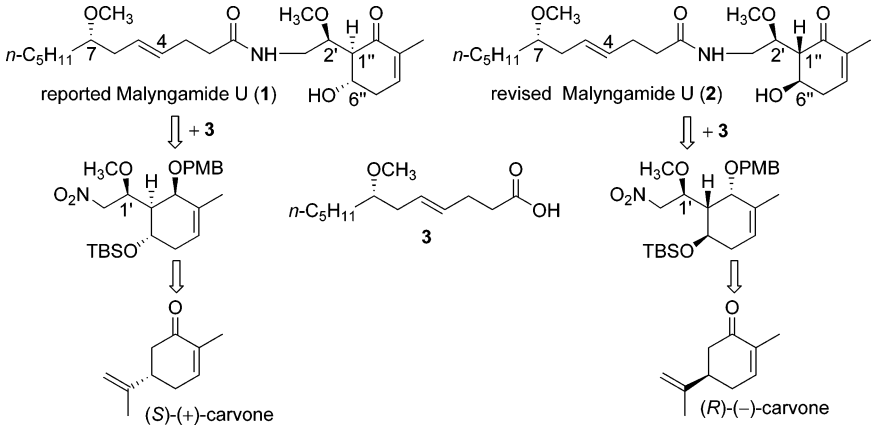
Received July 13, 2006



The enantioselective synthesis of the previously proposed structure of malyngamide U (**1**) was accomplished in 18 steps from (*S*)-(+)-carvone. The key steps involved a hydroxymethylation of (*S*)-(+)-carvone and an asymmetric Henry reaction of aldehyde (+)-**5**, as well as condensation with the acid **3**. The ^{1}H and ^{13}C NMR data of the synthetic compound **1** were not consistent with the data of the reported malyngamide U. The C-2′ epimer of compound **1** was therefore synthesized by a similar reaction sequence. While the NMR data of C-2′ epimer **23** were in full agreement with those of the reported product, the discrepancy in the specific rotation data suggested the correct structure of malyngamide U should be structure **2**, in which the absolute configuration of the amine part was enantiomeric with that in compound **23**. Then the correct absolute configuration of revised malyngamide U (**2**) was confirmed by the similar synthesis from (*R*)-(-)-carvone.

Introduction

The malyngamides are a class of secondary metabolites isolated from the marine cyanophyte *Lyngbya majuscula*. Up to now, 30 different malyngamides have been isolated including malyngamides A−X, serinol-derived malyngamides, toxic-type malyngamides (hermitamides A and B), and isomalyngamides.[1] Structurally, the malyngamides consist of a fatty acid side chain containing a 4*E* double bond and a 7*S* stereogenic center connected via an amide linkage to a heavily oxygenated six-membered ring or a heterocycle and/or with a functional unit of a vinylic chloride. These natural products were found to possess a wide range of biological properties such as antifeedant activity,[2] ichthyotoxicity,[1g,1l] cytotoxicity to marine animals,[1h−j] and anti-HIV,[1k] anti-leukemic, and anti-tumor activity.[1p] A survey of the literature revealed several reports on the synthesis of the fatty acid portions but a few on their total synthesis.[3] To provide materials for more extensive biological evaluations, we focused our interest on the synthesis of these malyngamides and therefore developed a feasible synthetic strategy for them. Herein we reported the asymmetric synthesis of malyngamide U (**1**) from (*S*)-(+)-carvone (**6**) and showed that two of the stereogenic centers on the cyclohexenone ring were incorrectly assigned in the original literature,[1q] as well as confirming the correct absolute configuration of revised malyngamide U (**2**) by the similar synthetic route from (*R*)-(−)-carvone (**6**).

Although the configuration of the fatty acid portion was proposed to have a (4*E*,7*S*) configuration on the basis of spectroscopic evidence and biosynthetic considerations,[1] the absolute configurations of the stereogenic centers on the amine

10.1021/jo061456n CCC: $37.00
Published on Web 03/09/2007

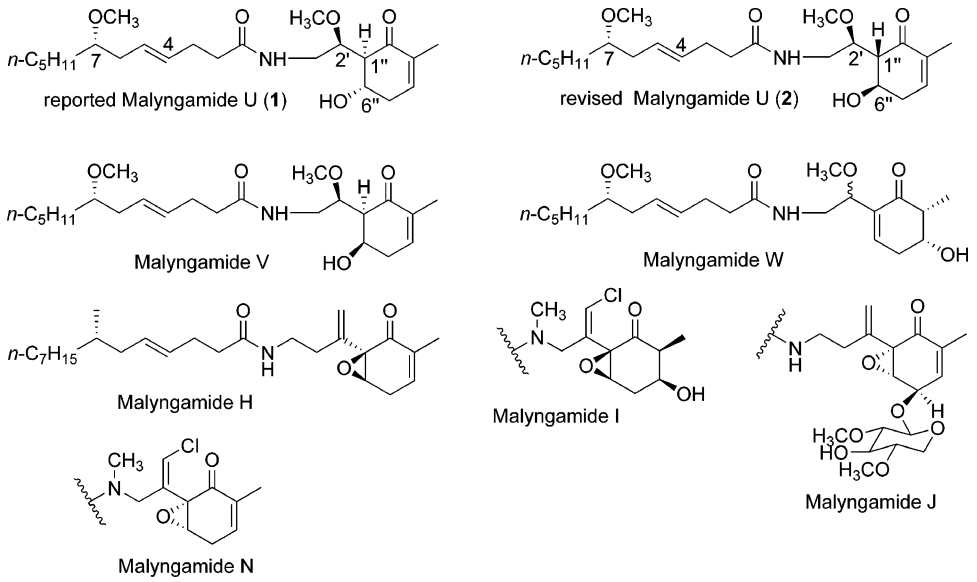


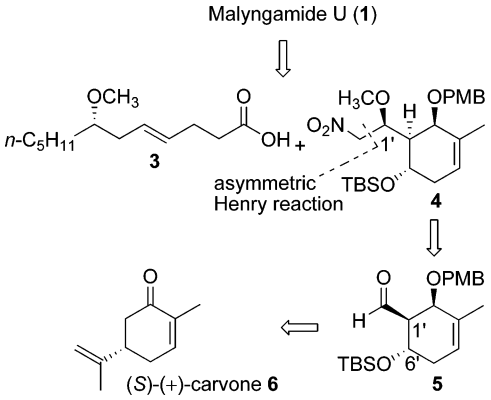
FIGURE 1. Structures of malyngamides: reported (**1**), revised (**2**), and V, W, H, I, J, and N.

moiety were not secured.[1q] Hence, the asymmetric synthesis of malyngamide U (**1**) and the confirmation of its absolute configuration should offer a reference point for the synthesis of other structurally related malyngamides, such as malyngamides V, W, H, I, J and N (Figure 1).

Results and Discussion

The structure of malyngamide U (**1**) consists of two structural features: a chiral fatty acid portion containing a 4*E* double bond and a 7*S* chiral center and an oxygenated α,β-unsaturated cyclohexenone moiety, and the two of them are connected by an amide linkage. A retrosynthetic analysis of **1** suggested the preparation of a carboxylic acid component **3** and a cyclohexene component **4** (Scheme 1). The chiral fatty acid **3**, (−)-(4*E*,7*S*)-7-methoxydodec-4-enoic acid had been synthesized earlier by us in eight steps starting from hexanal in 24% overall yield.[4]

SCHEME 1. Retrosynthetic Analysis



For the other key intermediate **4**, the chiral center at C-1′ could be prepared from an aldehyde (+)-**5** by an asymmetric Henry reaction.[5] The sense of chirality at C-1′ and C-6′ in (+)-**5** could be introduced into the cyclohexene ring via the hydroxymethylation of (*S*)-(+)-carvone **6** and subsequent stereoselective functional transformations.

The preparation of aldehyde (+)-**5** began with (*S*)-(+)-carvone (**6**) (Scheme 2). Thus, (*S*)-(+)-carvone was hydroxymethylated with LDA and CH_2O at −84 °C to afford cyclohexenone (+)-**7** as the sole isomer in 59% yield (based on 69% conversion).[6] Protection of the hydroxy group of (+)-**7** as its *tert*-butyldimethylsilyl (TBS) ether gave the corresponding silyl ether (−)-**8** (94%). Direct protection of the ketone function of (−)-**8** proved to be difficult. Hence it was reduced with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ to produce a cyclohexenyl alcohol (+)-**9** (89%).[7] Stereoselective epoxidation of (+)-**9** with

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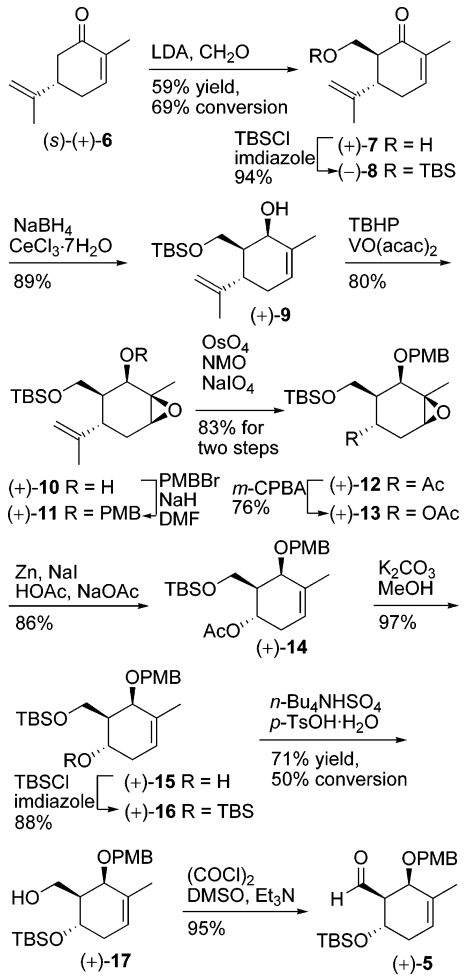
SCHEME 2. Preparation of Aldehyde (+)-5



tert-butyl hydroperoxide (TBHP) in the presence of $VO(acac)_2$ generated the desired epoxide (+)-**10** in 80% yield with benzene as the solvent.[8] As expected, the stereochemistry of the epoxidation was directed by the free hydroxyl group. Interestingly, the same epoxidation gave a complex mixture of products when it was conducted in CH_2Cl_2. The stereochemistry of (+)-**10** was unambiguously established by its X-ray crystal structure (CCDC no. 603438; see Supporting Information Figure 1). Subsequent protection of the hydroxyl function of epoxide (+)-**10** as its *p*-methoxybenzyl (PMB) ether produced compound (+)-**11**. In order to transform the isopropylene group in (+)-**11** to a hydroxyl functionality with retention of configuration, compound (+)-**11** was treated with OsO_4, with 4-methylmorpholine *N*-oxide (NMO) as a cooxidant, followed by cleavage of the generated diol with $NaIO_4$ to afford ketone (+)-**12** in 83% yield for two steps [from (+)-**10** to (+)-**12**]. It should be noted that the reaction time for the cleavage reaction of the diol should not be prolonged (<15 min); otherwise many byproducts were formed. Baeyer−Villiger rearrangement of ketone (+)-**12** with *m*-CPBA in a cosolvent of hexane and EtOAc (3/1) afforded acetate (+)-**13** in 76% yield.[9] After that, the epoxide functionality in compound (+)-**13** was removed by use of Zn powder and NaI to reinstall the C=C bond to give compound (+)-**14** in 86% yield.[10] The acetyl group in compound (+)-**14** was then converted into the corresponding TBS ether (+)-**16** in two steps. First, removal of acetyl group in the presence of K_2CO_3 in methanol generated the secondary alcohol (+)-**15** in 97% yield. Subsequently the alcohol (+)-**15** was protected by use of TBSCl to furnish the bis(TBS) ether (+)-**16** in 88% yield. After several experimentations, selective deprotection of the primary TBS ether could be realized with *n*-Bu_4NHSO_4 and *p*-TsOH·H_2O at −20 °C, giving the primary alcohol (+)-**17** in 71% yield on the basis of 50% conversion.[11] Finally, Swern oxidation of alcohol (+)-**17** generated aldehyde (+)-**5** in 95% yield.[12] Hence, compound (+)-**5** could be conveniently prepared in 12% yield in 12 steps from (*S*)-(+)-carvone in 2.4 g scale.

With the key (+)-aldehyde **5** in hand, the third chiral center was then introduced by an asymmetric Henry reaction (Scheme 3). For the choice of the chiral catalyst, Evans' copper acetate−bis(oxazoline) catalyst {Cu[(−)-**18**]}$(OAc)_2$[5] was reported to give high diastereoselectivities and high yields for aliphatic aldehydes.[13] Indeed, compound (+)-**5** gave the desired nitroalcohol **19a** with high diastereoselectivity (60:1) in 68% yield on the basis of 37% conversion. **19a** and (+)-**19b** could be separated by careful flash chromatography over silica gel. The structure of compound **19a** was confirmed by NOE experiment of its derivative **20**. Hence, selective irradiation of H-4α of **20** resulted in signal enhancements of H-4 and H-8α, while selective irradiation of H-4 resulted in signal enhancements of H-4α and H-8α. Hence the chiral center in compound **19a** has an *S* absolute configuration at C-1 position.[14]

In Scheme 4, treatment of compound **19a** with MeOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) afforded the methyl ether **4** in 67% yield. Then reduction of compound **4** with $NaBH_4$ and $NiCl_2$·$6H_2O$ gave the corresponding amine,[15] which was not stable and directly condensed with acid **3** in the presence of DCC, 1-hydroxybenzotriazole (HOBt), and 4-methylmorpholine (NMM) to afford amide **21** in 83% yield. Deprotection of the PMB group from **21** followed by oxidation of the generated allylic alcohol with DDQ furnished compound **22** in 85% yield. Finally, compound **22** was treated with TFA to remove the TBS group to give the target compound **1** in 75% yield. However, both the ^1H and ^{13}C NMR data of synthetic **1**, especially the ^{13}C NMR chemical shift value of the C-2′ atom, disagreed with the reported data for isolated malyngamide U.[16] As the absolute configuration of compound **1** had been confirmed by the crystal structure of compound (+)-**10** and the NOE experiments of compound **20**, our initial speculation was that the structure of malyngamide U should be **23**, with the absolute configuration at the C-2′ chiral center being opposite to that of compound **1** (i.e., *R* instead of *S*). To prove the correct structure of malyngamide U, the synthesis of compound **23** was thus pursued.

On the basis of the synthesis of compound **4**, compound **23** was prepared by similar procedures (Scheme 4). By use of the enantiomeric copper acetate−bis(oxazoline) catalyst {Cu[(+)-**18**]}$(OAc)_2$, (+)-**19b** was obtained in 66% yield on the basis of 58% conversion [ratio of (+)-**19b**/**19a** = 26/1]. Methylation of (+)-**19b** gave compound (+)-**24**, which was then condensed

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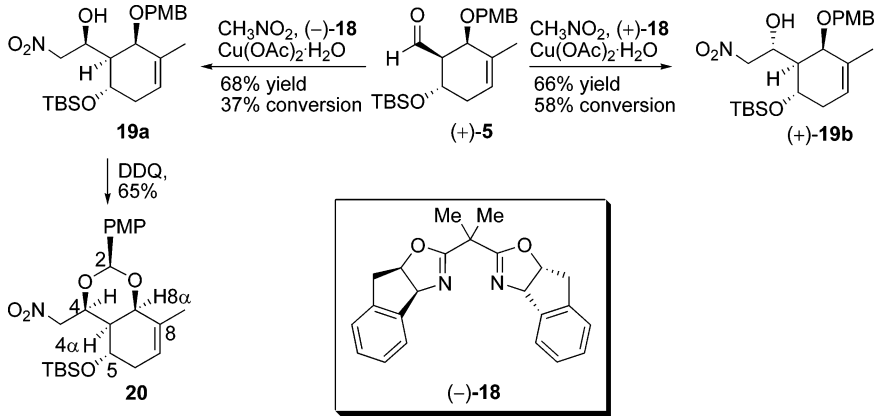
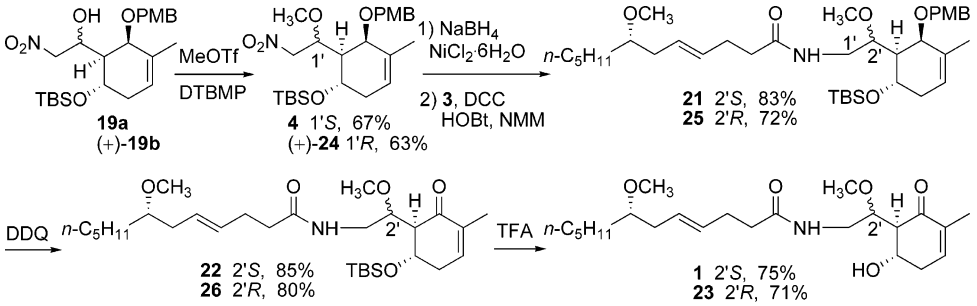
(16) See the Supporting Information.

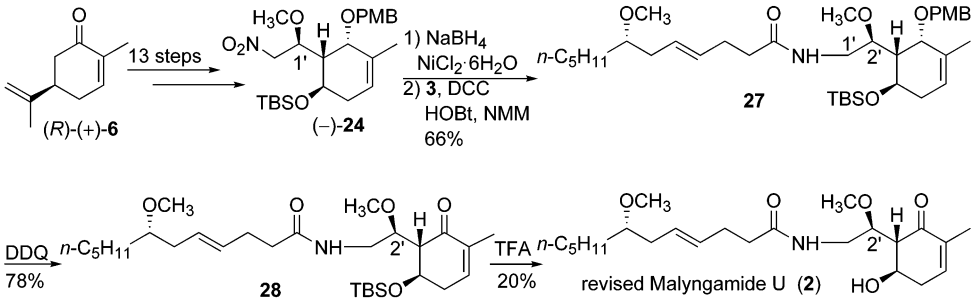
SCHEME 3. Preparation of Nitroalcohols 19a and (+)-19b and Compound 20



SCHEME 4. Preparation of Compounds 1 and 23



SCHEME 5. Preparation of Compound 2



with the acid **3** to furnish **25**. Removal of the PMB protective group followed by oxidation gave the TBS-protected compound **26**, and subsequent deprotection of the TBS moiety afforded compound **23**.

In the synthetic procedure for **23**, it was very interesting to find that **25** was treated with DDQ to give only the product of deprotected PMB group by TLC monitoring in 10 min under the same conditions as described for preparation of **22**. However, compound **26** was accomplished by adding 6 equiv of DDQ in 24 h in 80% yield. This result should be explained by the different steric factors[17] of the generated allylic alcohols from **21** and **25**. Thus we can imagine that if an enantiomeric catalyst {Cu[(−)-**18**]}$(OAc)_2$ or {Cu[(+)-**18**]}$(OAc)_2$ is not used, compounds **1** and **23** may be synthesized, respectively, because **22** and the allylic alcohol generated from **25** can be separated easily.

The ^{1}H and ^{13}C NMR data of synthetic malyngamide U (**23**) were in complete agreement with the data reported for the isolated malyngamide U (**1**). However, the specific rotation of compound **23** was found to be $[\alpha]_D^{14}$ +6 (*c* 0.35, $CHCl_3$), which was different from the reported value of $[\alpha]_D^{18}$ −15.8 (*c* 0.12, $CHCl_3$). As the acid portion of malyngamide U had been determined to be (−)-(4*E*,7*S*)-7-methoxydodec-4-enoic acid from biosynthetic considerations,[1] the only possible explanation was that the opposite configuration of the amine portion of the isolated malyngamide U was enantiomeric with the amine part of compound **23**. Hence the correct structure of malyngamide U should be structure **2** (Figure 1 and Scheme 5). The chiral centers between the fatty acid part and the amine part were too remote from each other, and hence one would expect compounds **23** and **2** would have identical ^{1}H and ^{13}C NMR spectral features. This deduction was further confirmed by our similar observations of the spectral data of serinol-derived malyngamides and their 1′-epi isomers[4] and the total synthesis of compound **2**. Thus, the key intermediate (−)-**24** was obtained from (*R*)-(−)-carvone (**6**) and {Cu[(−)-**18**]}$(OAc)_2$ was used as catalyst for asymmetric Henry reaction in 13 steps in 0.4% yield (Scheme 5). After amidation and deprotection, compound **2** was accomplished in 10% yield from (−)-**24**. The NMR data of synthetic **2** were identical with the data reported for the isolated malyngamide U. The specific rotation of **2** was found to be $[\alpha]_D^{20}$ −12 (*c* 0.20, $CHCl_3$), which is consistent with the reported value of $[\alpha]_D^{18}$ −15.8 (*c* 0.12, $CHCl_3$). These results

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showed that the correct absolute configuration of malyngamide U should be **2**.

Conclusion

The enantioselective total synthesis of the previously proposed structure of malyngamide U (**1**) was accomplished in 18 steps in 3% yield. The synthetic transformation utilized relatively inexpensive (*S*)-(+)-carvone as the starting material. The stereochemistry of the amine part were secured by a hydroxymethylation of (*S*)-(−)-carvone and an asymmetric Henry reaction of aldehyde (+)-**5**. It was found that the ^{1}H and ^{13}C NMR data of the synthesized product **1** were different from those reported in the literature. Synthesis of the C-2′ epimer of compound **1** (i.e., compound **23**) was then carried out, and although the NMR spectroscopic data of compound **23** agreed well with those of the isolated compound, specific rotation measurement suggested that malyngamide U should have a structure of compound **2** and then its correct absolute configuration was confirmed by further synthesis from (*R*)-(+)-carvone (**6**). The synthesis of the structurally related malyngamides V and W, as well as the malyngamides containing a heterocycle and/or with a vinylic chloride functionality, such as A, B, M, O, P, Q, and R, is also underway.

Experimental Section

(5*S*,6*S*)/(5*R*,6*R*)-6-(Hydroxymethyl)-2-methyl-5-(1-methylethenyl)-2-cyclohexen-1-one [(+)-7 and (−)-7]. To a 1 L, three-necked round-bottomed flask equipped with an argon inlet and outlet was added a solution of (*S*)-(+)-carvone (**6**) (29.24 g, 194.65 mmol) in THF (500 mL). LDA (107.21 mL, 2 M in THF) was added to the stirred solution via syringe over a period of 2 h at −84 °C [N_2 (l)/EtOAc] and the stirring was continued for another 1 h. Then a paraformaldehyde depolymerization apparatus was attached to the reaction vessel. The argon inlet was placed on the flask containing paraformaldehyde (61.50 g, 2.05 mol) and a brisk flow of argon was maintained. It was noticed that the temperature of the oil bath for depolymerization should be below 190 °C and the incoming argon should bubble well below the surface of the solution in the reaction vessel. Once all the paraformaldehyde had cracked, the depolymerization apparatus was removed and the reaction was allowed to warm to rt, followed by quenching with saturated NH_4Cl solution. The reaction mixture was extracted with EtOAc (3 × 300 mL) and the organic extracts were washed with H_2SO_4 solution (0.5 M, 500 mL) and brine (500 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 20:1) afforded cyclohexenone (+)-**7** as a pale yellow oil (14.28 g, 59% yield on the basis of 69% conversion): $[\alpha]_D^{25} = +17$ (*c* 1.0, $CHCl_3$); IR (neat) 3469, 2923, 1662, 1373, 1047, 897 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.74 (s, 3H, CH_3), 1.78 (t, J = 1.2 Hz, 3H, CH_3), 2.30 (dt, J = 18.6 and 4.8 Hz, 1H, H-4a), 2.44−2.54 (m, 2H, H-4b and H-5), 2.66−2.76 (m, 1H, H-6), 3.18 (br s, 1H, OH), 3.64−3.77 (m, 2H, H-3′), 4.86 (s, 2H, H-2′), 6.77−6.79 (m, 1H, H-3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6 (CH_3), 18.0 (CH_3), 31.1 (CH_2, C-4), 45.6 (CH, C-5), 50.2 (CH, C-6), 61.0 (CH_2, C-3′), 113.8 (CH_2, C-2′), 135.0 (C, C-2), 144.4 (C, C-1′), 145.2 (CH, C-3), 203.1 (C, C-1); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{16}NaO_2$ 203.1043, found 203.1037.

According to the preceding procedure, (*R*)-(−)-carvone (**6**) (30.00 g, 199.84 mmol) afforded (−)-**7** as a pale yellow oil (16.85 g, 47%). $[\alpha]_D^{20} = -17$ (*c* 1.0, $CHCl_3$); ^{1}H and ^{13}C NMR data for (−)-**7** are identical with those for (+)-**7**; LRMS (ESI) *m*/*z* [M + H]$^+$ found 181.0.

(1*R*,2*R*,3*S*,4*S*,6*S*)/(1*S*,2*S*,3*R*,4*R*,6*R*)-3-(1,1-Dimethylethyl)dimethylsilyoxymethyl-1-methyl-4-(1-methylethenyl)-7-oxa-bicyclo-[4.1.0]heptan-2-ol [(+)-10 and (−)-10]. To a stirred solution of (+)-**9** (18.86 g, 63.60 mmol) in dry PhH (100 mL) was added TBHP (36.34 mL, 2.63 M in toluene), followed by addition of $VO(acac)_2$ (337 mg, 1.27 mmol) at 0 °C. The stirring was continued for 2 h at rt, and then the reaction mixture was poured into 2% $NaHSO_3$ solution (50 mL) and extracted with EtOAc (3 × 80 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 15:1) afforded epoxide (+)-**10** as a white solid (15.90 g, 80% yield): $[\alpha]_D^{25} = +50$ (*c* 1.0, $CHCl_3$); mp 65−68 °C; IR (neat) 3504, 2929, 1251, 1092, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.01 (s, 6H, 2 × CH_3), 0.85 (s, 9H, 3 × CH_3), 1.36−1.46 (m, 1H), 1.41 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.71−1.81 (m, 1H), 1.96−2.14 (m, 2H), 2.31 (d, J = 8.7 Hz, 1H, OH), 3.18−3.20 (m, 1H, H-2), 3.39 (dd, J = 9.6 and 3.9 Hz, 1H, H-3′a), 3.55 (t, J = 9.6 Hz, 1H, H-6), 4.09 (dd, J = 9.6 and 3.9 Hz, 1H, H-3′b), 4.69 (s, 2H, H-2′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.6 (CH_3), −5.5 (CH_3), 18.2 (CH_3 and C), 22.2 (CH_3), 25.9 (3 × CH_3), 31.0 (CH_2, C-5), 34.3 (CH), 43.4 (CH), 60.1 (C, C-1), 61.4 (CH_2, C-3′), 62.1 (CH), 67.6 (CH), 112.9 (CH_2, C-2′), 144.9 (C, C-1′); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{32}NaO_3Si$ 335.2013, found 335.2018.

According to the preceding procedure, (−)-**9** (19.81 g, 66.88 mmol) afforded (−)-**10** as a waxy solid (16.33 g, 78%). $[\alpha]_D^{20} = -48$ (*c* 1.0, $CHCl_3$); ^{1}H and ^{13}C NMR data for (−)-**10** are identical with those for (+)-**10**; LRMS (ESI) *m*/*z* [M + H]$^+$ found 313.0.

(1*S*,3*S*,4*R*,5*R*,6*S*)/(1*R*,3*R*,4*S*,5*S*,6*R*)-4-[(1,1-Dimethylethyl)dimethylsilyoxymethyl]-5-(4-methoxybenzyloxy)-6-methyl-7-oxabicyclo[4.1.0]heptan-3-yl Acetate [(+)-13 and (−)-13]. To a stirred solution of (+)-**12** (14.81 g, 34.07 mmol) in hexane and EtOAc (120 mL, hexane/EtOAc = 3:1) was added *m*-CPBA (50%) (23.55 g, 68.23 mmol) in three portions carefully. The stirring was continued at rt for 3 days. Then the mixture was diluted with EtOAc and washed with saturated Na_2SO_3 solution (3 × 100 mL). The organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 10:1) afforded acetate (+)-**13** as a pale yellow oil (11.67 g, 76%): $[\alpha]_D^{22} = +5$ (*c* 1.0, $CHCl_3$); IR (neat) 2930, 1737, 1513, 1249, 1085, 839 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 6H, 2 × CH_3), 0.89 (s, 9H, 3 × CH_3), 1.34 (s, 3H, CH_3), 1.91 (dt, J = 15.9 and 3.6 Hz, 1H, H-2a), 2.01 (s, 3H, $COCH_3$), 2.27−2.37 (m, 2H, H-2b and H-4), 3.01 (d, J = 4.2 Hz, 1H, H-5), 3.70−3.83 (m, 2H, H-1 and H-1′a), 3.81 (s, 3H, OCH_3) 3.99 (d, J = 6.0 Hz, 1H, H-1′b), 4.51 (d, J = 11.1 Hz, 1H, ArCH-a), 4.65 (d, J = 11.1 Hz, 1H, ArCH-b), 5.14−5.19 (m, 1H, H-3), 6.89 (d, J = 8.7 Hz, 2H, 2 × ArH), 7.31 (d, J = 8.7 Hz, 2H, 2 × ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.4 (2 × CH_3), 18.2 (C), 20.8 (CH_3), 21.3 (CH_3), 25.9 (3 × CH_3), 27.5 (CH_2, C-2), 43.2 (CH, C-4), 55.2 (OCH_3), 58.6 (CH), 58.6 (C, C-1), 59.1 (CH_2, C-1′), 69.7 (CH), 71.5 ($ArCH_2$), 74.9 (CH), 113.7 (2 × CH), 129.6 (2 × CH), 130.1 (C), 159.2 (C), 170.0 (CO); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{38}NaO_6Si$ 473.2330, found 473.2327.

According to the preceding procedure, (−)-**12** (17.96 g, 41.36 mmol) afforded (−)-**13** as a pale yellow oil (13.59 g, 73%). $[\alpha]_D^{20} = -13$ (*c* 1.0, $CHCl_3$); ^{1}H and ^{13}C NMR data for (−)-**13** are identical with those for (+)-**13**; LRMS (ESI) *m*/*z* [M + H]$^+$ found 451.0.

[(1*S*,2*R*,6*S*)/(1*R*,2*S*,6*R*)-6-(1,1-Dimethylethyl)dimethylsilyoxy-2-(4-methoxybenzyloxy)-3-methylcyclohex-3-en-1-yl]carbaldehyde [(+)-5 and (−)-5]. To a stirred solution of $(COCl)_2$ (0.83 mL, 9.68 mmol) in CH_2Cl_2 (5 mL) was added a solution of DMSO (1.39 mL, 19.42 mmol) at −84 °C [N_2 (l)/EtOAc] in CH_2Cl_2 (5 mL). After 5 min of stirring, a solution of (+)-**17** (2.53 g, 6.44 mmol) in CH_2Cl_2 (10 mL) was added and the stirring was continued at this temperature for 15 min. Then Et_3N (4.51 mL, 32.42 mmol) was added and the reaction was allowed to warm to rt in 1 h, followed by quenching with saturated NH_4Cl solution. The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel

(petroleum ether/EtOAc = 30:1) afforded aldehyde (+)-**5** as a pale yellow oil (2.40 g, 95% yield): $[\alpha]_D^{13} = +140$ (*c* 1.0, $CHCl_3$); IR (neat) 2928, 1724, 1251, 1077, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 6H, 2 × CH_3), 0.85 (s, 9H, 3 × CH_3), 1.73 (s, 3H, CH_3), 1.93−2.01 (m, 1H, H-5′a), 2.37−2.48 (m, 1H, H-5′b), 2.48−2.54 (m, 1H, H-1′), 3.80 (s, 3H, OCH_3), 4.17 (d, J = 5.2, 1H, H-2′), 4.44−4.57 (m, 3H, $ArCH_2$ and H-6′), 5.39−5.41 (m, 1H, H-4′), 6.86 (dd, J = 6.9 and 2.1 Hz, 2H, 2 × ArH), 7.23 (dd, J = 6.9 and 2.1 Hz, 2H, 2 × ArH), 9.85 (d, J = 3.3 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.9 (CH_3), −4.1 (CH_3), 17.9 (C), 20.6 (CH_3), 25.7 (3 × CH_3), 34.4 (CH_2, C-5′), 55.2 (OCH_3), 58.2 (CH, C-1′), 65.3 (CH), 74.0 ($ArCH_2$), 77.6 (CH), 113.7 (2 × CH), 122.9 (CH, C-4′), 129.7 (2 × CH), 130.0 (C), 133.6 (C), 159.3 (C), 205.4 (C, C-1); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{34}NaO_4Si$ 413.2119, found 413.2120.

According to the preceding procedure, (−)-**17** (2.07 g, 5.28 mmol) afforded (−)-**5** as a pale yellow oil (1.92 g, 93%): $[\alpha]_D^{20} = -137$ (*c* 1.0, $CHCl_3$); ^1H and ^{13}C NMR data for (−)-**5** are identical with those for (+)-**5**; LRMS (ESI) *m*/*z* $[M + H]^+$ found 391.0.

(1*S*)-[(1*S*,2*R*,6*S*)-6-(1,1-Dimethylethyl)dimethylsilyoxy-2-(4-methoxybenzyloxy)-3-methylcyclohex-3-en-1-yl]-2-nitroethan-1-ol and (1*R*)-[(1*S*,2*R*,6*S*)/(1*S*)-[(1*R*,2*S*,6*R*)-6-(1,1-dimethylethyl)-dimethylsilyoxy-2-(4-methoxybenzyloxy)-3-methylcyclohex-3-en-1-yl]-2-nitroethan-1-ol [19a, (+)-19b, and (−)-19b]. To a stirred solution of $Cu(OAc)_2 \cdot H_2O$ (42 mg, 0.21 mmol) in EtOH (2 mL) was added chiral catalyst (−)-**18** (82 mg, 0.23 mmol). After the mixture was stirred for 1 h at rt, CH_3NO_2 (2.25 mL, 41.65 mmol) was added, followed by a solution of (+)-**5** (1.63 g, 4.17 mmol) in EtOH (6 mL). The stirring was continued at rt for 7 days. Then the reaction mixture was concentrated in vacuo and flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 20:1) afforded nitroethanol **19a** (473 mg, 68% yield) and nitroethanol (+)-**19b** (12 mg, 1% yield) as pale yellow oils (on the basis of 37% conversion). **19a**: $[\alpha]_D^{13} = +138$ (*c* 1.0, $CHCl_3$); IR (neat) 3436, 2927, 1554, 1251, 1034, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.10 (s, 3H, CH_3), 0.12 (s, 3H, CH_3), 0.90 (s, 9H, 3 × CH_3), 1.88 (s, 3H, CH_3), 1.85−2.05 (m, 2H, H-1′ and H-5′a), 2.43 (dt, J = 17.7 and 4.8 Hz, 1H, H-5′b), 3.74 (br s, 1H, OH), 3.81 (s, 3H, OCH_3), 4.04 (d, J = 3.3 Hz, 1H, H-2′), 4.22−4.31 (m, 1H, H-6′), 4.46−4.80 (m, 5H, $ArCH_2$, H-1 and 2), 5.47−5.49 (m, 1H, H-4′), 6.88−6.92 (m, 2H, 2 × ArH), 7.25−7.29 (m, 2H, 2 × ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.6 (CH_3), −4.1 (CH_3), 17.8 (C), 22.4 (CH_3), 25.8 (3 × CH_3), 36.4 (CH_2, C-5′), 48.9 (CH, C-1′), 55.2 (OCH_3), 66.8 (CH), 70.1 (CH), 73.7 (CH_2), 79.4 (CH_2), 79.6 (CH), 114.0 (2 × CH), 124.6 (CH, C-4′), 129.6 (C), 129.6 (2 × CH), 133.1 (C), 159.5 (C); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{37}NNaO_6Si$ 474.2282, found 474.2284.

According to the preceding procedure, with (+)-**18** as chiral catalyst, (+)-**5** (909 mg, 2.33 mmol) afforded **19a** (10 mg, 3% yield) and (+)-**19b** (402 mg, 66%) as pale yellow oils (on the basis of 53% conversion). (+)-**19b**: $[\alpha]_D^{13} = +94$ (*c* 1.0, $CHCl_3$); IR (neat) 3464, 2929, 1555, 1252, 1035, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.10 (s, 3H, CH_3), 0.12 (s, 3H, CH_3), 0.90 (s, 9H, 3 × CH_3), 1.89 (s, 3H, CH_3), 1.91−2.05 (m, 2H, H-1′ and H-5′a), 2.38−2.47 (m, 1H, H-5′b), 3.81 (s, 3H, OCH_3), 3.91 (d, J = 8.4 Hz, 1H, OH), 4.11−4.19 (m, 2H, H-2′ and H-6′), 4.46−4.77 (m, 5H, $ArCH_2$, H-1 and H-2), 5.47−5.49 (m, 1H, H-4′), 6.89 (d, J = 8.4 Hz, 2H, 2 × ArH), 7.27 (d, J = 8.4 Hz, 2H, 2 × ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.0 (CH_3), −4.0 (CH_3), 17.8 (C), 22.3 (CH_3), 25.7 (3 × CH_3), 36.0 (CH_2, C-5′), 48.4 (CH, C-1′), 55.1 (OCH_3), 65.9 (CH), 69.5 (CH), 73.7 (CH_2), 78.6 (CH), 80.2 (CH_2), 114.0 (2 × CH), 124.3 (CH, C-4′), 129.2 (C), 129.8 (2 × CH), 132.9 (C), 159.5 (C); HRMS (ESI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{23}H_{41}N_2O_6Si$ 469.2728, found 469.2726.

According to the preceding procedure, with (−)-**18** as chiral catalyst, (−)-**5** (1.82 g, 4.66 mmol) afforded (−)-**19b** (483 mg, 23% yield) as a pale yellow oil. $[\alpha]_D^{20} = -104$ (*c* 1.0, $CHCl_3$); ^1H and ^{13}C NMR data for (−)-**19b** are identical with those for (+)-**19b**; HRMS (ESI) *m*/*z* $[M + NH_4]^+$ calcd for $C_{23}H_{41}N_2O_6Si$ 469.2728, found 469.2723.

{(2*S*,4*S*,4α*R*,5*S*,8α*R*)-2-(4-Methoxyphenyl)-8-methyl-4-(nitromethyl)-4α,5,6,8α-tetrahydro-4*H*-benzo[*d*][1,3]dioxin-5yloxy}(1,1-dimethylethyl)-dimethylsilane (20). To a stirred solution of **19a** (40 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) was added DDQ (41 mg, 0.18 mmol) at rt, and the stirring was continued for 12 h. The reaction mixture was concentrated in vacuo, and flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 15:1) afforded compound **20** (26 mg, 65% yield) as a pale yellow oil: $[\alpha]_D^{14} = +35$ (*c* 1.0, $CHCl_3$); IR (neat) 2927, 1557, 1251, 1082, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.12 (s, 3H, CH_3), 0.19 (s, 3H, CH_3), 0.94 (s, 9H, 3 × CH_3), 1.75 (s, 3H, CH_3), 1.74−1.79 (m, 1H, H-4α), 1.99−2.06 (m, 1H, H-6a), 2.45 (dt, J = 17.2 and 5.2 Hz, 1H, H-6b), 3.80 (s, 3H, OCH_3), 4.24 (d, J = 2.4 Hz, 1H, H-8α), 4.46−4.53 (m, 1H, H-5), 4.58 (dd, J = 14 and 1.6 Hz, 1H, $CHNO_2$), 4.83−4.86 (m, 1H, H-4), 5.04 (dd, J = 14 and 10 Hz, 1H, $CHNO_2$), 5.51 (dd, J = 4.6 and 1.6 Hz, 1H, H-7), 5.62 (s, 1H, H-2), 6.88 (d, J = 8.8 Hz, 2H, 2 × ArH), 7.38 (d, J = 8.8 Hz, 2H, 2 × ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.0 (CH_3), −3.7 (CH_3), 18.0 (C), 20.2 (CH_3), 26.0 (3 × CH_3), 36.6 (CH_2, C-6), 43.8 (CH, C-4α), 55.3 (OCH_3), 65.3 (CH), 76.7 (CH), 79.2 (CH_2NO_2), 79.4 (CH), 101.9 (CH, C-2), 113.5 (2 × CH), 124.9 (CH, C-7), 127.4 (2 × CH), 130.3 (C), 132.0 (C), 160.0 (C); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{36}NO_6Si$ 450.2306, found 450.2303.

(4*E*,7*S*)-*N*-{(2*S*)-[(1*S*,6*S*)-6-Hydroxy-3-methyl-2-oxocyclohex-3-en-1-yl]-2-methoxyethyl}-7-methoxydodec-4-enamide, (4*E*,7*S*)-*N*-{(2*R*)-[(1*S*,6*S*)-6-hydroxy-3-methyl-2-oxocyclohex-3-en-1-yl]-2-methoxyethyl}-7-methoxydodec-4-enamide, and (4*E*,7*S*)-*N*-{(2*S*)-[(1*R*,6*R*)-6-hydroxy-3-methyl-2-oxocyclohex-3-en-1-yl]-2-methoxyethyl}-7-methoxydodec-4-enamide [1, 23, and 2]. To a stirred solution of **22** (15 mg, 0.03 mmol) in CH_2Cl_2 (7.5 mL) were added TFA (0.6 mL) and H_2O (0.15 mL) at 0 °C, and the stirring was continued at this temperature for 10 h. Then the reaction mixture was poured into brine (8 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were washed with saturated NH_4Cl solution, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum ether/EtOAc = 2:1) afforded amide **1** as a pale yellow oil (9 mg, 75% yield): $[\alpha]_D^{14} = +4$ (*c* 0.8, $CHCl_3$); IR (neat) 3352, 2924, 1651, 1438, 1369, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J = 6.0 Hz, 3H, H-12), 1.27−1.42 (m, 8H, H-8, H-9, H-10, and H-11), 1.78 (s, 3H, CH_3), 2.18−2.49 (m, 8H, H-2, H-3, H-6, H-1″, and H-5″a), 2.69−2.76 (m, 1H, H-5″b), 3.01−3.06 (m, 1H), 3.14−3.18 (m, 1H), 3.31−3.33 (m, 1H), 3.35 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.83−3.87 (m, 1H), 4.09−4.11 (m, 1H), 4.20−4.28 (m, 1H), 5.47−5.49 (m, 2H, H-4 and H-5), 6.20 (br s, 1H, NH), 6.67−6.69 (m, 1H, H-4″); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4 (CH_3, C-12), 16.3 (2″-CH_3), 23.0 (CH_2, C-11), 25.4 (CH_2, C-9), 29.0 (CH_2, C-3), 32.4 (CH_2, C-10), 33.7 (CH_2, C-8), 35.1 (CH_2, C-5″), 36.8 (CH_2, C-6), 37.0 (CH_2, C-2), 41.8 (CH_2, C-1′), 54.0 (CH, C-1″), 56.9 (7-OCH_3), 58.9 (2′-OCH_3), 68.5 (CH, C-6″), 78.4 (CH, C-2′), 81.1 (CH, C-7), 128.2 (CH, C-5), 131.1 (CH, C-4), 136.1 (C, C-3″), 142.4 (CH, C-4″), 173.7 (C, C-1), 199.0 (C, C-2″); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{40}NO_5$ 410.2901. found 410.2896.

According to a previous procedure, **26** (9 mg, 0.02 mmol) afforded amide **23** (5 mg, 71% yield) as a pale yellow oil: $[\alpha]^{14}{}_D = +6$ (*c* 0.35, $CHCl_3$); IR (neat) 3372, 2922, 1654, 1459, 1368, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 6.4 Hz, 3H, H-12), 1.28−1.43 (m, 8H, H-8, H-9, H-10, and H-11), 1.76 (s, 3H, CH_3), 2.20−2.27 (m, 4H, H-2 and H-6), 2.35−2.41 (m, 3H, H-3 and H-5″a), 2.73 (dt, J = 18.0 and 5.2 Hz, 1H, H-5″b), 2.82 (dd, J = 10.8 and 3.2 Hz, 1H, H-1″), 3.15−3.18 (m, 1H, H-7), 3.33 (s, 3H, 7-OCH_3), 3.46 (s, 3H, 2′-OCH_3), 3.48−3.57 (m, 2H, H-1′), 4.21−4.29 (m, 2H, H-2′ and 6″), 5.45−5.48 (m, 2H, H-4 and H-5), 5.91 (br s, 1H, NH), 6.67−6.69 (m, 1H, H-4″); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4 (CH_3, C-12), 16.1 (2″-CH_3), 23.0 (CH_2,

C-11), 25.4 (CH_2, C-9), 28.9 (CH_2, C-3), 32.4 (CH_2, C-10), 33.7 (CH_2, C-8), 34.7 (CH_2, C-5″), 36.8 (CH_2, C-6), 36.9 (CH_2, C-2), 40.0 (CH_2, C-1′), 54.8 (CH, C-1″), 56.9 (7-OCH_3), 58.6 (2′-OCH_3),68.9 (CH, C-6″), 80.3 (CH, C-2′), 81.2 (CH, C-7), 127.9 (CH, C-5), 131.2 (CH, C-4), 136.5 (C, C-3″), 142.6 (CH, C-4″), 172.8 (C, C-1), 198.0 (C, C-2″); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{40}NO_5$ 410.2901, found 410.2908.

According to the preceding procedure, **28** (25 mg, 0.05 mmol) afforded amide **2** (4 mg, 20% yield) as a pale yellow oil. $[\alpha]_D^{20} = -12$ (*c* 0.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 6.4 Hz, 3H, H-12), 1.27−1.43 (m, 8H, H-8, H-9, H-10, and H-11), 1.76 (s, 3H, CH_3), 2.19−2.26 (m, 4H, H-2 and H-6), 2.33−2.41 (m, 3H, H-3 and H-5″a), 2.73 (dt, J = 18.0 and 5.2 Hz, 1H, H-5″b), 2.81 (dd, J = 10.8 and 3.2 Hz, 1H, H-1″), 3.14−3.17 (m, 1H, H-7), 3.33 (s, 3H, 7-OCH_3), 3.47 (s, 3H, 2′-OCH_3), 3.48−3.56 (m, 2H, H-1′), 4.21−4.28 (m, 2H, H-2′ and H-6″), 5.47−5.50 (m, 2H, H-4 and H-5), 5.91 (br s, 1H, NH), 6.67−6.68 (m, 1H, H-4″); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4 (CH_3, C-12), 16.1 (2″-CH_3), 23.0 (CH_2, C-11), 25.4 (CH_2, C-9), 28.9 (CH_2, C-3), 32.4 (CH_2, C-10), 33.7 (CH_2, C-8), 34.7 (CH_2, C-5″), 36.8 (CH_2, C-6), 36.9 (CH_2, C-2), 40.0 (CH_2, C-1′), 54.8 (CH, C-1″), 56.9 (7-OCH_3), 58.6 (2′-OCH_3), 68.9 (CH, C-6″), 80.3 (CH, C-2′), 81.2 (CH, C-7), 127.9 (CH, C-5), 131.2 (CH, C-4), 136.5 (C, C-3″), 142.6 (CH, C-4″), 172.8 (C, C-1), 198.0 (C, C-2″); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{40}NO_5$ 410.2901, found 410.2906.

Acknowledgment. This project (20472025 and QT 20621091) was supported by the National Natural Science Foundation of China. We gratefully acknowledge Professor Hak-Fun Chow, The Chinese University of Hong Kong, for his helpful guidance in the preparation of the manuscript and Professor Da-Qi Wang, Laocheng University, for X-ray crystallographic analyses.

Supporting Information Available: Experimental procedures; list of spectral data for other compounds; ^{1}H and ^{13}C NMR and DEPT 135 spectra of compounds (+)-**7**, (+)-**10**, (+)-**13**, (+)-**5**, **19a**, (+)-**19b**, **20** (NOE), (−)-**24**, **1**, **23,** and **2**; X-ray structure of epoxide (+)-**10**; and crystallographic file (CIF, CCDC no. 603438). This material is available free of charge via the Internet at http://pubs.acs.org.

JO061456N