JOC*Note*

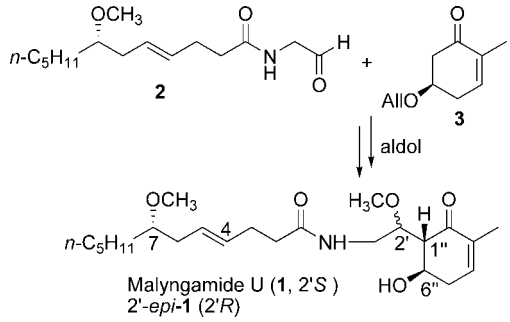
An Improved Asymmetric Synthesis of Malyngamide U and Its 2′-Epimer

Jian-Peng Feng, Zi-Fa Shi, Yang Li, Jun-Tao Zhang, Xian-Liang Qi, Jie Chen, and Xiao-Ping Cao*

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

caoxplzu@163.com

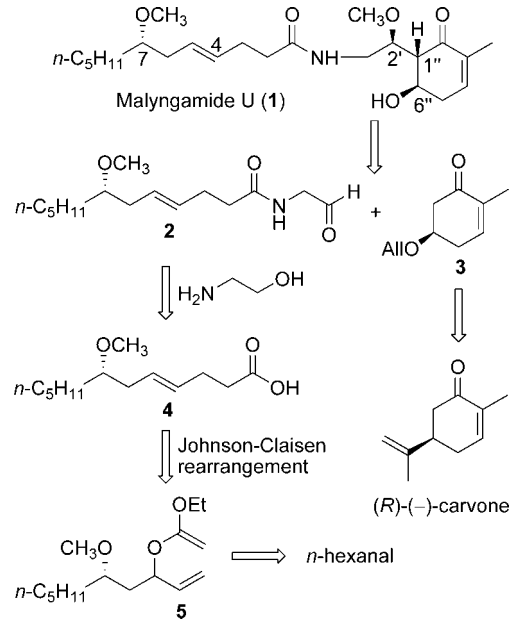
Received April 28, 2008



An accelerated and improved asymmetric synthesis of malyngamide U (**1**) and its 2′-epimer (2′-*epi*-**1**) was accomplished from readily available *n*-hexanal, ethanolamine and (*R*)-(−)-carvone. The key steps involved a Johnson−Claisen rearrangement in the synthesis of an unsaturated carboxylic acid **4** and an aldol reaction in the construction of the skeleton of **1** and 2′-*epi*-**1**. There are 13 steps in the synthesis, with a 2.7% overall yield for **1** and a 0.4% yield for 2′-*epi*-**1**.

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. These natural products were found to possess a wide range of biological properties such as antifeedant activity, ichthyotoxicity and cytotoxicity to marine animals, as well as anti-HIV, antileukemic, antitumor, antitubercular, and antimalarial activity.[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. In some cases, such as malyngamide X, the fatty acid moiety is linked via a tripeptide backbone to a heterocycle.[2] A survey on the literature revealed that, apart from a recent synthesis of malyngamide X, synthetic studies on these natural products were scarcely reported. Recently, our group reported the first total synthesis and revised the correct absolute configuration of malyngamide U (**1**),[3] which was isolated in 2003 by Gerwick.[1b] The scarcity of malyngamides from natural sources has hampered a thorough biological evaluation of these fascinating molecules. To provide materials for more extensive biological evaluations, herein we reported an improved and efficient asymmetric synthesis of malyngamide U (**1**) and its 2′-epimer from (*R*)-(−)-carvone using minimal protecting-group manipulations. This new method greatly shortened the number of synthetic steps and improved the overall yield of the target molecule.

SCHEME 1. Retrosynthetic Analysis



As showed in retrosynthesis analysis (Scheme 1), the structure of malyngamide U (**1**) can be divided into an aldehyde moiety **2** and a cyclohexane part **3**. The aldehyde part **2** can be prepared from ethanolamine and a chiral fatty acid **4**. Compound **4** could be formed stereoselectivity by performing a Johnson−Claisen rearrangement reaction[4] of **5**, which in turn could be prepared by an asymmetric allylation of hexanal.[5] The cyclohexane portion **3** could be derived from (*R*)-(−)-carvone via functional transformations. The chirality at C-2′ and C-1″ positions in the target molecule could be controlled by conducting an aldol reaction between components **2** and **3**.

There are a few works reporting the synthesis of acid **4** and its homologues.[2,6] However, the relatively long reaction sequence and/or stringent reaction operations,[6c] and the problem-

(1) (a) Tan, L. T.; Okino, T.; Gerwick, W. H. *J. Nat. Prod.* **2000**, *63*, 952. (b) McPhail, K. L.; Gerwick, W. H. *J. Nat. Prod.* **2003**, *66*, 132. Brief overview of the family of the related malyngamides. For the most recent and, see ref and references cited therein.

(2) (a) Suntornchashwej, S.; Suwanborirux, K.; Koga, K.; Isobe, M. *Chem. Asian J.* **2007**, *2*, 114. (b) Suntornchashwej, S.; Suwanborirux, K.; Isobe, M. *Tetrahedron* **2007**, *63*, 3217.

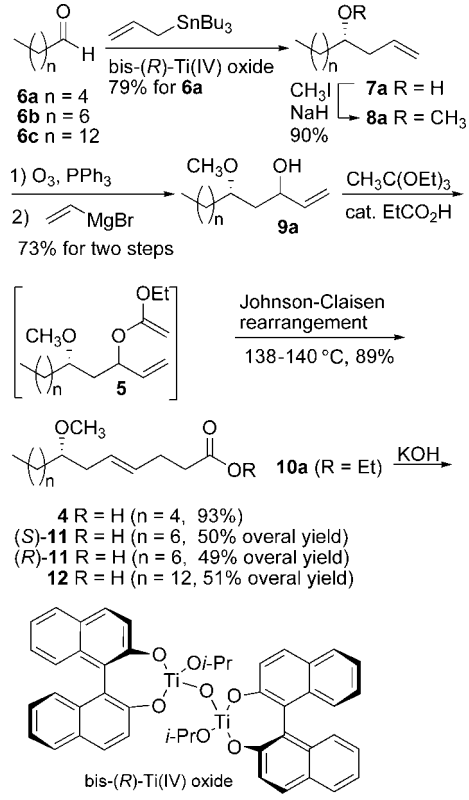
(3) Li, Y.; Feng, J. P.; Wang, W. H.; Chen, J.; Cao, X. P. *J. Org. Chem.* **2007**, *72*, 2344.

(4) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T. T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(5) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708.

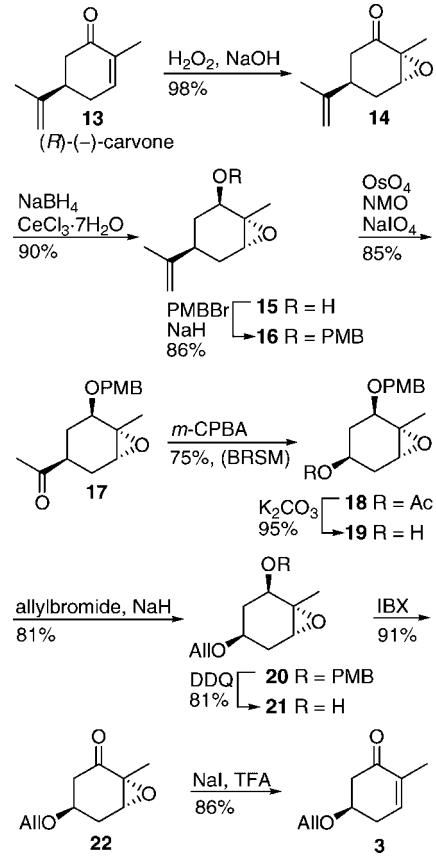
10.1021/jo800876u CCC: $40.75 © 2008 American Chemical Society
Published on Web 07/26/2008

SCHEME 2. Preparation of Fatty Acids



atic *cis*/*trans* olefin isomerization[6a,e] are drawbacks for a large-scale synthesis of the optical pure fatty acid **4**. Hence, an efficient asymmetric synthesis of compound **4** was first sought. As shown in Scheme 2, the homoallylic alcohol **7a** could be obtained by asymmetric allylation of hexanal **6a** ($n = 4$) with allyltributyltin in the presence of a catalytic amount of the bis{[(*R*)-binaphthoxy](isopropoxy)titanium} oxide [bis-(*R*)-Ti(IV) oxide] in 79% yield (99% ee).[5] Alcohol **7a** was then converted to the corresponding methyl ether **8a** in 90% yield by treatment with MeI in the presence of NaH.[7] Oxidative cleavage of the terminal double bond of **8a** with ozone followed by PPh_3 workup afforded the corresponding aldehyde,[8] which was immediately treated with vinylmagnesium bromide to yield a 1:1 diastereomeric mixture (determined by ^1H NMR analysis) of allylic alcohols **9a** in 73% yield.[9] The alcohols **9a** were subjected to the Johnson−Claisen rearrangement to provide the γ,δ-unsaturated ethyl ester **10a** in 89% yield in exclusive (*E*)-stereoselectivity.[4] Saponification of the ester **10a** with KOH gave the fatty acid (*S*)-**4** in 93% yield.[10] Based on the synthetic route of **4**, the higher homologues, (*S*)-**11** and **12** were also prepared in 50% and 51% overall yield from **6b** and **6c**, respectively. Incidentally, the enantiomeric (*R*)-**11** was also synthesized from

SCHEME 3. Preparation of Ketone 3



6b using the enantiomeric catalyst bis-(*S*)-Ti(IV) oxide in 49% overall yield. The spectral data of the unsaturated acids **4**, (*R*)-**11**, (*S*)-**11**, and **12** are in good agreement with those reported in the literature.[6g,2,6h]

The preparation of the α,β-unsaturated cyclohexenone **3** began with (*R*)-(−)-carvone **13** (Scheme 3). Base-catalyzed epoxidation of (*R*)-(−)-carvone using hydrogen peroxide led to the epoxide ketone **14** in 98% yield.[11] Reduction of ketone moiety in compound **14** under Luche's conditions generated an epoxy alcohol **15** in 90% yield.[12] The hydroxyl group was then protected as its *p*-methoxybenzyl (PMB) ether by alkylation of *p*-methoxybenzyl bromide[13] in the presence of NaH to give compound **16** in 86% yield.[14] In order to transform the isopropylene group of **16** to a hydroxyl group with retention of configuration, compound **16** was treated with OsO_4 using 4-methylmorpholine *N*-oxide (NMO) as a cooxidant, followed by cleavage of the generated diol with $NaIO_4$ to afford ketone **17** in 85% yield. Baeyer−Villiger rearrangement of ketone **17** with *m*-CPBA in a cosolvent of hexane and EtOAc (hexane/EtOAc = 3:1) afforded an acetate **18** in 75% yield based on recovered starting material (BRSM).[15] Removal of acetyl group in the presence of K_2CO_3 in methanol generated the secondary alcohol **19** in 95% yield. Subsequently the alcohol **19** was protected using allylbromide in the presence of NaH to furnish

(6) (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. Chem.* **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. (g) Li, Y.; Chen, J.; Cao, X. P. *Synthesis* **2006**, 320. (h) Chen, J.; Li, Y.; Cao, X. P. *Tetrahedron: Asymmetry* **2006**, *17*, 933.

(7) Liu, B.; Zhou, W. S. *Org. Lett.* **2004**, *6*, 71.

(8) Felzmann, W.; Arion, V. B.; Mieusset, J. L.; Mulzer, J. *Org. Lett.* **2006**, *8*, 3849.

(9) Crimmins, M. T.; McDougall, P. J.; Emmitte, K. A. *Org. Lett.* **2005**, *7*, 4033.

(10) Sonnet, P. E. *J. Org. Chem.* **1969**, *34*, 1147.

(11) Hatakeyama, S.; Numata, H.; Osanai, K.; Takano, S. *J. Org. Chem.* **1989**, *54*, 3515.

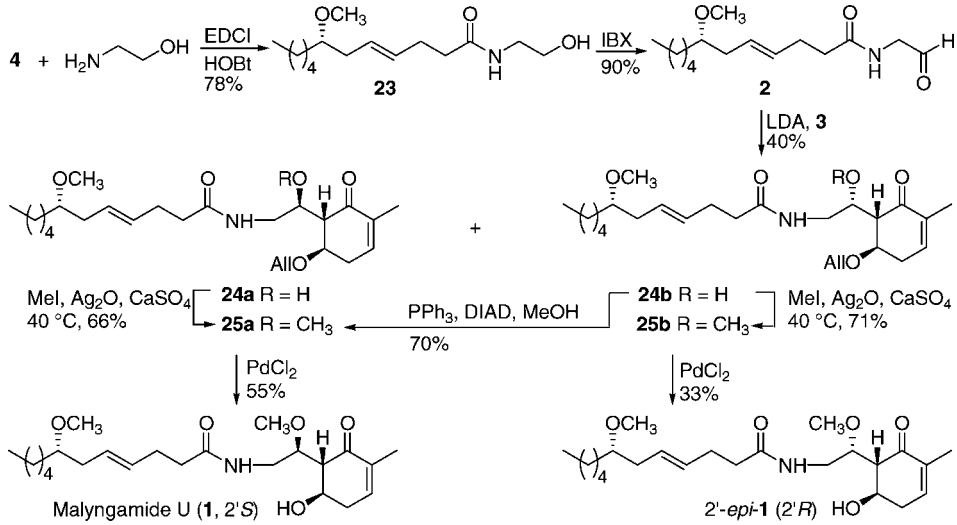
(12) Kirsch, S.; Bach, T. *Synthesis* **2003**, 1827.

(13) Burke, S. D.; Hong, J.; Lennox, J. R.; Mongin, A. P. *J. Org. Chem.* **1998**, *63*, 6952.

(14) Paquette, L. A.; Chang, J.; Liu, Z. *J. Org. Chem.* **2004**, *69*, 6441.

(15) Kabat, M. M.; Garofalo, L. M.; Daniewski, A. R.; Hutchings, S. D.; Liu, W.; Okabe, M.; Radinov, R.; Zhou, Y. *J. Org. Chem.* **2001**, *66*, 6141.

SCHEME 4. Completion the Synthesis of 1 and Its 2′-Epimer by Aldol Reaction



the allyl ether **20** in 81% yield.[16] The PMB protecting group was then removed in the presence of DDQ,[17] followed by IBX oxidation[18] of the resulting alcohol to provide the corresponding ketone **22** in 74% yield in two steps. Attempts to reduce the epoxide **22** by using Zn powder and NaI was unsuccessful.[19] After several experimentations, a practical method of reducing the epoxide based on the work of Adams[20] was realized by using NaI/TFA as the reductant. Thus, the preparation of the optically pure α,β-unsaturated cyclohexenone **3** was accomplished in 10 steps and 24% overall yield from (*R*)-(−)-carvone.

With the acid **4** and α,β-unsaturated cyclohexenone **3** in hand, we focused our efforts on the formation of the malyngamide U skeleton by an aldol reaction (Scheme 4.) Thus, amidation of acid **4** with ethanolamine in the presence of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) produced **23** in 78% yield.[21] Oxidation of the primary alcohol **23** with IBX provided the key intermediate amido-aldehyde **2**.[18] Aldol condensation of **2** with the enolate of α,β-unsaturated cyclohexenone **3** generated in the presence of LDA in THF at −78 °C afforded the desired product **24a** and its 2′-epimer **24b** in a diastereomeric ratio of 4:1. The desired major product **24a** could be readily separated from the minor epimer **24b** by column chromatography. The absolute configuration of C-2′ in compound **24a** was confirmed by a modified method described by Mosher.[22] Hence, compound **24a** was converted to its (*S*)- and (*R*)-MTPA esters. The chemical shift values of H-1′ and H-1″ protons were ascertained for both esters from COSY experiments. The $\Delta\delta$ ($= \delta_S - \delta_R$) values (+0.05 ppm for H-1′, +0.68 ppm for NH, and −0.04 ppm for H-1″) revealed that the absolute configuration of C-2′ was (*S*) for **24a**. At this stage, we were faced with the task of methylating the β-hydroxy ketone **24** without promoting epimerization of the C-1″ stereocenter, retro-aldol cleavage, or dehydration reactions. Several procedures, including MeI/Ag_2O, various catalyzed diazomethane variants, Meerwein's salt in the presence of excess Proton Pronge, methyl triflate and 2,6-di-*tert*-butyl-4-methylpyridine were met with limited success.[23] It was ultimately found that treatment **24a** and **24b** with Ag_2O in neat MeI in the presence of dry $CaSO_4$ smoothly promoted methylation to give **25a** and **25b** in 66% yield and 71% yield, respectively.[24] Compound **25a** could also be obtained by Mitsunobu reaction of **24b** in 70% yield.[25] Finally, removal of the allyl protecting group with $PdCl_2$ in MeOH/CH_2Cl_2 = 3:2 completed the synthesis of malyngamide U (**1**) and 2′-*epi*-**1**.[26] The spectral data of **1** were in good agreement with those reported in literature.[3]

In summary, an efficient synthesis of malyngamide U (**1**) and 2′-*epi*-**1** was accomplished in 13 steps in 2.7% and 0.4% overall yield, respectively. This compared favorably with our previous reported method in which 18 steps were involved and the target compound was obtained in only 0.04% overall yield.[3] The preparation of the chiral γ,δ-unsaturated acid **4** was achieved in 6 steps and 43% overall yield from *n*-hexanal. The efficient asymmetric synthesis of malyngamide U (**1**) and its 2′-epimer should offer a convenient entry to other structurally related malyngamides (Figure 1). Further studies on the total synthesis of these malyngamides are currently underway in our laboratory.

Experimental Section

(4*E*,7*S*)-*N*-{(2*S*)-[(1*R*,6*R*)-6-Allyloxy-3-methyl-2-oxocyclohex-3-en-1-yl]-2-hydroxyethyl}-7-methoxydodec-4-enamide (24a) and (4*E*,7*S*)-*N*-{(2*R*)-[(1*R*,6*R*)-6-allyloxy-3-methyl-2-oxocyclohex-3-en-1-yl]-2-hydroxyethyl}-7-methoxydodec-4-enamide (24b). To a solution of amide alcohol **23** (180 mg, 0.66 mmol) in dry EtOAc (7 mL) was added IBX (557 mg, 1.99 mmol). The resulting suspension was immersed in an oil bath set to 80 °C and stirred vigorously under atmosphere for 7 h. The reaction was cooled to room temperature and filtered through a medium glass frit. The filter cake was washed with EtOAc (3 mL), and the filtrate was concentrated in vacuo. Flash chromatography of the residue over silica gel using

(16) Sezer, S.; Özdemirhan, D.; Şahin, E.; Tanyeli, C. *Tetrahedron: Asymmetry* **2006**, *17*, 2981.
(17) Schmidt, J. P.; Beltrán-Rodil, S.; Cox, R. J.; McAllister, G. D.; Reid, M.; Taylor, R. J. K. *Org. Lett.* **2007**, *9*, 4041.
(18) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.
(19) Cane, D. E.; Yang, G.; Coates, R. M.; Pyun, H. J.; Hohn, T. M. *J. Org. Chem.* **1992**, *57*, 3454.
(20) Adams, J.; Lepine-Frenette, C.; Spero, D. M. *J. Org. Chem.* **1991**, *56*, 4494.
(21) Nicolaou, K. C.; Chen, D. Y. K.; Huang, X.; Ling, T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 12888.
(22) Ohtanoi, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(23) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448.
(24) Brummond, K. M.; Hong, S. *J. Org. Chem.* **2005**, *70*, 907.
(25) Mitsunonu, O. *Synthesis* **1981**, 1.
(26) König, C. M.; Harms, K.; Koert, U. *Org. Lett.* **2007**, *9*, 4777.

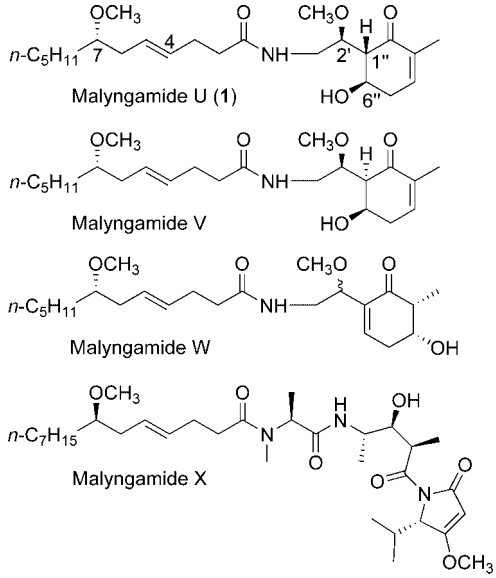


FIGURE 1. Structures of malyngamide U, V, W, and X.

EtOAc as an eluent yield the crude aldehyde **2**. To a solution of LDA (0.32 mL, 2 M in THF, 0.64 mmol) in THF (5 mL) was added a solution of the ketone **3** (100 mg, 0.60 mmol) in THF (3 mL) dropwise over 5 min at −78 °C. The mixture was maintained at this temperature for 45 min, the freshly prepared crude aldehyde **2** in THF (2 mL) was then added. The resulting solution was stirred for 30 min at −78 °C, then saturated NH_4Cl solution was added at this temperature. The mixture was extracted with EtOAc (4 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica gel (petroleum/EtOAc = 3:2) afforded **24a** (84 mg, 32%) and its 2′-epimer **24b** (20 mg, 8%). Pure **24a** cannot be obtained due to contamination of aldehyde **2**, which has the same R_f value as **24a**. Fortunately, they could be separated from each other after methylation. Spectral data for **24b**: $[\alpha]^{20}_D = -63$ (*c* 1.0, $CHCl_3$); IR (KBr): 3373, 2922, 2853, 1726, 1459, 1379, 1092, 879 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J = 6.6 Hz, 3H, CH_3, H-12), 1.28−1.36 (m, 6H), 1.40−1.42 (m, 2H), 1.76 (s, 3H, CH_3), 2.18−2.21 (m, 2H), 2.27−2.48 (m, 5H), 2.75−2.83 (m, 2H), 3.09−3.18 (m, 2H), 3.32 (s, 3H, OCH_3), 3.61−3.68 (m, 1H), 3.97−4.10 (m, 4H, H-7″, H−6″ and H-2′), 5.17 (d, J = 10.8 Hz, 1H, H-9″a), 5.26 (d, J = 16.8 Hz, 1H, H-9″b), 5.49 (s, 2H, H-4 and H-5), 5.85−5.94 (m, 1H, H-8″), 6.27 (brs, 1H, NH), 6.65 (s, 1H, H-4″); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0 (CH_3, C-12), 15.7 (CH_3), 22.6 (CH_2), 24.9 (CH_2), 28.5 (CH_2), 30.2 (CH_2), 31.9 (CH_2), 33.2 (CH_2), 36.2 (2 × CH_2), 43.7 (CH, C-1′), 55.9 (CH, C-1″), 56.4 (OCH_3), 69.9 (CH), 69.9 (CH_2, C-7″), 74.7 (CH), 80.6 (CH, C-7), 117.3 (CH_2, C-9″), 127.7 (CH), 130.5 (CH), 134.5 (CH, C-8″), 135.7 (C, C-3″), 142.1 (CH, C-4″), 174.3 (C, C-1), 200.4(CO); HRMS (ESI) *m*/*z* $C_{25}H_{41}NO_5Na$ $[M + Na]^+$ calcd for 458.2877, found 458.2877.

Acknowledgment. We are grateful to the National Basic Research Program (973 Program) of China (Grant No. 2007CB108903), and the National Natural Science Foundation of China (Grant No. 20621091 and 20472025) for the financial support. We also gratefully acknowledge Professor Hak-Fun Chow, The Chinese University of Hong Kong, for his helpful guidance in revising the manuscript.

Supporting Information Available: Experimental procedures, list of spectral data for other compounds, ^1H, ^{13}C NMR, and DEPT 135 spectra of compounds **3**, **4**, **9a**−**c**, **10a**−**c**, (*R*)-**11**, (*S*)-**11**, **12**, **14**, **15**, **16**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, **24b**, **25a**, **25b**, **1**, 2′-*epi*-**1**, (*S*)- and (*R*)-Mosher ester of **24a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800876U