JOC The Journal of Organic Chemistry

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# Prediction and Determination of the Stereochemistry of the 1,3,5-Trimethyl-Substituted Alkyl Chain in Verucopeptin, a Microbial Metabolite

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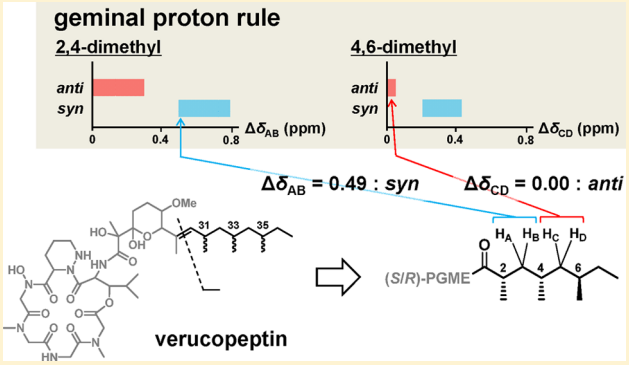
Supporting Information

**ABSTRACT:** For the prediction of the relative stereochemistry of 1,3-dimethyl substitution in alkyl chains, a simple approach based on $^1$H NMR data was recently proposed; $\Delta\delta$ values of methylene protons located between methyl-substituted methine carbons can be diagnostic for predicting it. Here we applied this empirical "geminal proton rule" to verucopeptin, a lipopeptide from *Streptomyces* sp. To determine the absolute stereochemistry of the 1,3,5-trimethyl-substituted alkyl chain in verucopeptin, we converted the corresponding alkyl chain to a carboxylic acid by oxidative cleavage. The geminal proton rule clearly predicted the relative stereochemistry as 31*S**,33*S**,35*R**. This prediction was definitely confirmed by synthesizing four possible diastereomers and comparing their NMR spectra. Furthermore, we reinvestigated the geminal proton rule using reported compounds and our synthesized compounds. Our result strongly suggests that the rule was solid, at least for predicting the stereochemistry of 2,4-dimethylated and 2,4,6-trimethylated fatty acids.




## INTRODUCTION

Natural products occupy a wide chemical space and exhibit unique and sometimes medically important biological activities.[1,2] However, their complex chemical structures often hamper structure determination. For example, determination of the stereochemistry of acyclic structures is a challenging task in spite of the advancement of spectroscopic and chemical methodologies.

Several NMR techniques have been developed for determination of the stereochemistry in acyclic compounds.[3] *J*-based configurational analysis (JBCA), developed by Murata and co-workers, allows the assignment of *anti* or *gauche* relationships of two adjacent stereogenic centers.[4,5] This method exploits $^1$H−$^1$H and $^1$H−$^{13}$C coupling constants. By integrating the *J* information and NOESY correlations, we can determine relative stereochemistries of contiguous or 1,3-skipped stereogenic centers. The universal NMR database (UDB) is another powerful means constructed by Kishi and co-workers.[6−8] This database includes $^1$H and $^{13}$C NMR chemical shifts for diastereomers of polyol or related chain structures. We can compare the NMR data of a compound of interest with the database to identify the most likely diastereomer. In addition to database approaches, calculation of NMR chemical shifts is effective for predicting the stereochemistry.[3] Quantum chemistry methods can calculate NMR chemical shifts for candidate diastereomers, which can be compared with those of a molecule in question.

One of the challenging structures often found in natural products is the 1,3-dimethyl-substituted system. We can elucidate its stereochemistry by adopting JBCA, whereas measurement and/or calculation of NMR chemical shift values can predict it. However, even these excellent methods are not always applicable and alternative analytical means are required. Recently, a simple and highly sensitive method only analyzing the $^1$H NMR data has been proposed: $^1$H NMR chemical shifts of the methylene protons located between two methyl-bearing methine carbons in acyclic 1,3-dimethyl systems can be diagnostic (Figure 1).[9−11] In 2003, Ishibashi and co-workers noticed this phenomenon when they synthesized diastereomers of the partial structure of TT-1/rasfonin.[9] In 2010 and 2012, Breit and co-workers generalized this as an empirical rule by investigating more than 80 compounds.[10,11]

In the proposed empirical rule, when the difference of $^1$H NMR chemical shifts for the methylene protons $H_A$ and $H_B$ is small, the configuration might be *anti* and vice versa (Figure 1). This rule (here we call this the "geminal proton rule") can be logically explained as described previously.[11,12] Basically, the

**Received:** April 24, 2014
**Published:** July 11, 2014

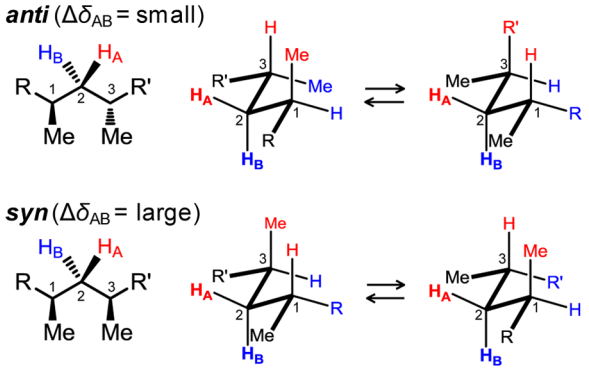



**Figure 1.** Conformational preference of 1,3-dimethyl-substituted structures and assignment of the relative stereochemistry. $\Delta\delta$ values for the methylene protons ($H_A$ and $H_B$) are diagnostic for distinguishing the *syn* and *anti* configurations. However, the differential values are sometimes largely affected by the species of R and R′.

preferentially populated conformations of an acyclic 1,3-dimethyl system are determined by the avoidance of *syn*-pentane interactions. Therefore, the only two conformers that are free of *syn*-pentane interactions are preferred, as shown in Figure 1. In each conformer, $H_A$ and $H_B$ in an *anti* conformation are homotopic, each being *syn* to one proton and *syn* to one methyl group on the adjacent carbons in the chain. In contrast, the two protons in a *syn* conformation are diastereotopic, owing to a different chemical environment even when R = R′.[9] Next, R and R′ functions can affect the molecular environment experienced by $H_A$ and $H_B$. This may change the absolute chemical shift values of $H_A$ and $H_B$, whereas the effect against differential values between $H_A$ and $H_B$ in the *anti* configuration remains small, judging from the literature values for more than 80 compounds.[10,11] However, the range of differential values depends on the functional groups R and R′.[11] In addition, ambiguity can arise when compounds have bulky or shielding substituents. For a correct assignment, it is important to define the structure types that are compatible with the geminal proton rule and the corresponding differential values.

In the course of our screening for bioactive metabolites from natural sources, we isolated tumescenamide C and verucopeptin, both of which possess a 1,3-dimethyl-substituted system in acyclic structures. We reported the stereochemistry of 2,4-dimethylheptanoic acid in tumescenamide C by comparing the NMR spectra of the natural product derived compounds and synthesized authentic samples.[13] In this paper, we first confirmed the applicability of the geminal proton rule to tumescenamide C and its degradation products. We then applied the rule to verucopeptin for predicting the stereochemistry of a 1,3,5-trimethyl-substituted aliphatic chain. Analysis of the $^1$H NMR data for the fragment structures of verucopeptin predicted the 31*S**,33*S**,35*R** stereochemistry, which was definitely confirmed by synthesizing authentic compounds. Our results indicate that the geminal proton rule is a reliable method to determine the relative stereochemistry of 2,4-dimethyl and 2,4,6-trimethyl fatty acids.

## RESULTS AND DISCUSSION

**2,4-Dimethyl Carboxylic Acids in Tumescenamides.** Recently, we reported the isolation and structure elucidation of a cyclic lipodepsipeptide, tumescenamide C (**1**), from *Streptomyces* sp. (Figure 2a).[13] The absolute stereochemistry of

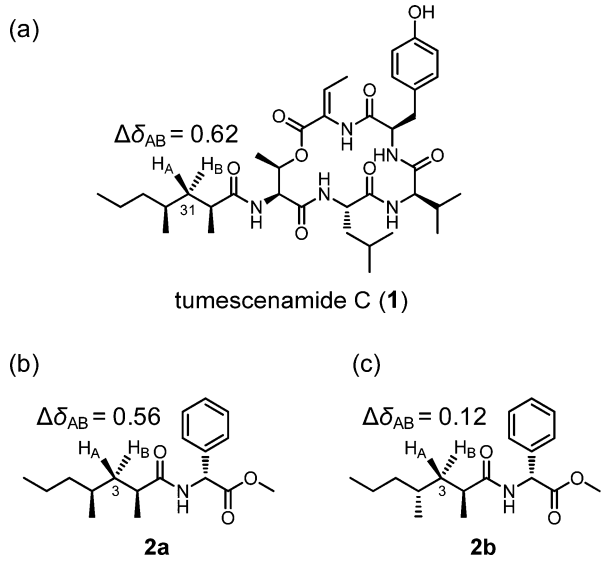



**Figure 2.** $\Delta\delta$ values for tumescenamide C (**1**). $\Delta\delta$ values for methylene protons at C31 for the intact natural product (a) and synthesized molecules (b, c) are shown. $\Delta\delta$ values are shown in ppm.

2,4-dimethylheptanoic acid in **1** was determined to be 2*S*,4*S* by chemical degradation and asymmetric synthesis; we synthesized the phenylglycine methyl ester (PGME) derivative **2a** and its diastereomer **2b** (Figure 2b,c) and compared their physicochemical properties with those of the PGME derivatives of 2,4-dimethylheptanoic acid that were obtained by hydrolysis of the natural product **1**. To investigate whether the geminal proton rule can be applicable to compound **1**, we reanalyzed the $^1$H NMR chemical shift values of the methylene protons at C31. The difference of the two geminal protons was large enough (0.62 ppm), suggesting that the two methyl groups at C30 and C32 are located in a *syn* configuration (Figure 2a). This prediction was consistent with our previous results.[13] The $\Delta\delta$ values for methylene protons at C3 in synthetic **2a**,**b** were 0.56 and 0.12 ppm, respectively, confirming the utility of the geminal proton rule. In addition, the $^1$H NMR spectrum of tumescenamide A, a diastereomer of tumescenamide C, also showed a large chemical shift difference (0.65 ppm) for the geminal protons at C31, suggesting the *syn* configuration of the two methyl groups.[14] This prediction was also consistent with the reported structure that was deduced by the JBCA method.[14]

**NMR Analysis of Verucopeptin.** Verucopeptin (**3**) is an antitumor compound originally reported from *Actinomadura verrucosospora* Q886-2.[15,16] This metabolite is composed of a cyclic depsipeptide and a polyketide side chain possessing three branched methyl groups. We reisolated verucopeptin (**3**) from the culture broth of *Streptomyces* sp. KUSC_A08. Because the stereochemistry had not been determined, we tried to predict the configuration of the 1,3,5-trimethylated alkyl chain by using the geminal proton rule. However, heavily overlapping signals due to the dynamic equilibrium between a cyclic hemiacetal form and a linear keto form hampered the complete assignment of $^1$H NMR signals.[16] To overcome this problem, we converted compound **3** to the linear derivative **4** using $NaBH_4$ (Figure 3a).[16,17] We successfully assigned the $^1$H NMR signals (Table S1, Supporting Information) and obtained $\Delta\delta$ values for $H_2$-32 and $H_2$-34 (Figure 3a). The $\Delta\delta$ value for $H_2$-34 (0 ppm) implied the *anti* relationship of the two methyl groups at C33 and C35. However, the $\Delta\delta$ value for $H_2$-32 (0.14 ppm) was not significant enough to predict the stereochemistry. As analyzed previously,[11] the $\Delta\delta$


dx.doi.org/10.1021/jo500906v | J. Org. Chem. 2014, 79, 6858−6867

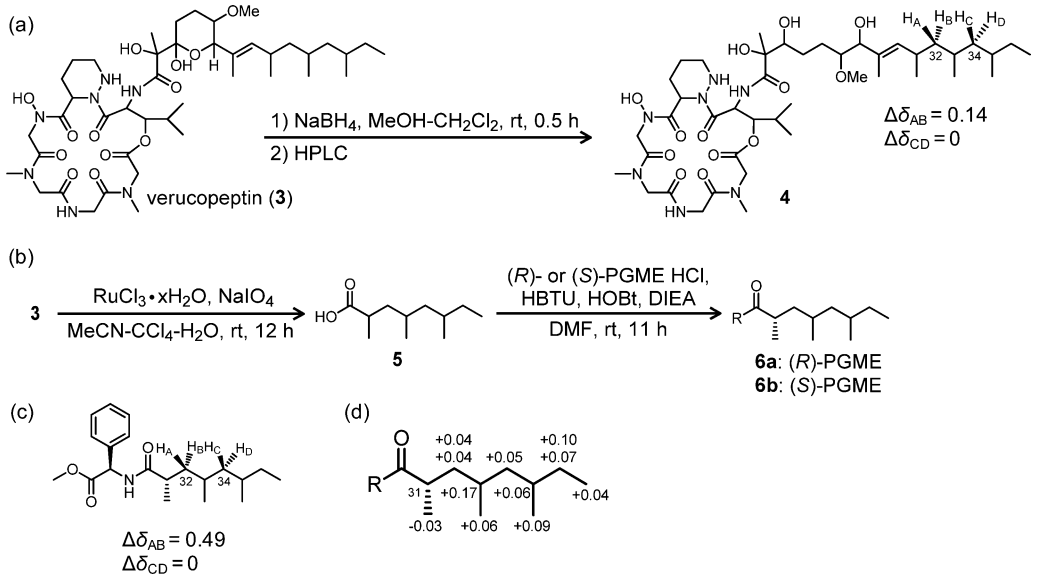
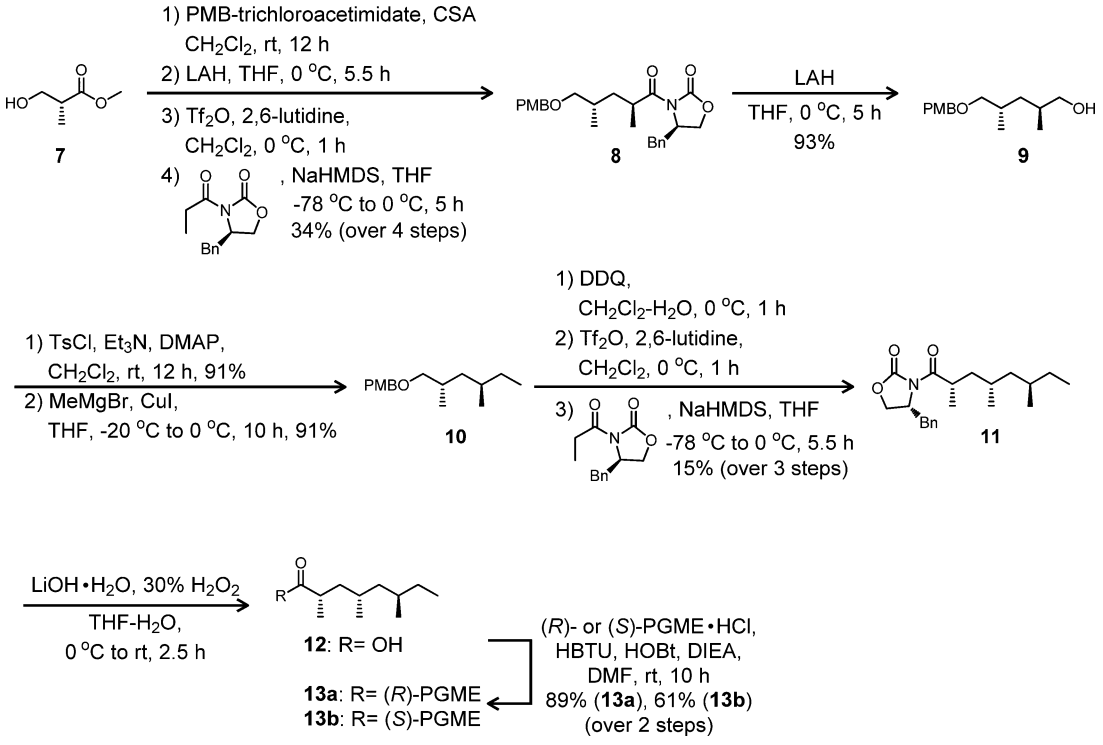



**Figure 3.** Prediction of the stereochemistries of C31, C33, and C35 in verucopeptin (**3**): (a) preparation of the reduced derivative **4** and $\Delta\delta$ values at C32 and C34; (b) preparation of PGME derivatives **6a,b**; (c) $\Delta\delta$ values for C32 and C34 in **6a**; (d) $\Delta\delta$ ($\delta_{(S)\text{-PGME}}$-$\delta_{(R)\text{-PGME}}$) values for **6a,b**. $\Delta\delta$ values are shown in ppm.

**Scheme 1. Synthesis of (2*S*,4*S*,6*R*)-2,4,6-Trimethyloctanoic Acid (12) and Its Derivatives**




values for the *syn* configuration and those for the *anti* configuration sometimes do not show a clear difference when the alkenyl group was located just beside the methyl group. In addition, the cyclic depsipeptide portion could affect the conformation of the side chain. In fact, the $\Delta\delta$ value was very large (0.57 ppm) for the methylene protons in bitungolide A in spite of its *anti* configuration, probably because the lactone ring adjacent to the 1,3-methyl structure affects the stability of the conformer.[11] Another example is atpenin A5: a very large $\Delta\delta$ value (0.40 ppm) was observed for its *anti* configuration, which can be due to the presence of a 2,4-dihydroxy 5,6-dimethoxypyridine ring that may constrain the conformation and/or exert a magnetic shielding effect.[11]

As suggested by Breit and co-workers, and as shown above using tumescenamides, 2,4-dimethyl and 2,4,6-trimethyl carboxylic acids seem to give clear results by the geminal proton rule. Hence, we decided to obtain the side chain of compound **3** as a carboxylic acid. For this purpose, we tested several oxidation conditions: e.g., $OsO_4$, $H_2WO_4$, and $RuCl_3$. We found that oxidative cleavage using $RuCl_3$ and $NaIO_4$ successfully furnished the carboxylic acid **5**. We converted the carboxylic acid **5** to PGME derivatives **6a,b** and analyzed their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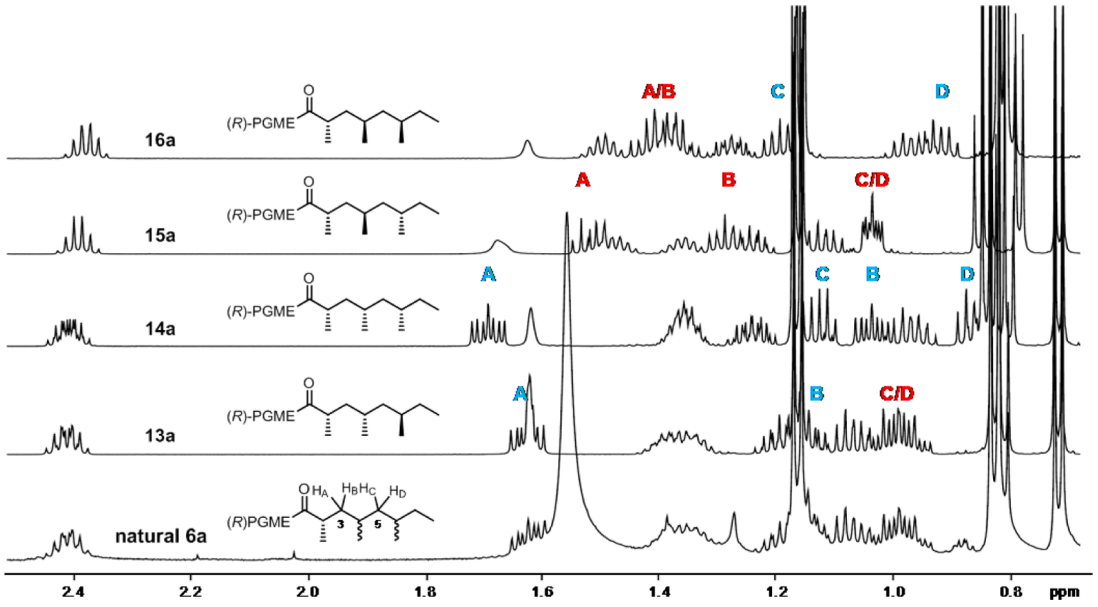



**Figure 4.** Comparison of the $^1$H NMR spectra for PGME derivatives of 2,4,6-trimethyloctanoic acids. The aliphatic region of the spectra for natural product derived **6a** (natural) and the synthesized diastereomers **13a**−**16a** is shown. Red and blue indicate *anti* and *syn* configurations, respectively. Spectra were measured in $CDCl_3$ (500 MHz).

NMR spectra (Figure 3b). The $\Delta\delta$ values for positions 32 and 34 in **6a** were 0.49 and 0 ppm, respectively (Figure 3c), indicating that the three methyl groups are located in a *syn*,*anti* configuration. The $^1$H NMR spectrum of **6b** gave a same result (shown in the Supporting Information).

The result obtained by the geminal proton rule was consistent with the previous prediction,[18] in which Hoffmann and co-workers calculated $^{13}$C NMR chemical shift values for possible diastereomers and compared them with that of the degradation product of verucopeptin (**3**). Although the difference in the chemical shift values was subtle between *syn*,*anti* and *syn*,*syn* isomers, calculated $^{13}$C NMR chemical shift values suggested that the natural product may have the former configuration. In contrast, the geminal proton rule gave more clear differences, especially in the case of fatty acid derivatives (see below). It is noted that we could determine the absolute stereochemistry of C31 by converting the carboxylic acid **5** to PGME derivatives (Figure 3d).[19] In combination with the above prediction, verucopeptin (**3**) was predicted to have an absolute stereochemistry of 31*S*,33*S*,35*R*.

**Synthesis of a 2,4,6-Trimethyl Carboxylic Acid.** To prove our prediction, we planned to synthesize four possible diastereomers of 2,4,6-trimethyloctanoic acid: 2*S*,4*S*,6*R*, 2*S*,4*S*,6*S*, 2*S*,4*R*,6*R*, and 2*S*,4*R*,6*S*. Our synthetic scheme for (2*S*,4*S*,6*R*)-2,4,6-trimethyloctanoic acid (**12**) is shown in Scheme 1. The synthesis of **12** was started with (*R*)-Roche ester **7**, and two stereogenic centers were constructed by stereoselective alkylation reactions using chiral oxazolidinones.[19] We first protected the hydroxyl group of Roche's ester **7** with a *p*-methoxybenzyl (PMB) group under acidic conditions, followed by reduction of the methyl ester to a hydroxyl group by LAH. The obtained alcohol was converted to a triflate, which was immediately subjected to diastereoselective alkylation by (4*R*)-propionyloxazolidinone[19] to give oxazolidinone **8** and its diastereomer.[20] Although these two diastereomers were not separated by $SiO_2$ column chromatography, oxazolidinone **8** was successfully purified by C18 reversed-phase HPLC (dr = 10:1). Reductive cleavage of the chiral auxiliary from oxazolidinone **8** yielded the alcohol **9**. After tosylation of the alcohol **9**, one-carbon elongation was achieved with MeMgBr and CuI to yield the protected alcohol **10**. After deprotection of PMB, a second Evans asymmetric alkylation was conducted to give oxazolidinone **11** and its diastereomer. These two diastereomers were separated by C30 reversed-phase HPLC (dr = 48:1). Purified oxazolidinone **11** was subjected to oxidative hydrolysis with alkaline hydrogen peroxide to give the carboxylic acid **12**. The carboxylic acid **12** was condensed with (*R*)- or (*S*)-PGME to give **13a**,**b**, respectively. Three other diastereomers and their PGME derivatives were synthesized in the same manner.

**$^1$H NMR Analysis of 2,4,6-Trimethyloctanoic Acid Derivatives.** With all four diastereomers in hand, we first compared $^1$H NMR spectra of the PGME derivatives, including synthesized compounds **13a**−**16a**, and the natural product derived compound **6a** (Figure 4). The synthesized diastereomers exhibited apparently different spectra, especially signals for methylene protons at C3 and C5. The $^1$H NMR spectrum of **6a** closely resembled that of **13a**, confirming the above prediction; we unambiguously concluded that the stereochemistry of **6a** is 31*S*,33*S*,35*R*.

We next calculated $\Delta\delta$ values for the methylene protons at C3 and C5 in the synthesized compounds **13a**−**16a** and their diastereomers **13b**−**16b** (Figure 4, compound list **S1**). The $\Delta\delta$ values of methylene protons at C3 were 0.47−0.67 ppm, when two methyl groups at C2 and C4 were located in a *syn* configuration. In contrast, the values were 0−0.23 ppm when the methyl groups were in an *anti* configuration. The difference was large enough to distinguish the relative stereochemistry of the 2,4-dimethyl carboxylic acid. The $\Delta\delta$ values of methylene protons at C5 were 0.24−0.28 ppm when in a *syn* configuration, whereas they were 0 ppm when in an *anti* configuration. Although the $\Delta\delta$ values at C5 were smaller than those at C3, the difference between *syn* and *anti* forms was apparent enough to predict the configuration.

**Reinvestigation of the Geminal Proton Rule.** The trends for $\Delta\delta$ values depending on functional groups adjacent to the stereogenic centers were analyzed by Breit and


dx.doi.org/10.1021/jo500906v | J. Org. Chem. 2014, 79, 6858−6867

co-workers previously.[11] We summarized the Δδ values of methylene geminal protons in 86 compounds, including our isolated or synthesized compounds in addition to those already analyzed by Breit and co-workers (Figure 5, bottom). The Δδ values for *anti* configurations were plotted between 0 and 0.4 ppm, whereas those for *syn* configurations ranged from 0.1 to 0.8 ppm, indicating that the correct stereochemistries cannot be predicted when the Δδ values are from 0.1 to 0.4 ppm. In contrast, such ambiguity was not observed for carboxylic acids. In the case of 1,3-dimethylated systems, the difference was apparent. We plotted 31 examples in Figure 5 (top). The Δδ values for $CH_2$-3 were larger than 0.4 ppm when 2,4-dimethyl groups were in the *syn* form. In contrast, the values were less than 0.3 ppm when the configurations were *anti*, with two exceptions: atpenin B and atenin A5. These compounds have a 2,4-dihydroxy-5,6-dimethoxypyridine ring, which seems to contribute to the unexpectedly large Δδ values due to the conformation constraint and/or magnetic shielding effect. We also analyzed the Δδ values for $CH_2$-5 from 17 compounds. The Δδ values for $CH_2$-5 also gave a clear result, although the values were relatively small (Figure 5, middle). The Δδ values were more than 0.2 when 4,6-dimethyl groups were in *syn* configurations. The values were almost 0 when the configurations were *anti*. These data revealed that the geminal proton rule is reliable in 2,4-dimethyl and 2,4,6-trimethyl fatty acids. By using this rule, we could predict the relative stereochemistry of the acyl group in another tumescenamide congener, tumescenamide B (**17**),[8] whose configuration has not been determined (Figure 6). The Δδ values for $CH_2$-31 and -33 were 0.75 and 0.34, respectively, suggesting the *syn,syn* configuration.

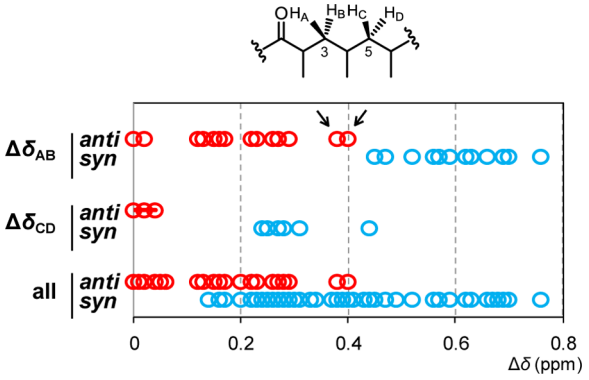



**Figure 5.** Tendencies for Δδ values. Values for *syn* configurations are plotted in blue and *anti* in red. Δδ values for $H_A$ and $H_B$ (31 compounds, top), Δδ value for $H_C$ and $H_D$ (17 compounds, middle), and Δδ values for any methylene protons located between methyl-bearing methane carbons (86 compunds, bottom) are plotted. Arrows indicate exceptionally large values for atpenin B and atpenin A5, as mentioned in the text. The compound list is included in the Supporting Information.

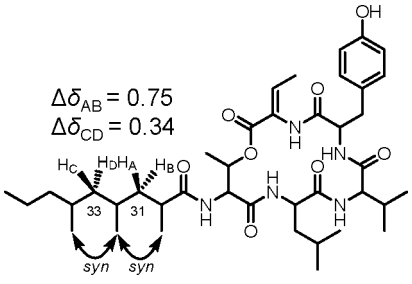



**Figure 6.** Structure of tumescenamide B (**17**) with proposed stereochemistry. The Δδ values for C31 and C33 are shown in ppm.

## CONCLUSION

We have reinvestigated the utility of an empirical NMR approach, the geminal proton rule, for determination of the configuration of 1,3-dimethylated systems. Our data indicated that the emerging rule is highly reliable when predicting the stereochemistry of 2,4-dimethyl or 2,4,6-trimethyl fatty acids. In fact, the stereochemistry of the 1,3,5-trimethylated system in verucopeptin (**3**) was successfully predicted after conversion of the system to a 2,4,6-trimethyl fatty acids. In addition, we could deduce the relative stereochemistry of the acyl chain in tumescenamide B (**17**) from the reported NMR data. So far, many natural products with methyl branched fatty acids have been reported. There remain many compounds with unknown stereochemistries: e.g., dactylfungins[21] and totopotensamides.[22] The geminal proton rule would be helpful for elucidating the stereochemistry of such compounds.

## EXPERIMENTAL SECTION

**General Considerations.** All reagents and solvents were used as received from commercial suppliers and were used without further purification. IR spectra were measured using an FTIR spectrometer equipped with a ZnSe ATR plate. Optical rotations were determined using the sodium D line (589 nm). NMR spectra were measured on a 500 MHz instrument. $^1H$ and $^{13}C$ chemical shifts are shown relative to the solvent: $\delta_H$ 7.26 and $\delta_C$ 77.0 for $CDCl_3$. Chemical shifts ($\delta$) are shown in parts per million (ppm), and coupling constants ($J$) are in hertz (Hz). The following abbreviations are used to describe multiplicities: s, singlet; d, doublet; dd, doublet of doublets; m, multiplet. Mass spectral data were collected with FAB MS or ESI IT-TOF MS. Flash column chromatography was performed over Silica Flash F60 (SiliCycle) using an elution system as described for each experiment.

**Isolation of Verucopeptin (3).** *n*-BuOH extracts of the culture broth of *Streptomyces* sp. KUSC_A08 (16 L) were extracted with 90% MeOH three times. The combined extracts were evaporated and extracted with $CHCl_3$ three times. The $CHCl_3$ extracts were combined and concentrated in vacuo. The residue was dissolved in $CHCl_3$/MeOH (50/50) and fractionated on a LH-20 gel filtration column with $CHCl_3$/MeOH (50/50). Fractions containing verucopeptin were combined and chromatographed on a silica gel column with $CHCl_3$/MeOH (45/1 to 20/1). Fractions eluted by $CHCl_3$/MeOH (45/1) were subjected to ODS HPLC on CAPCELL PAK UG120 (i.d. 20 × 250 mm) with MeCN/$H_2O$ (75/25) to afford verucopeptin (**3**; 121.61 mg) as a colorless amorphous solid: $[\alpha]_D^{20}$ = = −91.0° (*c* 0.12, $CHCl_3$); IR (neat) 3352, 2955, 1644, 1406, 1241, 754 $cm^{-1}$; $^1H$ NMR for the major acetal form ($CDCl_3$, 500 MHz) $\delta$ 9.11 (*N*-OH), 7.32 (d, $J$ = 9.7 Hz), 7.12 (d, $J$ = 5.9 Hz), 6.08 (dd, $J$ = 9.8, 3.1 Hz, 1H), 5.31 (m, 1H), 5.27 (d, $J$ = 15.5 Hz, 1H), 5.16 (m, 1H), 5.04 (d, $J$ = 16.9 Hz, 1H), 4.90 (m, 1H), 4.77 (dd, $J$ = 9.8, 3.1 Hz, 1H), 4.64 (d, $J$ = 16.3 Hz, 1H), 4.11 (m, 1H), 4.09 (m), 3.88 (d, $J$ = 15.5 Hz, 1H), 3.65 (dd, $J$ = 17.2, 6.5 Hz, 1H), 3.55 (d, $J$ = 17.2 Hz, 1H), 3.44 (m), 3.28 (s, 3H), 3.11 (s, 3H/m), 3.04 (m, 1H), 2.91 (s, 3H), 2.65 (m, 1H), 2.51 (m, 1H), 2.17 (m, 1H), 2.03 (m, 1H), 1.87 (m), 1.80 (m), 1.72 (m), 1.65 (s), 1.57 (m), 1.50 (m), 1.46 (m), 1.40 (s, 3H),1.37 (m), 1.26 (m), 1.20 (m), 1.13 (m), 1.06 (d, $J$ = 6.7 Hz), 1.02 (m), 0.97 (d, $J$ = 6.7 Hz), 0.86 (m), 0.84 (m), 0.80 (m), 0.77 (m); $^{13}C$ NMR for the major acetal form ($CDCl_3$, 125 MHz) $\delta$ 176.2, 172.0, 171.3, 170.8, 170.2, 167.1, 166.8, 137.0, 130.0, 98.4, 80.0, 79.6, 77.6, 75.7, 56.8, 52.5, 51.7, 51.3, 48.4, 46.9, 46.5, 46.1, 45.0, 42.4, 36.7, 34.7, 31.7, 30.4 (2C), 29.6, 27.7, 27.2, 24.1, 23.9, 21.3 (2C), 20.5, 19.4, 19.2, 19.1, 18.3, 11.4; HRMS (ESI) $m/z$ 918.5169 $[M + Na]^+$ calcd for $C_{43}H_{73}N_7NaO_{13}$, 918.5159. $^1H$ and $^{13}C$ NMR chemical shifts were in agreement with those reported previously.[23]


dx.doi.org/10.1021/jo500906v | J. Org. Chem. 2014, 79, 6858−6867

**Reduction of 3.** To a stirred solution of verucopeptin (**3**; 8.88 mg, 9.92 × $10^{-3}$ mmol) in $CHCl_3$/MeOH (1/1, 1.98 mL) was added $NaBH_4$ (5.62 mg, 0.15 mmol) at room temperature. After 30 min, PBS buffer was added to the reaction mixture. The organic layer was washed with PBS buffer (three times) and concentrated in vacuo. The residue was chromatographed on an ODS column with a stepwise elution of $H_2O$/MeOH (from 100/0 to 0/100). Fractions eluted with $H_2O$/MeOH (10/90 and 0/100) were combined and subjected to ODS HPLC on Cosmosil AR-II-C18 (i.d. 20 × 250 mm) with $H_2O$/MeCN (40/60) to afford the reduced verucopeptin derivative **4** (4.92 mg, 55%) as a colorless amorphous solid: $[\alpha]_D^{20}$ = −151.7° (*c* 0.06, $CHCl_3$); IR (neat) 3344, 2958, 2926, 1648 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.08 (NH), 7.04 (NH), 6.12 (dd, *J* = 3.0, 8.9 Hz, 1H), 5.27 (d, *J* = 15.2 Hz, 1H), 5.24 (m, 1H), 5.23 (m, 1H), 4.98 (dd, *J* = 2.9, 10.0 Hz, 1H), 4.92 (m, 1H), 4.78 (NH), 4.71 (d, *J* = 17.3 Hz, 1H), 4.15 (m, 1H), 4.13 (m, 1H), 3.88 (d, *J* = 15.5 Hz, 1H), 3.65 (dd, *J* = 4.1, 17.5 Hz, 2H), 3.44 (m, 1H), 3.43 (m, 1H), 3.40 (s, 3H), 3.28 (m, 1H), 3.11 (s, 3H/m, 1H), 2.91 (s, 3H), 2.67 (m, 1H), 2.51 (m, 1H), 2.23 (m, 1H), 1.87 (m, 1H), 1.79 (m, 1H), 1.76 (m, 1H), 1.70 (m, 2H), 1.63 (s, 3H) 1.60 (m, 1H), 1.56 (m, 1H), 1.46 (m, 1H), 1.41 (s, 3H), 1.39 (m, 1H), 1.25 (m, 1H), 1.20 (m, 1H), 1.15 (m, 1H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.06 (m, 1H), 1.02 (m, 2H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 3H), 0.85 (m, 3H), 0.80 (m, 3H), 0.79 (m, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 174.8, 171.6 171.4, 170.8, 170.7, 168.5, 167.0, 134,1 131.7, 82.3, 80.2, 76.7, 76.1, 57.6, 52.7, 51.7, 51.4, 48.8, 47.2, 46.9, 46.0, 44.8, 42.3, 36.6, 34.7, 31.7, 30.4, 29.7, 29.5, 27.9, 26.9, 26.0, 23.9, 21.4 (2C), 20.1, 19.5, 19.3, 19.0, 18.5, 13.1, 11.4; HRMS (ESI) *m*/*z* 920.5334 $[M + Na]^+$ calcd for $C_{43}H_{75}N_7NaO_{13}$, 920.5315.

**PGME Derivatives of the Natural Trimethyloctanoic Acid (6a,b).** To a stirred solution of **3** (4.26 mg, 4.76 × $10^{-3}$ mmol) in MeCN/$CCl_4$/$H_2O$ (2/2/3, 0.32 mL) were added $RuCl_3 \cdot xH_2O$ (6.50 mg, 0.03 mmol) and $NaIO_4$ (41.46 mg, 0.19 mmol). After the mixture was stirred at room temperature for 12 h, water was added. The mixture was chromatographed on an ODS column with a stepwise elution of $H_2O$/MeOH (from 100/0 to 0/100). Fractions eluted with $H_2O$/MeOH (40/60 to 0/100) were combined and concentrated in vacuo. The material was split into two portions. One portion of the material was mixed with HBTU (13.73 mg, 0.04 mmol), HOBt (6.17 mg, 0.05 mmol), DIEA (11.0 μL, 0.06 mmol), and (*R*)-PGME·HCl (7.86 mg, 0.04 mmol) in DMF (0.11 mL), which was stirred at room temperature. After 9 h, saturated aqueous $NH_4Cl$ was added to the reaction mixture. The organic layer was washed with saturated aqueous $NH_4Cl$ (three times) and concentrated in vacuo. The obtained residue was chromatographed on an ODS column with a stepwise elution of $H_2O$/MeOH (from 100/0 to 0/100) and $CHCl_3$/MeOH (1/1). Fractions eluted with $H_2O$/MeOH (0/100) were subjected to ODS HPLC on CAPCELL PACK C18 UG120 (i.d. 20 × 250 mm) with $H_2O$/MeCN (50/50) to afford **6a** (0.25 mg, 32%).

The remaining portion of the carboxylic acid (0.88 mg) was mixed with HBTU (19.63 mg, 0.05 mmol), HOBt (8.06 mg, 0.06 mmol), DIEA (16.35 μL, 0.1 mmol), and (*S*)-PGME·HCl (11.72 mg, 0.06 mmol) in DMF (0.16 mL), which was stirred for 11 h at room temperature. The reaction mixture was fractionated as described above to afford **6b** (0.25 mg, 32%).

*Compound **6a**:* $[\alpha]_D^{20}$ = −84.64° (*c* 0.02, $CHCl_3$); IR (neat) 3314, 2957, 2922, 2849, 1746, 1648, 1523 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.29−7.37 (5H), 6.4 (NH), 5.60 (d, *J* = 7.2 Hz, 1H), 3.73 (s, 3H), 2.39 (m, 1H), 1.61 (m, 1H), 1.37 (m, 1H), 1.33 (m, 1H), 1.16 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.13 (m, 1H), 0.98 (m, 2H), 0.81 (d, *J* = 6.9 Hz, 3H/t, *J* = 6.9 Hz, 3H), 0.70 (d, *J* = 6.6 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 176.2, 171.9, 128.9, 128.4, 127.2, 56.1, 52.8, 44.3, 42.6, 38.8, 31.5, 30.2, 27.8, 19.4, 18.8, 18.3, 11.3; HRMS (ESI) *m*/*z* 356.2196 $[M + Na]^+$ calcd for $C_{20}H_{31}NNaO_3$, 356.2196.

*Compound **6b**:* $[\alpha]_D^{20}$ = 154.73° (*c* 0.02, $CHCl_3$); IR (neat) 3293, 2960, 2927, 1748, 1647, 1527 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.30−7.37 (5H), 6.36 (NH), 5.59 (d, J= 7.3 Hz, 1H), 3.73 (s, 3H), 2.41 (m, 1H), 1.64 (m, 1H), 1.54 (m, 1H), 1.39 (m, 1H), 1.26 (m, 1H), 1.17 (m, 1H), 1.14 (m, 1H), 1.11 (d, *J* = 7.1 Hz, 3H), 1.03 (m, 2H), 0.87 (d, *J* = 6.3 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.79 (d, *J* = 6.4 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 175.9, 171.5, 129.0, 128.5, 127.2, 56.1, 52.7, 44.3, 42.5, 38.8, 31.6, 30.4, 27.9, 19.6, 18.9, 18.3, 11.4; HRMS (ESI) *m*/*z* 356.2191 $[M + Na]^+$ calcd for $C_{20}H_{31}NNaO_3$, 356.2196.

**PGME Derivatives of Synthetic (2*S*,4*S*,6*R*)-Trimethyloctanoic Acid (13a,b).** *(R)-4-Benzyl-3-((2S,4S)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentanoyl)oxazolidin-2-one (**8**).* To a stirred solution of methyl (*S*)-3-hydroxyisobutyrate (2.0 g, 16.90 mmol) in anhydrous $CH_2Cl_2$ (33.90 mL) were added CSA (0.33 g, 1.42 mmol) and PMB trichloroacetimidate (5.27 mL, 25.40 mmol). After the mixture was stirred for 12 h at room temperature, the reaction was quenched by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$, washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue in cooled hexane was filtered through Celite and concentrated in vacuo. The residue was suspended in *n*-hexane/EtOAc (10/1), filtered through a pad of silica, and used in the next reaction.

A solution of the residue (4.0 g) in anhydrous THF (84.50 mL) was cooled to 0 °C under a nitrogen atmosphere, to which LAH (0.67 g, 17.60 mmol) was added. After the reaction mixture was stirred for 5.5 h at 0 °C, it was quenched with $Na_2SO_4 \cdot 10H_2O$ and the slurry was stirred at room temperature. The mixture was filtered through a pad of silica and washed with $CHCl_3$. After concentration in vacuo, the residue was chromatographed ($SiO_2$, *n*-hexane/EtOAc 5/1 to 1/1) to give fractions that contained the target alcohol.

A stirred solution of the obtained alcohol (0.11 g) in 1.10 mL of anhydrous $CH_2Cl_2$ under a nitrogen atmosphere was cooled to 0 °C, and 2,6-lutidine (0.11 mL, 0.81 mmol) and $Tf_2O$ (0.14 mL, 0.81 mmol) were added. After the mixture was stirred for 1 h at 0 °C, the reaction was quenched with saturated aqueous $NH_4Cl$. The organic layer was washed with saturated aqueous $NH_4Cl$, saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The residue was chromatographed ($SiO_2$, *n*-hexane/EtOAc 10/1) to give fractions containing the triflate compound. The fractions were combined and concentrated, and the residue was immediately used in the next reaction.

A stirred solution of (*R*)-4-benzyl-3-propionyl-2-oxazolidinone (99.80 mg, 0.54 mmol) in anhydrous THF (5.40 mL) under a nitrogen atmosphere was cooled to −78 °C, and 0.34 mL of 1.9 M NaHMDS was added. After the mixture was stirred for 15 min at −78 °C, the triflate compound (0.22 g) in 21.60 mL of anhydrous THF was added dropwise. The reaction mixture was stirred at −78 °C, warmed to 0 °C, stirred for 5 h, and then quenched with saturated aqueous $NH_4Cl$. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. The residue was chromatographed ($SiO_2$, *n*-hexane/EtOAc 5/1) to give a mixture of **8** and its diastereomer. The mixture was subjected to reversed-phase HPLC (Cosmosil AR-II, i.d. 20 × 250 mm, $H_2O$/MeCN (35/65)) to give **8** (74.90 mg, 40%) as a colorless oil. The ratio of **8** and its diastereomer was 11:1, as judged from their yield. Compound **8**: $[\alpha]_D^{20}$ = −5.97° (*c* 1.10, $CHCl_3$); IR (neat) 2932, 2856, 1776, 1206, 701 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 6.86−7.34 (m, 9H), 4.64 (m, 1H), 4.42 (d, *J* = 4.6 Hz, 2H), 4.15 (dd, *J* = 8.5 Hz, 1H), 4.08 (dd, *J* = 3.3, 9.1 Hz, 1H), 3.88 (m, 1H), 3.80 (s, 3H), 3.29 (m, 2H), 3.26 (m, 1H), 2.50 (dd, *J* = 10.5, 13.4 Hz, 1H), 1.88 (m, 1H), 1.66 (ddd, *J* = 7.2, 8.2, 14.0 Hz, 1H), 1.51 (ddd, *J* = 6.6, 8.7, 14.0 Hz, 1H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 7.2 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 177.4, 159.0, 153.0, 135.5, 130.7, 129.34, 129.31, 128.8, 127.2, 113.7, 75.8, 72.7, 65.89, 55.3, 55.2, 38.0, 37.8, 35.3, 31.3, 17.06 (2C); HRMS (ESI) *m*/*z* 448.2111 $[M + Na]^+$ calcd for $C_{25}H_{31}NNaO_5$, 448.2094.

*(2S,4S)-5-((4-Methoxybenzyl)oxy)-2,4-dimethylpentan-1-ol (**9**).* A stirred solution of **8** (0.17 g, 0.39 mmol) in anhydrous THF (1.90 mL) under a nitrogen atmosphere was cooled to 0 °C, and LAH (18.0 mg, 0.48 mmol) was added. After the mixture was stirred for 5 h at 0 °C, the reaction was quenched with $Na_2SO_4 \cdot 10H_2O$ and the slurry was stirred at room temperature. The mixture was filtered through a pad of silica and washed with EtOAc. After concentration in vacuo, the residue was chromatographed ($SiO_2$, *n*-hexane/EtOAc 3/1 to 2/1) to yield **9** (90.77 mg, 93%) as a colorless oil: $[\alpha]_D^{20}$ = −14.4° (*c* 0.98, $CHCl_3$); IR (neat) 3410, 2910, 2851, 1244, 1033, 818 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.24 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.6 Hz,


dx.doi.org/10.1021/jo500906v | J. Org. Chem. 2014, 79, 6858−6867

2H), 4.42 (s, 2H), 3.79 (s, 3H), 3.44 (dd, $J$ = 6.4, 10.5 Hz, 1H), 3.39 (dd, $J$ = 6.4, 10.7 Hz, 1H), 3.26 (dd, $J$ = 6.7, 9.0 Hz, 1H), 3.23 (dd, $J$ = 6.3, 9.0 Hz, 1H), 1.87 (m, 1H), 1.73 (m, 1H), 1.19 (m, 2H), 0.89 (d, $J$ = 7.1 Hz, 3H), 0.88 (d, $J$ = 7.3 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 159.0, 130.6, 129.1, 113.7, 76.2, 72.6, 68.7, 55.2, 37.2, 32.9, 30.5, 16.9, 16.3; HRMS (ESI) $m/z$ 275.1619 $[M + Na]^+$ calcd for $C_{15}H_{24}NaO_3$, 275.1618.

*1-((((2S,4R)-2,4-Dimethylhexyl)oxy)methyl)-4-methoxybenzene (**10**).* To a stirred solution of **9** (0.65 g, 2.59 mmol) in 17.30 mL of anhydrous $CH_2Cl_2$ under a nitrogen atmosphere were added $Et_3N$ (0.90 mL, 6.48 mmol), DMAP (32.0 mg, 0.26 mmol), and TsCl (0.60 g, 3.17 mmol) at room temperature. After the mixture was stirred for 12 h, saturated aqueous $NH_4Cl$ was added. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. The residue was chromatographed ($SiO_2$, $n$-hexane/EtOAc 5/1) to give fractions containing tosylated compounds.

A mixture of CuI (0.45 g, 2.34 mmol) and 1 M MeMgBr (23.40 mL, 23.40 mmol) was cooled to −20 °C under a nitrogen atmosphere, and the tosylated material (0.95 g) in anhydrous THF was added. The mixture was warmed to 0 °C and stirred for 10 h. The reaction was quenched with saturated aqueous $NH_4Cl$ and filtered through Celite. The organic layer was washed with saturated aqueous $NH_4Cl$, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The residue was chromatopraphed ($SiO_2$, $n$-hexane/EtOAc 50/1) to yield **10** (0.53 g, 83% over two steps) as a colorless oil: $[\alpha]_D^{20}$ = −11.75° ($c$ 1.03, $CHCl_3$); IR (neat) 2957, 2911, 1512, 1245, 1096, 819 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.31 (d, $J$ = 9.0 Hz, 2H), 6.92 (d, $J$ = 8.7 Hz, 2H), 4.48 (d, $J$ = 2.6 Hz, 2H), 3.81 (s, 3H), 3.34 (dd, $J$ = 5.7, 8.9 Hz, 1H), 325 (dd, $J$ = 7.4, 9.2 Hz, 1H), 1.91 (m, 1H), 1.48 (m, 1H), 1.37 (m, 1H), 1.23 (m, 1H), 1.22 (m, 1H), 1.15 (m, 1H), 0.97 (d, $J$ = 6.8 z, 3H), 0.93 (t, $J$ = 7.4 Hz, 3H), 0.90 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 158.9, 130.8, 128,8, 113.5, 76.3, 72.5, 54.9, 40.6, 31.5, 30.8, 30.3, 18.8, 16.9, 11.3; HRMS (ESI) $m/z$ 273.1821 $[M + Na]^+$ calcd for $C_{16}H_{26}NaO_2$, 273.1825.

*(R)-4-Benzyl-3-((2S,4S,6R)-2,4,6-trimethyloctanoyl)oxazolidin-2-one (**11**).* A stirred solution of **10** (0.24 g, 0.95 mmol) in $CH_2Cl_2/H_2O$ (15/1, 9.50 mL) was cooled to 0 °C, and DDQ (0.33 g, 1.44 mmol) was added. After the mixture was stirred for 1 h at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The residue was chromatographed ($SiO_2$, $n$-hexane/$Et_2O$ 4/1) to give a fraction that contained the target alcohol.

A stirred solution of the obtained material (0.28 g) in anhydrous $CH_2Cl_2$ (4.40 mL) under a nitrogen atmosphere was cooled to 0 °C, and 2,6-lutidine (0.45 g, 3.27 mmol) and $Tf_2O$ (0.55 g, 3.27 mmol) were added. After the mixture was stirred for 1 h at 0 °C, the reaction was quenched with saturated aqueous $NH_4Cl$. The organic layer was washed with saturated aqueous $NH_4Cl$, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The residue was chromatographed ($SiO_2$, $n$-hexane/EtOAc 20/1) to give a fraction that contained triflated material. The fraction was concentrated in vacuo, and the residue was immediately used in the next reaction.

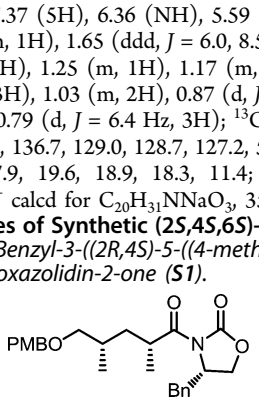
A stirred solution of (*R*)-4-benzyl-3-propionyl-2-oxazolidinone (0.16 g, 0.71 mmol) in anhydrous THF (7.10 mL) under a nitrogen atmosphere was cooled to −78 °C, and 0.45 mL of 1.9 M NaHMDS was added. After the mixture was stirred for 15 min at −78 °C, the triflated material (0.12 g) in 15.10 mL of anhydrous THF was added dropwise. The reaction mixture was stirred at −78 °C, warmed to 0 °C, stirred for 5.5 h, and then quenched with saturated aqueous $NH_4Cl$. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. The residue was chromatographed ($SiO_2$, $n$-hexane/EtOAc 5/1) to give a mixture of **11** and its diastereomer. The mixture was subjected to reversed-phase HPLC (YMC Carotenoid, i.d. 20 × 250 mm, $H_2O$/MeCN (35/65)) to yield **11** (50.6 mg, 15% over three steps) as a colorless oil. The ratio of **11** and its diastereomer was 48:1, as judged from their yield: $[\alpha]_D^{20}$ = −37.88° ($c$ 2.32, $CHCl_3$); IR (neat) 2959, 2924, 1779, 1697, 1384, 1206, 701 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.19−7.35 (5H), 4.68 (m, 1H), 4.17 (m, 2H), 3.94 (m, 1H), 3.29 (dd, $J$ = 3.6, 13.5 Hz, 1H), 2.72 (dd, $J$ = 9.7, 13.3 Hz, 1H), 1.82 (ddd, $J$ = b 6.4, 8.1, 14.1 Hz, 1H), 1.55 (m, 1H), 1.42 (m, 1H), 1.27 (m, 1H), 1.22 (m, 1H), 1.16 (m, 1H/d, $J$ = 6.7 Hz, 3H), 1.16 (d, $J$ = 6.7 Hz, 3H), 1.10 (m, 2H), 0.89 (d, $J$ = 6.8 Hz, 3H), 0.86 (t, $J$ = 7.5 Hz, 3H), 0.82 (d, $J$ = 12.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 177.7, 153.0, 135.4, 129.4, 128.9, 127.3, 65.9, 55.3, 43.9, 42.1, 38.0, 35.2, 31.6, 30.3, 28.2, 19.8, 18.9, 17.8, 11.4; HRMS (ESI) $m/z$ 368.2197 $[M + Na]^+$ calcd for $C_{21}H_{31}NNaO_3$, 368.2196.

*(R)-Methyl-2-phenyl-2-((2S,4S,6R)-2,4,6-trimethyloctamido)-acetate (**13a**).* To a stirred solution of **11** (24.90 mg, 5.85 × $10^{-2}$ mmol) in THF/$H_2O$ (4/1, 0.98 mL) was added LiOH·$H_2O$ (7.36 mg, 0.18 mmol) and 30% aqueous $H_2O_2$ (66.30 $\mu$L, 0.59 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C, warmed to room temperature, stirred for 2.5 h, and then quenched with saturated aqueous $Na_2S_2O_3$. After being acidified with 6 N HCl, the reaction mixture was extracted with $CHCl_3$. The organic layers were combined and concentrated in vacuo to give a residue containing **12**.

A half-portion of the material above containing **12** (18.20 mg), HBTU (76.80 mg, 0.20 mmol), HOBt (31.10 mg, 0.20 mmol), DIEA (33.70 mL, 0.20 mmol), and (*R*)-PGME·HCl (42.60 mg, 0.21 mmol) were dissolved in 0.98 mL of anhydrous DMF, and this mixture was stirred for 10 h at room temperature. The reaction was quenched with saturated aqueous $NH_4Cl$, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The residue was chromatographed ($SiO_2$, $n$-hexane/EtOAc 3/1) to yield **13a** (8.70 mg, 89%) as a colorless amorphous solid: $[\alpha]_D^{20}$ = −127.05° ($c$ 0.72, $CHCl_3$); IR (neat) 2959, 2924, 1779, 1697, 1384, 1206, 701 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.29−7.36 (5H), 6.42 (NH), 5.60 (d, $J$ = 7.5 Hz, 1H), 3.73 (s, 3H), 2.39 (m, 1H), 1.61 (m, 1H), 1.37 (m, 1H), 1.32 (m, 1H), 1.16 (m, 1H), 1.15 (d, $J$ = 7.0 Hz, 3H), 1.12 (m, 1H), 1.07 (m, 1H), 0.97 (m, 2H), 0.81 (d, $J$ = 7.4 Hz, 3H), 0.80 (t, $J$ = 7.4 Hz, 3H), 0.70 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 175.9, 171.5, 136.8, 128.9, 128.4, 127.2, 56.1, 52.7, 44.3, 42.7, 38.8, 31.5, 30.2, 27.9, 19.4, 18.8, 18.3, 11.3; HRMS (ESI) $m/z$ 356.2200 $[M + Na]^+$ calcd for $C_{20}H_{31}NNaO_3$, 356.2196.

*(S)-Methyl-2-phenyl-2-((2S,4S,6R)-2,4,6-trimethyloctamido)-acetate (**13b**).* A solution of the remaining half-portion of the above material containing **12** (19.10 mg), HBTU (78.50 mg, 0.21 mmol), HOBt (33.0 mg, 0.24 mmol), DIEA (35.50 mL, 0.21 mmol), and (*S*)-PGME·HCl (44.80 mg, 0.22 mmol) in 1.0 mL of anhydrous DMF was stirred for 10 h at room temperature. The reaction mixture was quenched with saturated aqueous $NH_4Cl$, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The residue was chromatographed ($SiO_2$, $n$-hexane/EtOAc 3/1) to yield **13b** (6.0 mg, 61% over two steps) as a colorless oil: $[\alpha]_D^{20}$ = +113.41° ($c$ 0.50, $CHCl_3$); IR (neat) 3300, 2960, 2927, 1749, 1647 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.30−7.37 (5H), 6.36 (NH), 5.59 (d, $J$ = 7.4 Hz, 1H), 3.73 (s, 3H), 2.41 (m, 1H), 1.65 (ddd, $J$ = 6.0, 8.5, 14.0 Hz, 1H), 1.54 (m, 1H), 1.39 (m, 1H), 1.25 (m, 1H), 1.17 (m, 1H), 1.14 (m, 1H), 1.11 (d, $J$ = 6.4 Hz, 3H), 1.03 (m, 2H), 0.87 (d, $J$ = 6.8 Hz, 3H), 0.85 (t, $J$ = 7.2 Hz, 3H), 0.79 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 175.9, 171.5, 136.7, 129.0, 128.7, 127.2, 56.1, 52.7, 44.3, 42.5, 38.2, 31.6, 30.4, 27.9, 19.6, 18.9, 18.3, 11.4; HRMS (ESI) $m/z$ 356.2201 $[M + Na]^+$ calcd for $C_{20}H_{31}NNaO_3$, 356.2196.

**PGME Derivatives of Synthetic (2*S*,4*S*,6*S*)-Trimethyloctanoic Acid (14a,b).** *(S)-4-Benzyl-3-((2R,4S)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentanoyl)oxazolidin-2-one (**S1**).*

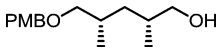



This compound was synthesized in the same manner as that of **8** (1.7 g, 53% over four steps). The ratio of **S1** and its diastereomer was 27:1, as judged from their yield: $[\alpha]_D^{20}$ = +21.49° ($c$ 0.73, $CHCl_3$); IR (neat) 2957, 2931, 2854, 1775, 1694, 1207, 702 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 6.84−7.34 (9H), 4.66 (m, 1H), 4.44 (s, 2H), 4.09−4.18 (m, 2H), 3.96 (m, 1H), 3.77 (s, 3H), 3.28 (dd, $J$ = 3.2, 13.5 Hz, 1H), 3.41 (dd, $J$ = 5.5, 8.7 Hz, 1H), 3.24 (dd, $J$ = 6.7, 9.1 Hz, 1H), 2.67 (dd, $J$ = 10.3, 13.9 Hz, 1H), 1.96 (ddd, $J$ = 6.2, 7.5, 14.0 Hz, 1H),


dx.doi.org/10.1021/jo500906v | J. Org. Chem. 2014, 79, 6858−6867

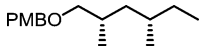
1.86 (m, 1H), 1.25 (ddd, $J$ = 6.3, 7.5, 13.6 Hz, 1H), 1.20 (d, $J$ = 6.7 Hz, 3H), 1.0 (d, $J$ = 6.7 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 177.1, 158.9, 152.9, 135.3, 130.7, 129.2, 128.9, 128.8, 127.1, 113.6, 75.2, 72.4, 65.8, 55.2, 55.1, 37.9 (2C), 35.1, 31.3, 17.9, 17.6; HRMS (ESI) $m/z$ 448.2119 $[M + Na]^+$ calcd for $C_{25}H_{31}NNaO_5$, 448.2094; colorless oil.

*(2R,4S)-5-((4-Methoxybenzyl)oxy)-2,4-dimethylpentan-1-ol (**S2**).*



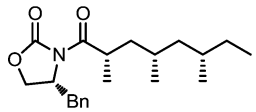

This compound was synthesized in the same manner as that of **9** (0.8 g, 87%): $[\alpha]_D^{20}$ = +5.73° ($c$ 1.07, $CHCl_3$); IR (neat) 3405, 2910, 2869, 1512, 1246, 1035 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.23 (d, $J$ = 8.9 Hz, 2H), 6.85 (d, $J$ = 8.9 Hz, 2H), 4.40 (d, $J$ = 3.4 Hz, 2H), 3.75 (s, 3H), 3.40 (dd, $J$ = 5.3, 10.8 Hz, 1H), 3.31 (dd, $J$ = 5.8, 10.3 Hz, 1H), 3.28 (dd, $J$ = 5.8, 8.9 Hz, 1H), 3.19 (dd, $J$ = 6.4, 9.7 Hz, 1H), 1.83 (m, 1H), 1.66 (m, 1H), 1.45 (m, 1H), 0.93 (d, $J$ = 7.5 Hz, 3H), 0.91 (d, $J$ = 6.9 Hz, 3H), 0.90 (m, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 158.8, 130.4, 128.9, 113.5, 75.4, 72.4, 67.3, 54.9, 37.4, 32.9, 30.7, 17.9, 17.4; HRMS (ESI) $m/z$ 275.1616 $[M + Na]^+$ calcd for $C_{15}H_{24}NaO_3$, 275.1618; colorless oil.

*1-((((2S,4S)-2,4-Dimethylhexyl)oxy)methyl)-4-methoxybenzene (**S3**).*



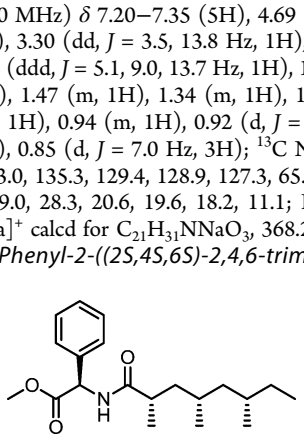

This compound was synthesized in the same manner as that of **10** (0.6 g, 75% over two steps): $[\alpha]_D^{20}$ = +12.06° ($c$ 0.84, $CHCl_3$); IR (neat) 2956, 2910, 1511, 1245, 1095, 819 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.30 (d, $J$ = 8.3 Hz, 2H), 6.91 (d, $J$ = 9.5 Hz, 2H), 4.47 (d, $J$ = 7.6 Hz, 2H), 3.82 (s, 3H), 3.37 (dd, $J$ = 7.2, 9.2 Hz, 1H), 3.22 (dd, $J$ = 5.3, 9.1 Hz, 1H), 1.90 (m, 1H), 1.47 (m, 1H), 1.40 (m, 1H), 1.39 (m, 1H), 1.14 (m, 1H), 0.99 (d, $J$ = 6.7 Hz, 3H), 0.97 (m, 1H), 0.92 (d, $J$ = 6.7 Hz, 3H), 0.91 (t, $J$ = 6.7 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 158.9, 130.9, 128.9, 113.6, 75.7, 72.5, 55.0, 41.1, 31.5, 30.8, 29.0, 19.7, 17.9, 11.1; HRMS (ESI) $m/z$ 273.1823 $[M + Na]^+$ calcd for $C_{16}H_{26}NaO_2$, 273.1825; colorless oil.

*(R)-4-Benzyl-3-((2S,4S,6S)-2,4,6-trimethyloctanoyl)oxazolidin-2-one (**S4**).*



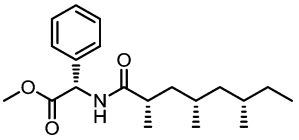

This compound was synthesized in the same manner as that of **11** (41.2 mg, 11% over three steps). The ratio of **S4** and its diastereomer was 54:1, as judged from their yield: $[\alpha]_D^{20}$ = −20.58° ($c$ 0.83, $CHCl_3$); IR (neat) 2957, 2913, 1778, 1696, 1383, 1204 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.20−7.35 (5H), 4.69 (m, 1H), 4.16 (m, 2H), 3.97 (m, 1H), 3.30 (dd, $J$ = 3.5, 13.8 Hz, 1H), 2.73 (dd, $J$ = 9.8, 13.3 Hz, 1H), 1.92 (ddd, $J$ = 5.1, 9.0, 13.7 Hz, 1H), 1.71 (d, $J$ = 6.8 Hz, 3H), 1.51 (m, 1H), 1.47 (m, 1H), 1.34 (m, 1H), 1.26 (m, 1H), 1.11 (m, 1H), 1.08 (m, 1H), 0.94 (m, 1H), 0.92 (d, $J$ = 7.1 Hz, 3H), 0.86 (t, $J$ = 7.8 Hz, 3H), 0.85 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 177.6, 153.0, 135.3, 129.4, 128.9, 127.3, 65.8, 55.3, 44.5, 41.3, 38.0, 35.1, 31.4, 29.0, 28.3, 20.6, 19.6, 18.2, 11.1; HRMS (ESI) $m/z$ 368.2197 $[M + Na]^+$ calcd for $C_{21}H_{31}NNaO_3$, 368.2196; colorless oil.

*(R)-Methyl 2-Phenyl-2-((2S,4S,6S)-2,4,6-trimethyloctamido)-acetate (**14a**).*



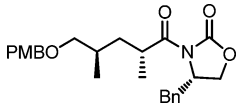

This compound was synthesized in the same manner as that of **13a** (8.08 mg, 86% over two steps): $[\alpha]_D^{20}$ = −102.90° ($c$ 0.81, $CHCl_3$); IR (neat) 3293, 2956, 2926, 1746, 1648 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.29−7.36 (5H), 6.42 (NH), 5.60 (d, $J$ = 7.3 Hz, 1H), 3.73 (s, 3H), 2.39 (m, 1H), 1.68 (ddd, $J$ = 4.6, 9.7, 14.0 Hz, 1H), 1.34 (m, 2H), 1.22 (m, 1H), 1.15 (d, $J$ = 6.7 Hz, 3H), 1.10 (m, 1H), 1.02 (m, 1H), 0.95 (m, 1H), 0.85 (m, 1H), 0.83 (d, $J$ = 6.7 Hz, 3H), 0.79 (t, $J$ = 7.5 Hz, 3H), 0.70 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 175.8, 171.6, 136.8, 128.9, 128.4, 127.2, 56.1, 52.7, 44.9, 41.9, 38.9, 31.3, 28.0, 29.0, 20.2, 19.5, 18.6, 11.2; HRMS (ESI) $m/z$ 356.2199 $[M + Na]^+$ calcd for $C_{20}H_{31}NNaO_3$, 356.2196; colorless oil.

*(S)-Methyl 2-Phenyl-2-((2S,4S,6S)-2,4,6-trimethyloctamido)-acetate (**14b**).*



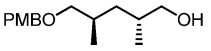

This compound was synthesized in the same manner as that of **13b** (9.2 mg, 91% over two steps): $[\alpha]_D^{20}$ = 114.56° ($c$ 0.92, $CHCl_3$); IR (neat) 3296, 2957, 2927, 1748, 1645, 697 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.30−7.37 (5H), 6.36 (NH), 5.59 (d, $J$ = 7.3 Hz, 1H), 3.73 (s, 3H), 2.41 (m, 1H), 1.72 (ddd, $J$ = 4.8, 9.5, 14.1 Hz, 1H), 1.53 (m, 1H), 1.41 (m, 1H), 1.32 (m, 1H), 1.12 (d, $J$ = 6.5 Hz, 3H), 1.17 (m, 1H), 1.05 (m, 1H), 1.04 (m, 1H), 0.92 (m, 1H), 0.89 (d, $J$ = 7.0 Hz, 3H), 0.84 (t, $J$ = 7.4 Hz, 3H), 0.80 (d, $J$ = 6.7 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 175.8, 171.5, 136.7, 129.0, 128.4, 127.2, 56.2, 52.7, 45.0, 41.7, 38.9, 31.5, 29.1, 28.0, 20.3, 19.7, 18.7, 11.2; HRMS (ESI) $m/z$ 356.2204 $[M + Na]^+$ calcd for $C_{20}H_{31}NNaO_3$, 356.2196; colorless oil.

**PGME Derivatives of Synthetic (2*S*,4*R*,6*R*)-Trimethyloctanoic acid (15a,b).** *(R)-4-Benzyl-3-((2S,4R)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentanoyl)oxazolidin-2-one (**S5**).*



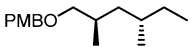

This compound was synthesized in the same manner as that of **8** (1.7 g, 33% over four steps). The ratio of **S5** and its diastereomer was 10:1, as judged from their yield: $[\alpha]_D^{20}$ = +7.02° ($c$ 0.71, $CHCl_3$); IR (neat) 2976, 2934, 2857, 1776, 1695, 1206, 1093, 701 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 6.86−7.33 (9H), 4.62 (m, 1H), 4.42 (s, 2H), 4.13 (m, 1H), 4.06 (dd, $J$ = 3.0, 9.1 Hz, 1H), 3.89 (m, 1H), 3.79 (s, 3H), 3.25 (dd, $J$ = 3.2, 13.4 Hz, 1H), 3.30 (m, 2H), 2.51 (dd, $J$ = 10.2, 13.2 Hz, 1H), 1.89 (m, 1H), 1.67 (ddd, $J$ = 7.0, 8.0, 14.6 Hz, 1H), 1.52 (ddd, $J$ = 6.4, 7.5, 13.8 Hz, 1H), 1.16 (d, $J$ = 7.0 Hz, 3H), 0.97 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 177.3, 159.0, 152.9, 135.5, 130.7, 129.9 (2C), 113.6, 128.8, 127.1, 75.8, 72.7, 65.8, 55.6 (2C), 37.9, 37.8, 35.2, 31.2, 17.0 (2C); HRMS (ESI) $m/z$ 448.2115 $[M + Na]^+$ calcd for $C_{25}H_{31}NNaO_5$, 448.2094; colorless oil.

*(2S,4R)-5-((4-Methoxybenzyl)oxy)-2,4-dimethylpentan-1-ol (**S6**).*




This compound was synthesized in the same manner as that of **9** (0.7 g, 77%): $[\alpha]_D^{20}$ = +15.03° ($c$ 0.92, $CHCl_3$); IR (neat) 3405, 2912, 2869, 1512, 1244, 1033, 819 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.24 (d, $J$ = 8.3rrr Hz, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 4.42 (s, 2H), 3.77 (s, 3H), 3.41 (dd, $J$ = 6.5, 10.5 Hz, 1H), 3.36 (dd, $J$ = 6.3, 10.5 Hz, 1H), 3.27 (dd, $J$ = 6.3, 8.8 Hz, 1H), 3.23 (dd, $J$ = 6.9, 9.2 Hz, 1H), 1.87 (m, 1H), 1.71 (m, 1H), 1.18 (m, 2H), 0.89 (d, $J$ = 6.6 Hz, 3H), 0.87 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 158.9, 139.0, 130.5, 113.5, 76.0, 72.5, 68.4, 55.0, 37.0, 32.8, 30.4, 16.8, 16.2; HRMS (ESI) $m/z$ 275.1616 $[M + Na]^+$ calcd for $C_{15}H_{24}NaO_3$, 275.1618; colorless oil.

*1-((((2R,4R)-2,4-Dimethylhexyl)oxy)methyl)-4-methoxybenzene (**S7**).*

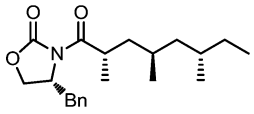



This compound was synthesized in the same manner as that of **10** (0.6 g, 96% over two steps): $[\alpha]_D^{20}$ = +12.09° ($c$ 0.82, $CHCl_3$), IR (neat) 2956, 2910, 2850, 1511, 1246, 1096, 820 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.31 (d, $J$ = 8.4 Hz, 2H), 6.92 (d, $J$ = 8.9 Hz, 2H), 4.49 (d, $J$ = 2.5 Hz, 2H), 3.81 (s, 3H), 3.35 (dd, $J$ = 5.8, 8.9 Hz, 1H), 3.25 (dd, $J$ = 7.1, 8.9 Hz, 1H), 1.92 (m, 1H), 1.48 (m, 1H), 1.38 (m, 1H), 1.23 (m, 2H), 1.16 (m, 1H), 0.97 (d, $J$ = 6.7 Hz, 3H), 0.94 (t, $J$ = 7.4 Hz, 3H), 0.91 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 158.9, 130.8, 128.9, 113.6, 76.3, 72.4, 55.0, 40.6, 31.5, 30.8, 30.3, 18.8, 16.9, 11.3; IR


dx.doi.org/10.1021/jo500906v | J. Org. Chem. 2014, 79, 6858−6867

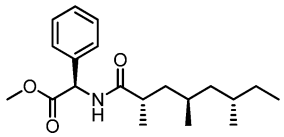
(neat) 2956, 2910, 2810, 1511, 1245, 1096, 819 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz); HRMS (ESI) $m/z$ 273.1823 $[M + Na]^+$ calcd for $C_{16}H_{26}NaO_2$, 273.1825; colorless oil.

*(R)-4-Benzyl-3-((2S,4R,6R)-2,4,6-trimethyloctanoyl)oxazolidin-2-one (**S8**).*



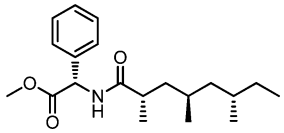
This compound was synthesized in the same manner as that of **11** (36.3 mg, 16% over 3 steps). The ratio of **S8** and its diastereomer was 3:1, as judged from their yield: $[\alpha]_D^{20} = -15.79°$ ($c$ 0.94, $CHCl_3$); IR (neat) 2960, 2916, 1780, 1698, 1383, 1209 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.20−7.35 (5H), 4.68 (m, 1H), 4.16 (m, 2H), 3.89 (m, 1H), 3.32 (dd, $J$ = 3.6, 13.9 Hz, 1H), 2.69 (dd, $J$ = 10.1, 13.0 Hz, 1H), 1.63 (m, 1H), 1.59 (m, 1H), 1.41 (m, 1H), 1.35 (m, 1H), 1.29 (m, 1H), 1.16 (m, 1H/d, $J$ = 7.0 Hz, 3H), 1.10 (m, 2H), 0.89 (d, $J$ = 5.8 Hz, 3H), 0.87 (t, $J$ = 7.3 Hz, 3H), 0.83 (d, $J$ = 6.7 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 177.8, 153.0, 135.5, 129.4, 128.9, 127.3, 65.9, 55.4, 44.7, 41.7, 38.1, 35.3, 31.6, 30.2, 27.9, 19.0 (2C), 16.8, 11.4; HRMS (ESI) $m/z$ 368.2198 $[M + Na]^+$ calcd for $C_{21}H_{31}NNaO_3$, 368.2196; colorless oil.

*(R)-Methyl 2-Phenyl-2-((2S,4R,6R)-2,4,6-trimethyloctamido)-acetate (**15a**).*



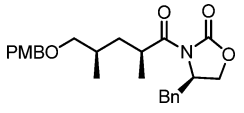
This compound was synthesized in the same manner as that of **13a** (8.0 mg, 82% over two steps): $[\alpha]_D^{20} = -82.39°$ ($c$ 0.74, $CHCl_3$); IR (neat) 3282, 2959, 2920, 1751, 1634 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.29−7.36 (5H), 6.38 (NH), 5.60 (d, $J$ = 7.8 Hz, 1H), 3.73 (s, 3H), 2.38 (m, 1H), 1.50 (m, 1H), 1.46 (m, 1H), 1.35 (m. 1H), 1.27 (m, 1H), 1.23 (m, 1H), 1.15 (d, $J$ = 6.7 Hz, 3H), 1.02 (m, 2H), 0.96 (m, 1H), 0.83 (t, $J$ = 7.7 Hz, 3H), 0.77 (d, $J$ = 6.5 Hz, 3H), 0.70 (d, $J$ = 6.7 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 176.1, 171.6, 136.7, 128.9, 128.4, 128.3, 56.2, 52.8, 44.4, 42.3, 38.8, 31.6, 30.4, 27.8, 19.4, 18.8, 17.8, 11.4; HRMS (ESI) $m/z$ 356.2200 $[M + Na]^+$ calcd for $C_{20}H_{31}NNaO_3$, 356.2196; colorless amorphous solid.

*(S)-Methyl 2-Phenyl-2-((2S,4R,6R)-2,4,6-trimethyloctamido)-acetate (**15b**).*



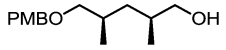
This compound was synthesized in the same manner as that of **13b** (8.5 mg, 88% over two steps): $[\alpha]_D^{20} = +128.66°$ ($c$ 0.73, $CHCl_3$); IR (neat) 3295, 2959, 2926, 1748, 1647 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.23−7.37 (5H), 6.38 (NH), 5.58 (d, $J$ = 6.5 Hz, 1H), 3.73 (s, 3H), 2.38 (m, 1H), 1.54 (m, 1H), 1.53 (m, 1H), 1.40 (m, 1H), 1.31 (m, 1H), 1.27 (m, 1H), 1.14 (m, 1H), 1.10 (d, $J$ = 7.0 Hz, 3H), 1.08 (m, 2H), 0.86 (t, $J$ = 7.4 Hz, 3H), 0.83 (d, $J$ = 6.6 Hz, 3H), 0.81 (d, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 176.1, 171.5, 136.8, 128.9, 128.5, 127.2, 56.2, 52.7, 44.5, 42.4, 38.8, 31.7, 30.4, 27.8, 19.4, 18.9, 17.6, 11.4; HRMS (ESI) $m/z$ 356.2195 $[M + Na]^+$ calcd for $C_{20}H_{31}NNaO_3$, 356.2196; colorless oil.

**PGME Derivatives of Synthetic (2*S*,4*R*,6*S*)-Trimethyloctanoic Acid (16a,b).** *(S)-4-Benzyl-3-((2R,4R)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentanoyl)oxazolidin-2-one (**S9**).*



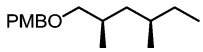
This compound was synthesized in the same manner as that of **8** (1.9 g, 32% over four steps). The ratio of **S9** and its diastereomer was 23:1, as judged from their yield: $[\alpha]_D^{20} = -21.85°$ ($c$ 0.93, $CHCl_3$); IR (neat) 2958, 2931, 2854, 1775, 1695, 1385, 1207, 1092, 819, 702 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 6.85−7.35 (9H), 4.67 (m, 1H), 4.45 (s, 2H), 4.11−4.19 (m, 2H), 3.96 (m, 1H), 3.41 (dd, $J$ = 5.8, 9.5 Hz, 1H), 3.29 (dd, $J$ = 3.5, 13.2 Hz, 1H), 3.24 (dd, $J$ = 7.0, 9.3 Hz, 1H), 2.67 (dd, $J$ = 9.7, 13.2 Hz, 1H), 1.97 (ddd, $J$ = 6.2, 8.2, 14.1 Hz, 1H), 1.86 (m, 1H), 1.25 (ddd, $J$ = 6.4, 7.5, 13.6 Hz, 1H), 1.20 (d, $J$ = 6.8 Hz, 3H), 1.00 (d, $J$ = 6.6 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 177.2, 158.9, 153.0, 135.3, 130.8, 129.3, 129.0, 128.8, 127.2, 113.6, 75.2, 72.5, 65.8, 55.3, 55.1, 38.0, 37.9, 35.1, 31.3, 18.0, 17.7; HRMS (ESI) $m/z$ 448.2106 $[M + Na]^+$ calcd for $C_{25}H_{31}NNaO_5$, 448.2094; colorless oil.

*(2R,4R)-5-((4-Methoxybenzyl)oxy)-2,4-dimethylpentan-1-ol (**S10**).*



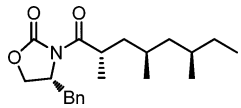
This compound was synthesized in the same manner as that of **9** (0.8 g, 85%): $[\alpha]_D^{20} = -5.22°$ ($c$ 1.05, $CHCl_3$); IR (neat) 3362, 2911, 2869, 1511, 1246, 1033, 822 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.23 (d, $J$ = 9.2 Hz, 2H), 6.85 (d, $J$ = 8.3 Hz, 2H), 4.40 (d, $J$ = 3.5 Hz, 2H), 3.75 (s, 3H), 3.40 (dd, $J$ = 5.3, 10.2 Hz, 1H), 3.31 (dd, $J$ = 6.2, 10.5 Hz, 1H), 3.28 (dd, $J$ = 6.0, 9.1 Hz, 1H), 3.19 (dd, $J$ = 7.1, 9.4 Hz, 1H), 1.83 (m, 1H), 1.66 (m, 1H), 1.45 (m, 1H), 0.93 (d, $J$ = 6.9 Hz, 3H), 0.91 (d, $J$ = 6.4 Hz, 3H), 0.90 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 158.9, 130.4, 128.9, 113.5, 75.4, 72.5, 67.3, 54.9, 37.5, 32.9, 30.7, 17.9, 17.4; HRMS (ESI) $m/z$ 275.1613 $[M + Na]^+$ calcd for $C_{15}H_{24}NaO_3$, 275.1618; colorless oil.

*1-((((2R,4S)-2,4-Dimethylhexyl)oxy)methyl)-4-methoxybenzene (**S11**).*



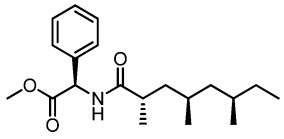
This compound was synthesized in the same manner as that of **10** (0.6 g, 76% over two steps): $[\alpha]_D^{20} = -10.43°$ ($c$ 1.21, $CHCl_3$); IR (neat) 2910, 2851, 1512, 1245, 1095, 819 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.30 (d, $J$ = 8.3 Hz, 2H), 6.91 (d, $J$ = 8.7 Hz, 2H), 4.67 (d, $J$ = 7.6 Hz, 2H), 3.82 (s, 3H), 3.36 (dd, $J$ = 5.5, 9.0 Hz, 1H), 3.21 (dd, $J$ = 7.3, 9.3 Hz, 1H), 1.89 (m, 1H), 1.46 (m, 1H), 1.40 (m, 1H), 1.38 (m, 1H), 1.13 (m, 1H), 0.98 (d, $J$ = 6.9 Hz, 3H), 0.97 (m, 1H), 0.91 (d, $J$ = 6.3 Hz, 3H/t, $J$ = 6.3 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 159.0, 130.9, 128.9, 113.6, 75.7, 72.5, 55.0, 41.1, 31.5, 30.9, 29.0, 19.7, 18.0, 11.1; HRMS (ESI) $m/z$ 273.1821 $[M + Na]^+$ calcd for $C_{16}H_{26}NaO_2$, 273.1825; colorless oil.

*(R)-4-Benzyl-3-((2S,4R,6S)-2,4,6-trimethyloctanoyl)oxazolidin-2-one (**S12**).*



This compound was synthesized in the same manner as that of **11** (39.4 mg, 15% over three steps). The ratio of **S12** and its diastereomer was 4:1, as judged from their yield: $[\alpha]_D^{20} = -41.31°$ ($c$ 0.75, $CHCl_3$); IR (neat) 2959, 2915, 1779, 1697, 1209 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.20−7.34 (5H), 4.67 (m, 1H), 3.85 (m, 1H), 3.30 (dd, $J$ = 2.8, 13.7 Hz, 1H), 2.70 (dd, $J$ = 10.0, 13.5 Hz, 1H), 1.61 (m, 1H), 1.52 (m, 1H), 1.43 (m, 1H), 1.42 (m, 1H), 1.34 (m, 1H), 1.24 (m, 1H), 1.15 (d, $J$ = 7.0 Hz, 3H), 1.08 (m, 1H), 0.99 (m, 1H), 0.91 (d, $J$ = 6.4 Hz, 3H), 0.86 (t, $J$ = 6.7 Hz, 3H), 0.85 (d, $J$ = 6.7 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 177.8, 152.9, 135.4, 129.4, 128.9, 127.3, 65.9, 55.3, 45.1, 40.6, 38.0, 35.3, 31.5, 29.2, 27.7, 19.7, 19.5, 16.4, 11.2; HRMS (ESI) $m/z$ 368.2198 $[M + Na]^+$ calcd for $C_{21}H_{31}NNaO_3$, 368.2196; colorless oil.

*(R)-Methyl 2-Phenyl-2-((2S,4R,6S)-2,4,6-trimethyloctamido)-acetate (**16a**).*

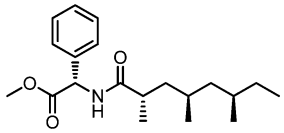


This compound was synthesized in the same manner as that of **13a** (10.7 mg, 87% over two steps): $[\alpha]_D^{20} = -117.43°$ ($c$ 0.89, $CHCl_3$); IR (neat) 3275, 2959, 2915, 1752, 1641, 1535 $cm^{-1}$; $^1H$ NMR


dx.doi.org/10.1021/jo500906v | J. Org. Chem. 2014, 79, 6858−6867

($CDCl_3$, 500 MHz) $\delta$ 7.30−7.37 (5H), 6.40 (NH), 5.60 (d, $J$ = 8.1 Hz, 1H), 3.73 (s, 3H), 2.36 (m, 1H), 1.48 (m, 1H), 1.38 (m, 2H), 1.37 (m, 1H), 1.26 (m, 1H), 1.17 (m, 1H), 1.14 (d, $J$ = 7.0 Hz, 3H), 0.97 (m, 1H), 0.90 (m, 1H), 0.80 (m, 3H), 0.79 (m, 3H) 0.78 (m, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 176.2, 171.6, 136.7, 129.0, 128.5, 127.3, 56.2, 52.7, 44.9, 41.3, 38.7, 31.4, 29.0, 27.8, 20.1, 19.7, 17.5, 11.2; HRMS (ESI) $m/z$ 356.2205 $[M + Na]^+$ calcd for $C_{20}H_{31}NNaO_3$, 356.2196; colorless oil.

*(S)-Methyl 2-Phenyl-2-((2S,4R,6S)-2,4,6-trimethyloctamido)-acetate (**16b**).*



This compound was synthesized in the same manner as that of **13a** (11.3 mg, 92% over two steps): $[\alpha]_D^{20}$ = +104.87° ($c$ 0.94, $CHCl_3$); IR (neat) 3307, 2958, 2928, 1749, 1649, 1524 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.30−7.37 (5H), 6.39 (NH), 5.57 (d, $J$ = 6.9 Hz, 1H), 3.73 (s, 3H), 2.37 (m, 1H), 1.55 (m, 1H), 1.43 (m, 1H), 1.42 (m, 2H), 1.34 (m, 1H), 1.23 (m, 1H), 1.10 (d, $J$ = 6.8 Hz, 3H), 1.05 (m, 1H), 0.95 (m, 1H), 0.85 (m, 6H), 0.84 (m, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 176.1, 171.5, 136.7, 128.9, 128.5, 127.2, 56.2, 52.7, 44.5, 42.1, 38.8, 31.6, 30.4, 27.8, 20.9, 19.4, 17.6, 11.4; HRMS (ESI) $m/z$ 356.2203 $[M + Na]^+$ calcd for $C_{20}H_{31}NNaO_3$, 356.2196; colorless oil.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Text, a table, and figures giving $^1H$ and $^{13}C$ NMR spectra of synthesized materials and natural product derivatives and a list of analyzed compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported in part by research grants from the Japan Society for the Promotion of Sciences (JSPS), the Ministry of Health and Welfare of Japan, and the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

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(17) Reduction using $NaBH_4$ gave two diastereomers, compound **4** and its epimer at C24. The ratio of compound **4** and its diastereomer was 2.5:1.
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