Tetrahedron Letters 50 (2009) 7343–7345

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of palau'amide and its diastereomers: confirmation of its stereostructure

Hirokazu Sugiyama, Atsushi Watanabe, Toshiaki Teruya †, Kiyotake Suenaga *

Department of Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku, Yokohama 223-8522, Japan

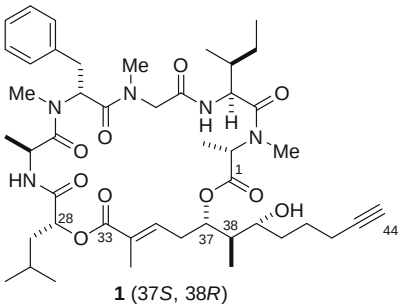
ARTICLE INFO

Article history:
Received 8 September 2009
Revised 12 October 2009
Accepted 13 October 2009
Available online 31 October 2009

ABSTRACT

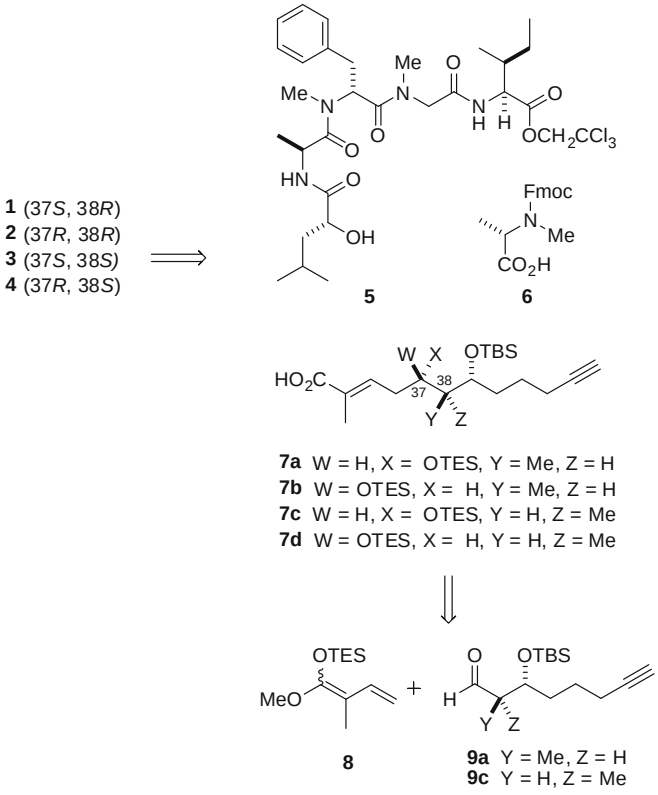
Four diastereomers of palau'amide (**1**–**4**), a cytotoxic cyclodepsipeptide, were synthesized. The ^{1}H NMR spectrum of **1** was identical to that of natural palau'amide. This established the complete stereostructure of palau'amide.

Palau'amide (**1**) is a 24-membered cyclodepsipeptide that was isolated in 2003 by Moore and co-workers from a species of the marine cyanobacterium *Lyngbya* collected at Palau. It has been shown to exhibit potent cytotoxicity against KB cells with an IC_{50} value of 13 nM (Fig. 1).[1] The absolute configurations of all but one (C37) of the nine chiral centers were determined by NMR analysis of **1** and the α-methoxyphenylacetic acid derivatives and chiral HPLC analysis of the acid hydrolysate of **1**. The stereochemistry of C37 was proposed based on NMR analysis of **1**, including NOE data and theoretical calculations. In 2005, Dawei Ma and co-workers achieved a total synthesis of the proposed structure of palau'amide (**1**),[2] however the NMR data of synthetic **1** were not identical to those of natural **1**. Recently, synthesis of the C33–C44 fragment of palau'amide was reported by Mohapatra and Nayak.[3] It is generally difficult to determine the stereochemistries of conformationally flexible systems. Since the stereochemistry of C39 was clearly determined by NMR analysis of the α-methoxyphenylacetic acid esters,[4] the stereochemistries of C37 and C38 should be reconsidered. To determine the stereochemistry of palau'amide, we began by synthesizing **1**. We describe here the synthesis of four possible diastereomers of palau'amide with reference to C37 and C38.



1 (37*S*, 38*R*)

Figure 1. Structure of palau'amide.



Scheme 1. Retrosynthesis of palau'amide and its diastereomers with regard to C37 and C38.

* Corresponding author. Tel./fax: +81 45 566 1819.
E-mail address: suenaga@chem.keio.ac.jp (K. Suenaga).
† Present address: Faculty of Education, University of the Ryukyus, 1 Senbaru, Nishihara, Okinawa 903-0213, Japan.

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.10.059

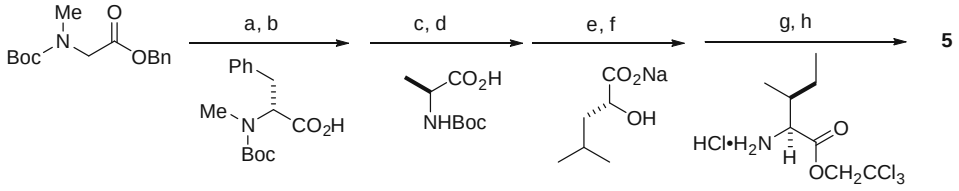
A retrosynthetic analysis of palau'amide and its diastereomers (**1**–**4**) is shown in Scheme 1. A key step in the synthesis of palau'amide is closure of the 24-membered ring. We planned to construct the cyclic structure by macrolactamization at the *N*-methylalanine-isoleucine site. The precursor of macrocyclization was synthesized from pentapeptide **5**, *N*-Fmoc-*N*-Me-L-Ala (**6**), and protected carboxylic acids (**7a**–**d**). Carboxylic acids (**7a**–**d**) could be synthesized by a vinylogous Mukaiyama aldol reaction[5] between 2-methyl-1-triethylsiloxy-1-methoxy-1,3-butadiene (**8**)[6] and aldehydes **9a** and **9b**.

The synthesis of pentapeptide **5** was carried out in a stepwise manner starting from *N*-Boc-*N*-methylglycine benzyl ester, and **5** was obtained in 64% overall yield (Scheme 2).

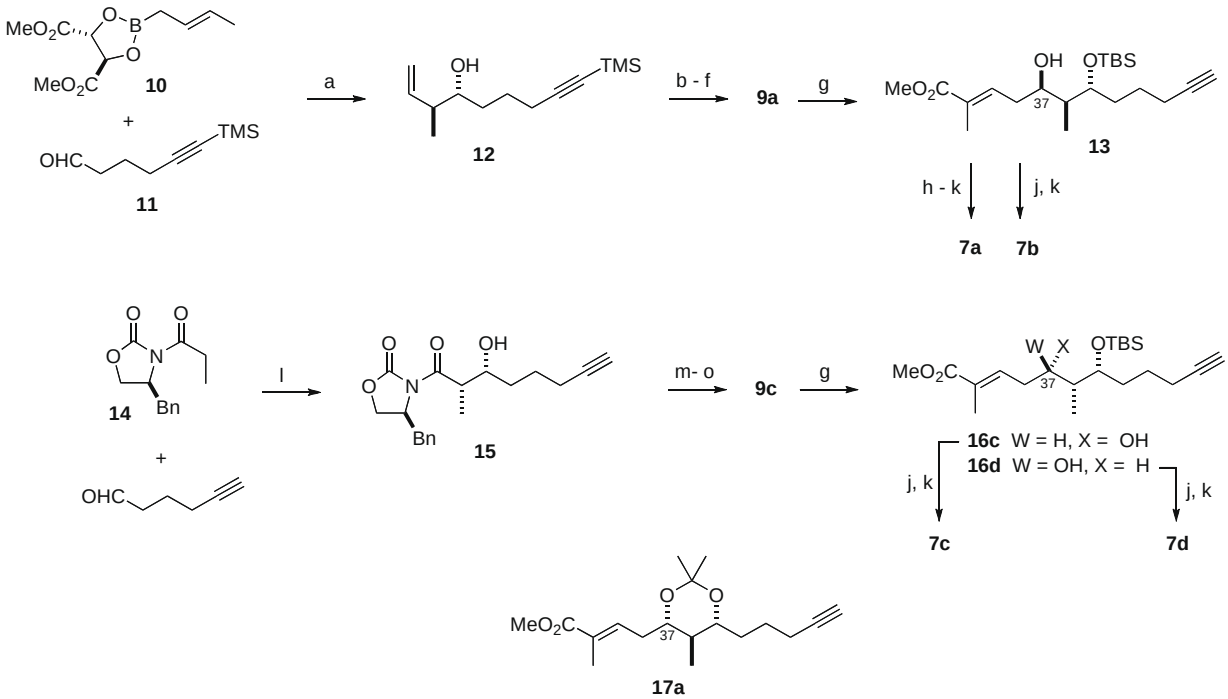
The synthesis of protected carboxylic acids **7a** and **7b** began with a Roush crotylboration reaction[7] between boronate **10** and 6-trimethylsilyl-5-hexynal to afford homoallylic alcohol **12** as a single diastereomer (Scheme 3). Silylation of a hydroxyl group of **12**, removal of a TMS group, re-silylation of a partially deprotected hydroxyl group, and oxidative cleavage of an olefin moiety provided aldehyde **9a**. The vinylogous Mukaiyama aldol reaction between **9a** and **8** gave alcohol **13** as a single diastereomer. Inversion of the stereochemistry of a hydroxyl group of **13**, silylation of a hydroxyl group, and hydrolysis of a methyl ester afforded carboxylic acid **7a** (see Supplementary data). On the other hand, manipulation of the protecting groups provided carboxylic acid **7b**. The stereochemistry of the newly formed hydroxyl group at C37 was determined based on the ^{13}C chemical shifts of the acetonide methyls (δ_C 30.1 and 19.6 ppm)[8] of the derived acetonide **17a**.

The synthesis of carboxylic acids **7c** and **7d** began with an Evans aldol reaction[9] between imide **14** and 5-hexynal to afford hydroxy imide **15** as a single diastereomer (Scheme 3). Transamidation and protection of a hydroxyl group of **15** followed by reduction of the amide provided aldehyde **9c**. The vinylogous Mukaiyama aldol reaction between **9c** and **8** gave alcohols **16c** and **16d** (dr = 8:1), which were transformed into **7c** and **7d**, respectively, in the same manner as described above. The stereochemistry of C37 in **7b**, **7c**, and **7d** was determined by ^{13}C NMR analysis of the derived acetonides, respectively.

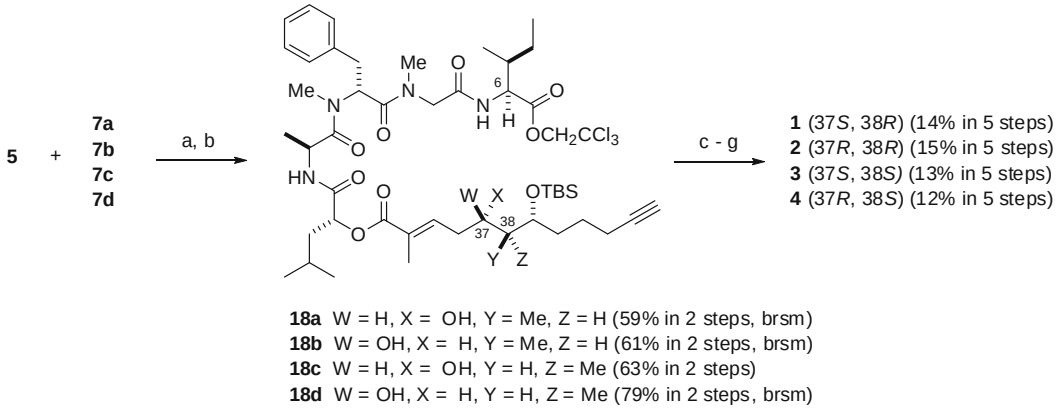
The condensation of carboxylic acids **7a**, **7b**, **7c**, and **7d** with pentapeptide **5** followed by selective desilylation afforded alcohols **18a**, **18b**, **18c**, and **18d**, respectively (Scheme 4). Esterification of **18a**, **18b**, **18c**, and **18d** with *N*-Fmoc-*N*-Me-L-Ala (**6**), removal of



Scheme 2. Synthesis of pentapeptide **5**. Reagents and conditions: (a) TFA, CH_2Cl_2, 0 °C, 1.5 h; (b) DEPC Et_3N, DMF, rt, 16 h, 94% in two steps; (c) TFA, CH_2Cl_2, 0 °C, 1.5 h; (d) DEPC Et_3N, DMF, rt, 17 h, 94% in two steps; (e) TFA, CH_2Cl_2, 0 °C, 1.5 h; (f) EDCI·HCl, HOBt, Et_3N, DMF, rt, 17 h, 75% in two steps; (g) H_2, 5% Pd–C, EtOH, rt, 5.5 h; (h) EDCI·HCl, HOBt, Et_3N, DMF, rt, 12.5 h, 96% in two steps.



Scheme 3. Synthesis of protected carboxylic acids. Reagents and conditions: (a) MS 4 Å, toluene, −78 °C, 3 h, quant.; (b) TBSCl, imidazole, DMF, rt, 3 h, 94%; (c) Bu_4NF, THF, rt, 1 h; (d) TBSCl, imidazole, DMF, rt, 2.5 h, 100% in two steps; (e) OsO_4, NMO, acetone–H_2O, rt, 75 min; (f) $NaIO_4$, acetone–H_2O, rt, 1.5 h, 56% in two steps (recovered diol 28%); (g) **8**, BF_3·Et_2O, CH_2Cl_2–Et_2O, –40 °C, 4.5 h; then aq HCl, (**13**) 80%, (**16c**) 81% based on recovered starting material (br sm), (**16d**) 10% br sm; (h) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, quant; (i) $NaBH_4$, MeOH, −78 °C, 1.5 h, 83%; (j) LiOH, H_2O, MeOH, 40 °C, 17 h; (k) TESCl, imidazole, DMF, rt, 4.5 h; (**7a**) 90% in two steps, (**7b**), 72% in two steps, (**7c**) 83% in two steps, (**7d**) 41% in two steps; (l) Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C, 2 h→rt, 1 h, quant; (m) $Me_2AlN(Me)OMe$, THF, toluene, −10 °C, 4 h, 79%; (n) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 4 h, 99%; (o) DIBAL, THF, hexane, −78 °C, 3 h, 91%.



Scheme 4. Synthesis of palau'amide and its diastereomers. Reagents and conditions: (a) EDCI·HCl, DMAP, CH_2Cl_2, rt, 16 h; (b) AcOH, H_2O, THF, rt, 6 h; (c) Fmoc-*N*-Me-L-Ala (**6**), 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, rt, 16 h; (d) Zn, NH_4OAc, THF, rt, 3 h; (e) Et_2NH, MeCN, rt 3 h; (f) EDCI·HCl, HOAt, Et_3N, DMF–CH_2Cl_2 (1:10, 1 mM), rt, 45 h; (g) HF·pyridine, pyridine, rt, 2 h.

the 2,2,2-trichloroethyl and Fmoc-protecting groups, and macrolactamization provided proposed palau'aminde and its diastereomers (**1**–**4**)[10] after desilylation, respectively. Among the ^{1}H NMR spectra of the four synthetic diastereomers, **1**, **2**, **3**, and **4**, that of **1** was identical to that of natural palau'amide, except for exchangeable protons (see Supplementary data). Furthermore, the ^{13}C NMR spectrum of synthetic **1**[9] was identical to that of natural palau'amide (see Supplementary data). Based on these findings, the complete stereostructure of palau'amide was determined, as shown in formula **1**.

In summary, the synthesis of four possible diastereomers of palau'amide with regard to C37 and C38 was achieved. Among the ^{1}H NMR spectra of the four synthetic diastereomers (**1**–**4**), that of **1** was identical to that of natural palau'amide. This established the complete stereostructure of palau'amide.

Acknowledgments

We thank Professor Philip Williams (University of Hawaii) for providing NMR data of natural palau'amide. This work was supported by a Grant-in-Aid for Scientific Research and a Grant for Private Education Institute Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and Keio Gijuku Academic Development Funds.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.059.

References and notes

1. Williams, P. G.; Yoshida, W. Y.; Quon, M. K.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2003**, *66*, 1545.
2. Zou, B.; Long, K.; Ma, D. *Org. Lett.* **2005**, *7*, 4237.
3. Mohapatra, D. K.; Nayak, S. *Tetrahedron Lett.* **2008**, *49*, 786.
4. Seco, J. M.; Latypov, S. K.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1997**, *62*, 7569.
5. (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503; (b) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413.
6. Suenaga, K.; Mutou, T.; Shibata, T.; Itoh, T.; Fujita, T.; Takada, N.; Hayamizu, K.; Takagi, M.; Irifune, T.; Kigoshi, H.; Yamada, K. *Tetrahedron* **2004**, *60*, 8509.
7. Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.
8. (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945; (b) Evans, D. A.; Rieger, D. L. *Tetrahedron Lett.* **1990**, *31*, 7099; (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.
9. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
10. *Compound* **1** (synthetic): $[\alpha]_D^{28}$ −16 (*c* 0.22, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 10.1 Hz, 0.5H), 7.81 (d, *J* = 9.6 Hz, 0.5H), 7.32–7.27 (m, 1.5H), 7.22–7.18 (m, 2H), 7.15 (t, *J* = 6.9 Hz, 0.5H), 7.14 (d, *J* = 7.1 Hz, 1H), 7.10 (d, *J* = 9.6 Hz, 0.5H), 6.84 (dd, *J* = 6.6, 6.2 Hz, 0.5H), 6.55 (br d, *J* = 10.2 Hz, 0.5H), 6.21 (d, *J* = 8.6 Hz, 0.5H), 5.53 (dd, *J* = 8.4, 3.7 Hz, 0.5H), 5.45 (dd, *J* = 10.8, 5.4 Hz, 0.5H), 5.27 (dt, *J* = 11.8, 3.3 Hz, 0.5H), 5.23 (dd, *J* = 10.4, 6.0 Hz, 0.5H), 5.15 (dd, *J* = 9.6, 4.3 Hz, 0.5H), 5.09 (dq, *J* = 10.1, 6.6 Hz, 0.5H), 4.95 (d, *J* = 17.2 Hz, 0.5H), 4.86 (t, *J* = 9.7 Hz, 0.5H), 4.82 (m, 0.5H), 4.68 (dd, *J* = 9.9, 4.0 Hz, 0.5H), 4.60 (dq, *J* = 8.6, 7.1 Hz, 0.5H), 4.50 (q, *J* = 6.9 Hz, 0.5H), 4.06 (d, *J* = 18.1 Hz, 0.5H), 3.61 (m, 0.5H), 3.59 (q, *J* = 7.1 Hz, 0.5H), 3.52 (m, 0.5H), 3.34 (s, 1.5H), 3.20 (m, 0.5H), 3.20 (d, *J* = 18.1 Hz, 0.5H), 3.20 (s, 1.5H), 3.12 (dd, *J* = 14.9, 10.8 Hz, 0.5H), 3.11–3.07 (m, 1.0H), 3.06–3.00 (m, 1H), 2.97 (s, 1.5H), 2.96 (s, 1.5H), 2.88 (m, 0.5H), 2.60 (s, 1.5H), 2.51 (s, 1.5H), 2.40 (m, 0.5H), 2.26–2.21 (m, 2H), 2.20 (m, 0.5H), 1.98 (m, 0.5H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.97–1.91 (m, 1.0H), 1.88 (br s, 1.5H), 1.87 (m, 0.5H), 1.84 (m, 0.5H), 1.81 (m, 0.5H), 1.78 (m, 0.5H), 1.75 (m, 1.0H), 1.74 (br s, 1.5H), 1.74–1.68 (m, 1.5H), 1.65–1.60 (m, 1.5H), 1.57 (m, 0.5H), 1.51 (d, *J* = 7.1 Hz, 1.5H), 1.49–1.41 (m, 2.5H), 1.39 (d, *J* = 6.9 Hz, 1.5H), 1.25 (m, 0.5H), 1.20 (d, *J* = 6.6 Hz, 1.5H), 0.983 (t, *J* = 7.5 Hz, 1.5H), 0.975 (d, *J* = 7.0 Hz, 1.5H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 1.5H), 0.903 (d, *J* = 6.5 Hz, 1.5H), 0.898 (d, *J* = 6.7 Hz, 3.0H), 0.86 (t, *J* = 7.4 Hz, 1.5H), 0.83 (d, *J* = 7.0 Hz, 1.5H), 0.76 (d, *J* = 7.1 Hz, 1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) (rotamer 1) δ 173.0, 171.3, 171.2, 170.1, 169.6, 168.6, 168.4, 139.8, 135.9, 129.0, 128.8, 128.4, 127.4, 84.1, 75.6, 73.4, 71.7, 68.9, 60.1, 53.7, 52.2, 51.12, 44.5, 42.1, 40.7, 38.2, 37.2, 36.6, 34.9, 33.9, 29.9, 28.5, 24.7, 24.45, 24.42, 23.1, 21.7, 18.0, 16.2, 15.0, 13.7, 12.5, 10.8, 10.4; (rotamer 2) δ 173.3, 172.9, 170.6, 169.7, 169.5, 168.2, 166.5, 138.9, 136.8, 130.6, 129.5, 128.0, 126.4, 84.4, 76.7, 72.2, 71.8, 68.7, 55.7, 54.6, 53.2, 51.08, 44.9, 42.4, 40.9, 38.5, 35.8, 35.5, 31.6, 31.5, 30.9, 27.7, 24.49, 24.13, 23.39, 23.1, 21.8, 18.3, 16.54, 16.50, 14.2, 13.5, 12.3, 12.3; HRESIMS *m/z* calcd for $C_{46}H_{69}O_{10}N_5$ $(M+H)^+$ 852.5123, found 852.5065.
Compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 7.27–7.17 (m, 5H), 6.94 (tq, *J* = 6.4, 1.2 Hz, 1H), 5.57 (q, *J* = 6.8 Hz, 1H) 5.36 (m, 1H), 5.05 (dd, *J* = 3.4, 4.0 Hz, 1H), 4.93 (dd, *J* = 5.2, 6.4 Hz, 1H), 4.78 (d, *J* = 17.6 Hz, 1H), 4.20 (dt, *J* = 5.0, 5.6 Hz, 1H), 3.77 (q, *J* = 6.0 Hz, 1H), 3.63–3.44 (m, 2H), 3.23 (s, 3H), 3.10 (s, 3H), 3.00 (m, 2H), 2.94 (s, 3H), 2.39 (dd, *J* = 5.6, 6.4 Hz, 2H), 2.20 (dt, *J* = 2.4, 6.8 Hz, 2H), 2.17 (m, 1H), 1.92 (t, *J* = 2.4 Hz, 1H), 1.85 (d, *J* = 1.2 Hz, 3H), 1.66–1.19 (m, 10H), 1.46 (d, *J* = 6.8 Hz, 3H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.16 (d, *J* = 6.0 Hz, 3H), 0.95 (t, *J* = 5.4 Hz, 3H), 0.94–0.85 (m, 6H). Signals due to three protons (NH × 2, OH) were not observed. The ratio of rotamers was ca. 13:3:1.
Compound **3**: ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 8.05 (d, *J* = 9.8 Hz, 1H), 7.27–7.12 (m, 6H), 6.46 (d, *J* = 9.8 Hz, 1H), 5.54 (dd, *J* = 3.2, 4.0 Hz, 1H), 5.20 (q, *J* = 6.4 Hz, 1H), 5.09 (d, *J* = 5.2 Hz, 1H), 4.96 (d, *J* = 17.2 Hz, 1H), 4.65 (m, 1H), 4.41 (q, *J* = 7.6 Hz, 1H), 4.20 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.58 (m, 1H), 3.23–3.12 (m, 2H), 3.19 (s, 3H), 3.06 (d, *J* = 17.2 Hz, 1H), 2.57 (s, 3H), 2.50 (s, 3H), 2.33 (dd, *J* = 4.0, 4.0 Hz, 2H), 2.23–2.21 (m, 2H), 1.99 (m, 1H), 1.86 (t, *J* = 4.0 Hz, 1H), 1.72 (s, 3H), 1.66–1.06 (m, 10H), 1.39 (d, *J* = 6.8 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.90–0.74 (m, 12H). A signal due to OH was not observed. The ratio of rotamers was ca. 13:1.
Compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 7.50–7.16 (m, 5H), 6.54 (t, *J* = 7.6 Hz, 1H), 5.33 (m, 2H), 5.10 (dd, *J* = 3.4, 6.8 Hz, 1H), 4.94 (m, 1H), 4.20 (m, 1H), 4.12 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.76–3.47 (m, 3H), 3.22 (s, 3H), 3.20–2.79 (m, 2H), 3.09 (s, 3H), 2.61 (s, 3H), 2.33 (dd, *J* = 7.6, 7.6 Hz, 2H), 2.21 (dt, *J* = 4.0, 8.0 Hz, 2H), 2.05–1.94 (m, 2H), 1.78 (s, 3H), 1.66–1.07 (m, 13H), 1.37 (d, *J* = 7.6 Hz, 3H), 0.99–0.78 (m, 15H). Signals due to three protons (NH × 2, OH) were not observed. The ratio of rotamers was ca. 15:1.