Synthesis of Majusculamides A and B

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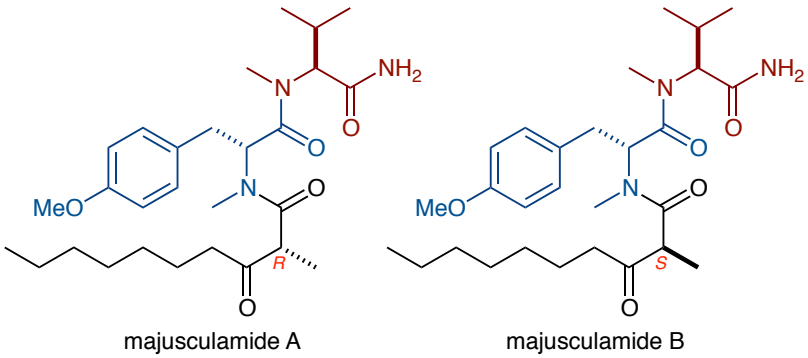

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Abstract The synthesis of two marine lipodipeptides, majusculamides A and B, is described. The key feature of this synthesis is the stereoselective construction of an α-methyl-β-keto-carboxamide moiety.

Key words marine natural products, peptides, polyketides, β-ketoamide, asymmetric aldol reaction

Marine natural products show a wide range of biological activities due to their structural diversity, which offers a rich source of biological tools as well as novel drugs.[1] Although the evaluation of their biological activities is sometimes restricted by their limited natural supply, chemical synthesis can provide sufficient amounts of samples and might expand possibility of identifying the potencies of the molecules. In connection with our campaign to discover biologically active molecules, we developed syntheses of the marine natural products, majusculamides A and B (Figure 1).

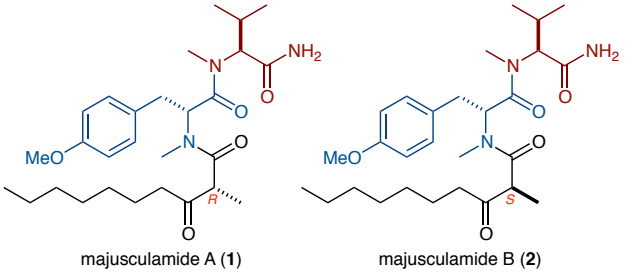


Figure 1 Structures of majusculamides A and B.

The first isolation of the majusculamides from cyanobacteria, *Lyngbya majuscula*, and their structural elucidation were reported by Moore, Clardy and co-workers in 1977.[2,3] These natural products feature a dipeptide moiety comprising *N*,*O*-dimethyl-D-tyrosine and *N*-methyl-L-valine, with a C-terminal primary amide. The α-methyl-β-keto-decanoyl group is bonded to the N-terminus of the dipeptide to form a tertiary amide. The methyl group in the decanoyl group generates two diastereomers, and the (*R*)- and (*S*)-diastereomers are majusculamides A (**1**) and B (**2**), respectively.

Although the α-methyl-β-keto-carboxamide moiety appears to be stereochemically labile, these two isomers could be separated. Isomerization of either isomer under heating in dimethyl sulfoxide at 140 °C was reported to be slow.[4,5] Conformational insights into the α-methyl-β-keto-imide moiety by Evans and coworkers explain the stereochemical stability of the system,[6] in which the C-H bond at the α-position is arranged almost coplanar with the plane of the amide so as to minimize the 1,3-allylic strain of the amide moiety (Figure 2).[7,8] This insight also suggests that the alkyl chains of the decanoyl groups in majusculamides A and B are oriented in different directions relative to the dipeptide core in preferable conformations, thereby differentiating the shapes of the two molecules.[9] The structural differences might confer distinct biological activities. In fact, a difference in cell cytotoxicity measured with an MTT assay was observed between majusculamides A and B. Majusculamide A showed cytotoxicity at 10 μM in cultured Hela S3 cells, while majusculamide B showed no cytotoxicity under the same conditions.[10]

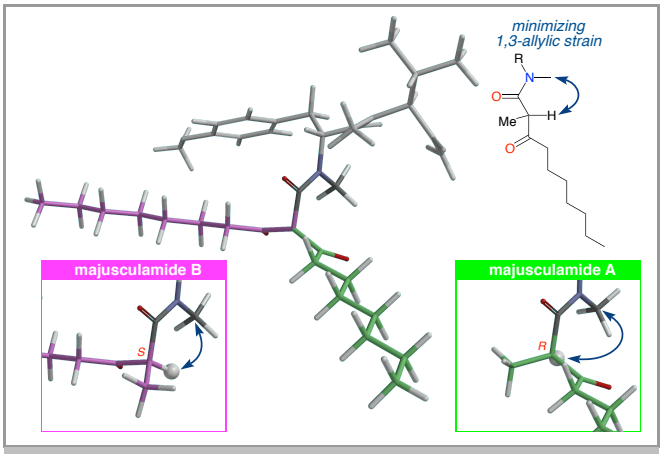
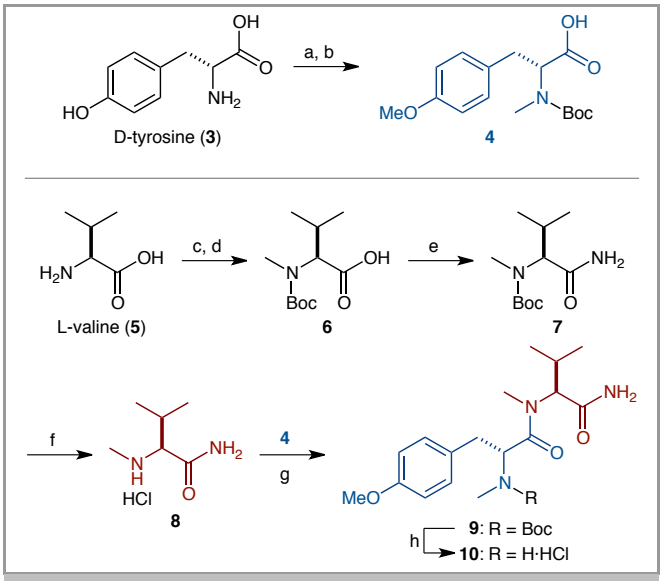


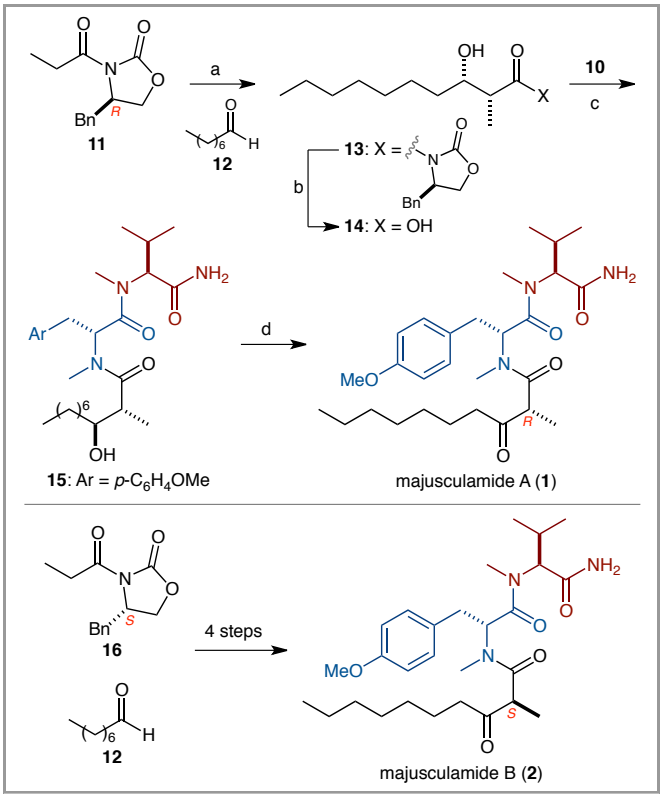
Figure 2 Structural comparison of majusculamides A and B. The dipeptide core, shown in gray, is based on the X-ray crystal structure of majusculamide B. The alkyl chains, shown in green and magenta for majusculamides A and B, respectively, are presented in extended forms.

The synthesis of majusculamides A and B began with the preparation of methylated amino acid units. Protection of D-tyrosine (**3**) with a Boc group,[11] followed by methylation with iodomethane in the presence of sodium hydride in tetrahydrofuran afforded *N*,*O*-dimethyl-*N*-Boc-tyrosine (**4**).[12] After protecting L-valine (**5**) with a Boc group, *N*-methylation was conducted under the same conditions.[13] The carboxylic acid moiety in **6** was then activated by treatment with isobutyl chloroformate and *N*-methylmorpholine in diethyl ether, and the resulting mixed anhydride was reacted with ammonia gas to furnish carboxamide **7**,[14] which was subjected to deprotection by treatment with methanolic hydrogen chloride, giving the hydrogen chloride salt of *N*-methylvaline carboxamide **8**. Condensation of these amino acid units thus obtained could be successfully carried out by using COMU to give dipeptide **9** in 74% yield.[15] Employing other condensation reagents such as HATU or EDCI-HOBt resulted in a lower yield due to the steric hindrance on the units. The Boc group in **9** was cleaved with methanolic hydrogen chloride to give **10**.



Scheme 1 Preparation of methylated amino acid units. Reagents and conditions: (a) Boc_2O, NaOH, 1,4-dioxane-H_2O, rt; (b) NaH, MeI, THF, 0 °C to rt, 84% (2 steps); (c) Boc_2O, NaOH, THF-H_2O, rt; (d) NaH, MeI, THF, 0 °C to rt; (e) *i*-BuOCOCl, *N*-methylmorpholine, Et_2O, –15 °C; NH_3 (gas), –15 °C to rt, 50% (3 steps); (f) HCl, MeOH, 0 °C to rt, 98%; (g) **4**, COMU, DMF, 0 °C, then **8**, Et_3N, 0 °C to rt, 74%; (h) HCl, MeOH, rt, quant.

The decanoic acid unit was prepared by an asymmetric aldol reaction. Sequential treatment of (*R*)-propanoyloxazolidinone **11** with titanium(IV) chloride, TMEDA and then octanal (**12**) afforded β-hydroxy-imide **13**,[16] which was hydrolyzed with lithium hydroperoxide to give carboxylic acid **14**.[17] Condensation of **14** with dipeptide **10** was conducted by using HATU to furnish **15** in 72% yield.[18,19] Since the primary carboxamide moiety in **10** was affected by HATU, premixing **14** and HATU before adding **10** effectively improved the yield. Finally, oxidation of the secondary alcohol moiety with Dess-Martin periodinane[20] in the presence of sodium bicarbonate produced majusculamide A (**1**).[21] Starting from (*S*)-propanoyloxazolidinone **16**, majusculamide B (**2**) could be obtained according to the same procedure.[22] The spectral data of the synthetic materials were identical to those of the natural samples.



Scheme 2 Syntheses of majusculamides A and B. Reagents and conditions: (a) $TiCl_4$, TMEDA, CH_2Cl_2, 0 °C, then octanal (**12**), 0 °C, 68%; (b) LiOH·H_2O, H_2O_2, THF-H_2O, 0 °C, quant.; (c) **14**, HATU, *i*-Pr_2NEt, DMF, 0 °C, then **10**, 0 °C to rt, 72%; (d) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 51%.

In summary, we achieved syntheses of majusculamides A and B via a longest linear sequence of 8 steps in 13% and 18% overall yields, respectively. The characteristic α-methyl-β-keto-carboxamide moiety could be constructed in a 2-step sequence, which includes condensation of the amine moiety in the peptide unit and the β-hydroxy-carboxylic acid units, followed by oxidation of the hydroxy group. The scheme can be used to synthesize analogues of majusculamides. Other biological

evaluation of the natural products and the analogues is currently underway and will be reported in due course.

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Supporting Information

YES

Primary Data

NO

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(3) Majusculamides A and B were also recently isolated by us from the marine cyanobacterium *Moorea producens* collected from the coast of Bise, Okinawa.

(4) No isomerization was observed in ^{1}H-NMR spectra of the pure amides in DMSO-d_6 at 140 °C after 10 minutes heating.

(5) The α-methyl-β-keto-carboxamide moiety is observed in the macrocyclic systems of some natural products. For synthetic studies toward such natural products, see: (a) Rinehart, K. L.; Kishore, V.; Nagarajan, S.; Lake, R. J.; Gloer, J. B.; Bozich, F. A.; Li, K.-M.; Maleczka, R. E.; Todsen, W. L.; Munro, M. H. G.; Sullins, D. W.; Sakai, R. *J. Am. Chem. Soc.* **1987**, *109*, 6846. (b) Plaza, A.; Garcia, R.; Bifulco, G.; Martinez, J. P.; Hüttel, S.; Sasse, F.; Meyerhans, A.; Stadler, M.; Müller, R. *Org. Lett.* **2012**, *14*, 2854. (c) Ghosh, A. K.; Rao, K. V.; Akasapu, S. *Tetrahedron Lett.* **2014**, *55*, 5191. (d) Qi, N.; Allu, S. R.; Wang, Z.; Liu, Q.; Guo, J.; He, Y. *Org. Lett.* **2016**, *18*, 4718. (e) Revu, O.; Prasad, K. R. *J. Org. Chem.* **2017**, *82*, 438. (f) Seo, C.; Yim, J. H.; Lee, H. K.; Park, S. M.; Sohn, J.-H.; Oh, H. *Tetrahedron Lett.* **2008**, *49*, 29. (g) Ghosh, A. K.; Xu, C.-X. *Org. Lett.* **2009**, *11*, 1963. (h) Reddy, K. M.; Shashidhar, J.; Pottireddygari, G. R.; Ghosh, S. *Tetrahedron Lett.* **2011**, *52*, 5987. (i) Kaneda, M.; Inuki, S.; Ohno, H.; Oishi, S. *J. Org. Chem.* **2018**, *83*, 3047.

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(8) In the case of *N*,*O*-dimethylhydroxamic acids, also known as Weinreb amides, α-methyl-β-keto compounds could be employed in further transformation under the appropriate conditions without isomerization, whereas the α-methyl-β-keto compounds could be used as substrates for asymmetric transfer hydrogenation with dynamic kinetic resolution. For examples, see: (a) Takamura, H.; Kadonaga, Y.; Kadota, I.; Uemura, D. *Tetrahedron* **2010**, *66*, 7569. (b) Kumaraswamy, G.; Narayanarao, V.; Shanigaram, P.; Balakishan, G. *Tetrahedron* **2015**, *71*, 8960.

(9) The structure of the α-methyl-β-keto-carboxamide moiety was supported by DFT calculations and NOESY experiments of simplified molecules. For details, see supporting information.

(10) Glucose uptake enhancement activity was also investigated. Both compounds had no effect on the glucose uptake up to a concentration of 30 μM in cultured L6 myotubes.

(11) Partial formation of an *N*,*O*-bis(Boc) product was observed under the conditions. The Boc group on the phenolic hydroxy group was easily cleaved during the ensuing methylation. For related reports, see: (a) Nakamura, K.; Nakajima, T.; Kayahara, H.; Nomura, E.; Taniguchi, H. *Tetrahedron Lett.* **2004**, *45*, 495. (b) Nishiyama, Y.; Ishizuka, S.; Shikama, S.; Kurita, K. *Chem. Pharm. Bull.* **2001**, *49*, 233.

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(19) **(2*R*,3*S*)-*N*-((*R*)-1-(((*S*)-1-amino-3-methyl-1-oxobutan-2-yl)(methyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)-3-hydroxy-*N*,2-dimethyldecanamide (15)** To a solution of carboxylic acid **14** (51.0 mg, 0.252 mmol) and *i*Pr_2NEt (0.048 mL, 0.28 mmol) in DMF (1.62 mL) was added HATU (106 mg, 0.278 mmol) at 0 °C. After stirring for 30 min, a solution of amine hydrochloride **10** (90.3 mg, 0.252 mmol) and *i*Pr_2NEt (0.097 mL, 0.56 mmol) in DMF (1.54 mL) was added dropwise at 0 °C. After the resulting mixture was stirred for 4 h at 25 °C, the reaction was quenched with 10% NaCl solution in water. The resulting mixture was extracted three times with AcOEt. The combined organic phases were washed with aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt / *n*-hexane 1:5 to 1:0) to give **15** (91.4 mg, 0.181 mmol, 72%) as a colorless oil. IR (film, cm^{-1}): 3397, 3205, 2929, 2856, 1691, 1627, 1514, 1466, 1405, 1301, 1249, 1178, 1095, 1036, 824; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ [7.14 (d, *J* = 8.8 Hz), 7.10 (d, *J* = 8.8 Hz), *all sum to* 2H), [6.81 (d, *J* = 8.8 Hz), 6.79 (d, *J* = 8.8 Hz), *all sum to* 2H], [6.71 (brs), 6.13 (brs), *all sum to* 1H], [5.70 (dd, *J* = 8.0, 7.6 Hz), 5.68 (dd, *J* = 8.0, 7.6 Hz), *all sum to* 1H], [5.58 (brs), 5.35 (brs), *all sum to* 1H], [4.50 (d, *J* = 10.8 Hz), 3.72 (d, *J* = 10.4 Hz), *all sum to* 1H], 3.80-3.60 (m, 1H), 4.15-4.06 (brs, 1H), [3.76(s), 3.76(s), *all sum to* 3H], 3.18-2.84 (m, 2H), [some signals including the followings: 3.06 (s), 2.99 (s), 2.96 (s), 2.91 (s), *all sum to* 6H], [2.57 (qd, *J* = 7.2, 2.0 Hz), 2.48 (qd, *J* = 7.2, 2.0 Hz), 1H], 2.34-2.15 (m, 1H), 1.48 (m, 2H), 1.34-1.17 (m, 10H), [0.97 (d, *J* = 6.4 Hz), 0.74 (d, *J* = 6.4 Hz), *all sum to* 3H], [0.93-0.81 (m), 0.65 (d, *J* = 6.4 Hz), 0.63 (d, *J* = 6.4 Hz), 6H], 0.89 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 178.6 (C), 178.1 (C), 172.1 (C), 171.8 (C), 171.6 (C), 169.1 (C), 158.6 (C), 158.5 (C), 130.3 (CH), 130.1 (CH), 128.2 (C), 128.0 (C), 113.9 (CH), 113.8 (CH), 71.2 (CH), 70.8 (CH), 63.5 (CH), 62.4 (CH), 55.3 (CH_3), 54.3 (CH), 53.9 (CH), 39.4 (CH), 39.0 (CH), 34.7 (CH_2), 34.6 (CH_2), 33.9 (CH_2), 33.5 (CH_2), 31.8 (CH_2), 31.1 (CH_3), 31.0 (CH_3), 30.7 (CH_3),

30.4 (CH_3), 29.6 (CH_2), 29.2 (CH_2), 27.3 (CH), 26.0 (CH_2), 25.9 (CH_2), 25.4 (CH), 22.6 (CH_2), 19.7 (CH_3), 19.3 (CH_3), 19.2 (CH_3), 18.3 (CH_3), 14.1 (CH_3), 9.3 (CH_3), 8.5 (CH_3); HRMS (ESI+) 528.3427 (calcd for $C_{28}H_{47}N_3NaO_5$ 528.3413); $[\alpha]_D^{23}$ −1.78° (*c* 0.310, $CHCl_3$).

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(21) **Majusculamide A (1)** To a solution of β-hydroxy amide **15** (26.1 mg, 0.0517 mmol) in CH_2Cl_2 (0.344 mL), were added $NaHCO_3$ (8.15 mg, 0.0971 mmol) and Dess-Martin periodinane (32.9 mg, 0.0775 mmol) at 0 °C. After stirring for 1 h at 25 °C, aq $NaHCO_3$ and aq $Na_2S_2O_3$ were added to the reaction mixture. The resulting solution was extracted three times with AcOEt. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by preparative TLC (AcOEt / *n*-hexane 5:1) to give **1** (13.3 mg, 0.0264 mmol, 51%) as a colorless oil. IR (film, cm^{-1}): 3335, 3208, 2930, 2863, 1688, 1635, 1510, 1463, 1400, 1297, 1250, 1178, 1107, 1040, 829; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ [7.14 (d, *J* = 8.4 Hz), 7.08 (d, *J* = 8.4 Hz), *all sum to* 2H], [7.01 (brs), 6.16 (brs), *all sum to* 1H], [6.80 (d, *J* = 8.4 Hz), 6.79 (d, *J* = 8.4 Hz), *all sum to* 2H], [5.71 (dd, *J* = 8.0, 8.0 Hz), 5.65 (dd, *J* = 9.2, 6.0 Hz), *all sum to* 1H], [5.50 (brs), 5.27 (brs), *all sum to* 1H], [4.54 (d, *J* = 10.8), 3.71 (d, *J* = 10.8 Hz), *all sum to* 1H], 3.77 (s, 3H), [3.59 (q, *J* = 7.0 Hz), 3.44 (q, *J* = 7.2 Hz), *all sum to* 1H], 3.20-2.85 (m, 2H), [some signals including the followings: 3.08 (s), 3.00 (s), 2.94 (s), 2.91 (s), *all sum to* 6H], 2.48-2.30 (m, 2H), [2.34-2.24 (m), 2.26-2.14 (m), *all sum to* 1H], 1.51 (m, 2H), 1.35-1.10 (m, 8H), [1.00-0.91 (m), 0.90-0.78 (m) 0.59 (d, *J* = 6.4 Hz), *all sum to* 6H], [1.22 (d, *J* = 7.0 Hz), 0.93 (d, *J* = 7.0 Hz), *all sum to* 3H] 0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 206.9 (C), 206.7 (C), 172.5 (C), 172.0 (C), 171.7 (C), 171.6 (C), 171.2 (C), 169.3 (C), 158.5 (C), 130.3 (CH), 130.1 (CH), 128.3 (C), 128.2 (C), 113.9 (CH), 113.8 (CH), 63.7 (CH), 62.5 (CH), 55.7 (CH), 55.3 (CH_3), 54.3 (CH), 51.2 (CH), 50.6 (CH), 40.5 (CH_2), 40.1 (CH_2), 34.9 (CH_2), 34.6 (CH_2), 31.6 (CH_2), 31.2 (CH_3), 30.9 (CH_3), 30.7 (CH_3), 29.6 (CH_3), 29.1 (CH_2), 27.6 (CH), 25.5 (CH), 23.5 (CH_2), 23.3 (CH_2), 22.6 (CH_2), 19.9 (CH_3), 18.8 (CH_3), 18.6 (CH_3), 18.4 (CH_3), 14.1 (CH_3), 13.4 (CH_3); HRMS (ESI+) 526.3252 (calcd for $C_{28}H_{45}N_3NaO_5$ 526.3257); $[\alpha]_D^{23}$ +33.2° (*c* 0.715, EtOH).

(22) **Majusculamide B (2)** To a solution of β-hydroxy amide (17.6 mg, 0.0348 mmol), prepared by condensation of *ent*-**14** with **10**, in CH_2Cl_2 (0.232 mL), were added $NaHCO_3$ (4.8 mg, 0.0568 mmol) and Dess-Martin periodinane (19.2 mg, 0.0453 mmol) at 0 °C. After stirring for 1 h at 25 °C, aq $NaHCO_3$ and aq $Na_2S_2O_3$ were added to the reaction mixture. The resulting solution was extracted three times with AcOEt. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by preparative TLC (AcOEt / *n*-hexane 5:1) to give **2** (10.8 mg, 0.0215 mmol, 62%) as a colorless oil. IR (film, cm^{-1}): 3336, 3209, 2958, 2931, 2856, 1722, 1691, 1633, 1514, 1467, 1400, 1301, 1249, 1178, 1128, 1101, 1073, 1038, 825; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ [7.16 (d, *J* = 8.6 Hz), 7.12 (d, *J* = 8.6 Hz), *all sum to* 2H], [6.80 (d, *J* = 8.6 Hz), 6.78 (d, *J* = 8.4 Hz), *all sum to* 2H], [6.74 (brs), 6.09 (brs), *all sum to* 1H], [5.77 (dd, *J* = 7.4, 7.4 Hz), 5.73 (dd, *J* = 8.8, 6.4 Hz), *all sum to* 1H], [5.48 (brs), 5.32 (brs), *all sum to* 1H], [4.48 (d, *J* = 10.8 Hz), 3.62 (d, *J* = 10.8 Hz), *all sum to* 1H], [3.76 (s), 3.75 (s), *all sum to* 3H], 3.61-3.43 (m, 1H), 3.18-2.85 (m, 2H), [some signals including the followings: 3.04 (s), 3.04 (s), 3.02 (s), 2.91 (s), *all sum to* 6H], 2.32-2.15 (m, 1H), [1.99 (dt, *J* = 17.6, 7.2 Hz), 1.93 (dt, *J* = 17.6, 7.2 Hz), 1.65-1.53 (m), *all sum to* 2H], 1.50-1.32 (m, 2H), 1.32-1.06 (m, 8H), 1.28 (d, *J* = 7.2 Hz, 3H), [0.97 (d, *J* = 6.4 Hz), 0.92 (d, *J* = 6.4 Hz), 0.91-0.84 (m), 0.75 (d, *J* = 6.8 Hz), 0.63 (d, *J* = 6.8 Hz), *all sum to* 6H], 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 206.6 (C), 205.5 (C), 172.2 (C), 171.8 (C), 171.5 (C), 171.4 (C), 171.0 (C), 169.2 (C), 158.5 (C), 130.3 (CH), 130.1 (CH), 128.3 (C), 113.9 (CH), 63.7 (CH), 62.4 (CH), 55.1 (CH_3), 55.0 (CH_3), 54.9 (CH), 54.3 (CH), 51.4 (CH), 50.7 (CH), 39.4 (CH_2), 39.3 (CH_2), 34.8 (CH_2), 34.6 (CH_2), 31.2 (CH_2), 31.6 (CH_3), 30.9 (CH_3), 30.5 (CH_3), 29.5 (CH_3), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 27.4 (CH), 25.4 (CH), 23.4 (CH_2), 23.4 (CH_2), 22.6 (CH_2), 19.7 (CH_3), 19.2 (CH_3), 19.2 (CH_3), 18.3 (CH_3), 14.1 (CH_3), 13.7 (CH_3), 13.6 (CH_3); HRMS (ESI+) 526.3278 (calcd for $C_{28}H_{45}N_3NaO_5$ 526.3257); $[\alpha]_D^{23}$ +25.5° (*c* 0.580, EtOH).