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A Synthetic Approach to Diverse 3-Acyltetramic Acids via *O*- to *C*-Acyl Rearrangement and Application to the Total Synthesis of Penicillenol Series

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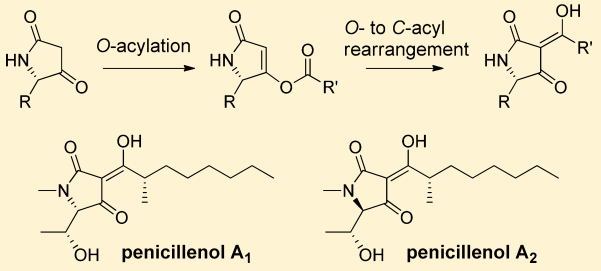
Supporting Information

ABSTRACT: For the efficient approach to medicinally important α-branched 3-acyltetramic acids, the key reaction of *O*- to *C*- acyl rearrangement using α-amino-acid-derived 4-*O*-acyltetramic acids was extensively examined in the presence of various metal salts. Use of $CaCl_2$ or NaI dramatically changed the results in the reaction efficiency and rapidly brought about the desired α-branched 3-acyltetramic acids in markedly improved yields. We also discuss an epimerization at C5 stereocenter under the rearrangement conditions as well as the tolerance for structural variation at C3 and C5. In addition to the preceding success in the total synthesis of new cytotoxic tetramic acid, penicillenol A_1, this methodology could be also applied to the first total synthesis of penicillenol A_2.



INTRODUCTION

2,4-Pyrrolidinedione derivatives, so-called tetramic acids, can serve as one of the basic building blocks for bioactive molecules found in a variety of natural products from marine organisms, fungi, and bacteria.[1] Among these compounds, 3-acyl-substituted tetramic acids (Figure 1) have proven particularly appealing to the medicinal community because of their remarkable potency such as antiviral and antitumor activities (tenuazonic acid),[2a] herbicidal activity (macrocidin A),[2b] inhibitory activities against bacterial RNA polymerases (streptolydigin),[2c,d] anti-HIV activity (Sch 213766),[2e] and cytotoxicity (penicillenols $A_{1,2}$).[2f] In particular, extensive research focused on streptolydigin, whose outstanding inhibitory activity against bacterial RNA polymerase has received particular attention over the past decade, provided an important stimulus for understanding mechanistic complexities of the biological events.[3] Despite the great significance of 3-acyltetramic acids, development of comprehensive and efficient protocols for this type of compound is substantially less advanced, because there is an intrinsic difficulty in accessing this structural system.[4−10] In this context, one of the conventional strategies for the preparation of this class of compounds has utilized Dieckmann-type cyclization of β-ketoamides **A** (Figure 2).[4,5] This synthetic method faces the risk of epimerization at the C5 stereocenter, which would be attributed to enolization equilibrium under the basic conditions, thus making this methodology unsuitable for stereoselective synthesis.[5d,e,h,j,l] Another possible synthetic strategy involves direct acylation of C3-unsubstituted tetramic acids **B** with the use of acid chlorides.[6] This has a limited functional group tolerance, because harsh conditions of operation employing Lewis acids such as $BF_3{\cdot}OEt_2$ are essential to drive the reaction smoothly. Alternatively, a synthetic approach based on *O*- to *C*-acyl rearrangement of 4-*O*-acyltetramic acids **C** has been demonstrated to enable indirect installation of acyl groups into the tetramic acid ring systems.[7] This methodology, however, has limited applicability only for the reactions of the substrates bearing linear migratory segments that would be preferred on steric grounds[6f,7d] and would be incompatible with complicated migratory segments such as α-branched alkylcarbonyl groups. In this regard, we have recently overcome this problem by the use of $CaCl_2$ as an effective additive, giving a marked improvement in the reaction efficiency for the formation of the 3-acyltetramic acid bearing α-methyloctanoyl moiety. Moreover, we accomplished the first total synthesis of penicillenol A_1 through *N*-methylation of amide and subsequent removal of TBS protecting group (Scheme 1).[8] Despite less accumulated information available for the synthesis of 3-acyltetramic acid derivatives, our previous work gave some indication of a rich opportunity for accessing diverse 3-acyltetramic acids with the other branched segments. In an attempt to examine the validity and generality of this synthetic methodology and to expand its utility, we explored the scope of the reaction with a diverse set of the substrates. In the present article, we provide a full account of our efforts in developing the synthetic approach to variously substituted 3-acyltetramic acids and demonstrate the versatility for the remaining synthetic challenge associated with the total synthesis of naturally occurring antibacterial penicillenol A_2.

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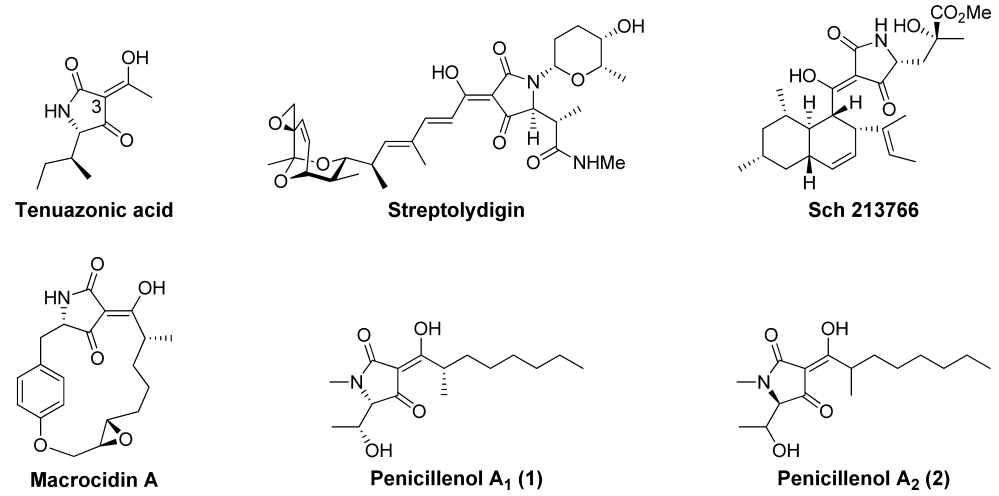


Figure 1. Structures of naturally occurring 3-acyltetramic acids.

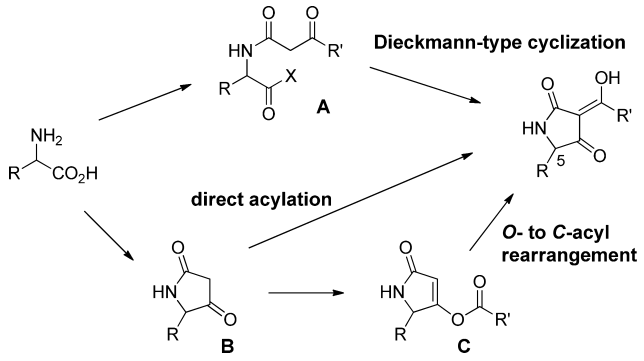


Figure 2. Conventional synthetic approaches to 3-acyltetramic acids.

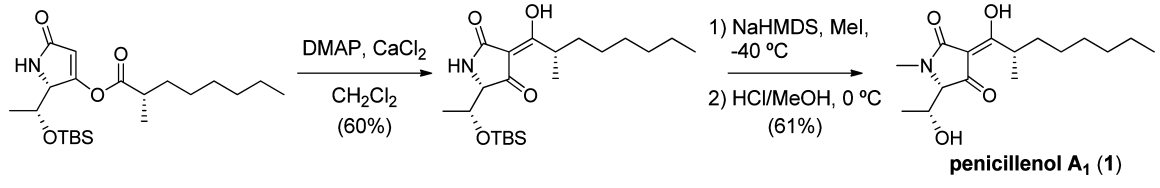
RESULTS AND DISCUSSION

4-*O*-Acyltetramic acids with a variety of substituents **5a**−**n** were prepared as shown in Figure 3.[6f,7d,11] A series of 3-unsubstituted tetramic acids **4a**−**e** obtained through condensation−decarboxylation sequences in good yields from *N*-Boc or *N*-Cbz protected amino acids **3a**−**e**[12] could be condensed with a range of carboxylic acids in the presence of DCC and DMAP to provide **5a**−**m**. For the preparation of **5n**, esterification of **4b** using Piv_2O as a condensing agent was preferred over the above synthetic protocol, affording the best yield of the desired product.

With these compounds in hand, we turned our focus toward investigating the *O*- to *C*-acyl rearrangement of **5** to obtain 3-acyltetramic acids **6**. To optimize this process, a similar series of experiments were undertaken with **5a** under various reaction conditions (Table 1). Without any metal salts, the reaction at room temperature led to give only a 10% yield of the desired product **6a** for a period of 24 h along with recovery of the starting material (entry 1). In contrast, the reaction in the presence of LiBr (1.5 equiv) showed complete consumption of the starting material and gave distinctly better yield of **6a** (43%, entry 2). Similarly, such effects could be observed for the reactions with the use of the other metal salts such as NaCl (entry 3), KF (entry 6), or $CeCl_3$ (entry 8) to afford **6a** in moderate yields, while $FeCl_3$ would be detrimental to the transformation to result in decomposition of the substrate (entry 9). Among the various metal salts examined, $CaCl_2$ (71%, entry 7) and NaI (70%, entry 4) exhibited the marked performances to generate **6a**, and we therefore conclude that these materials would be the optimal additives to promote the *O*- to *C*-acyl rearrangement processes efficiently. In an analogy to closely related systems, the mechanism of rearrangement could be understood on the basis of primary process, namely, a C−O bond-cleavage and recombination of the migrating ion pairs.[13] The presence of ionic species in the metal salts may help in stabilization of the in situ generated ion pairs that would be bound together by weak Coulombic attraction, thus facilitating the formation of 3-acyltetramic acids.

As seen in Figure 4, a wide variety of 4-*O*-acyl tetramic acids **5** were shown to undergo the intramolecular transformations in the presence of $CaCl_2$ to give the corresponding 3-acyltetramic acids **6**. Indeed, the substrates bearing the substituted benzoyl and α-branched alkylcarbonyl moieties **5a**−**m** showed remarkably high reactivities to generate **6a**−**m** in satisfactory yields (51−79%), respectively, whereas the sterically demanding *tert*-butyl analogue **5n** failed to afford the desired compound, decomposing to **4n** under conditions identical to those for the other substrates. Furthermore, no obvious difference was observed in the reaction efficiency when the C5-substituent on the tetramate core was varied, and all the series of 4-*O*-acyl tetramic acids derived from isoleucine **5b**−**g**, phenylalanine **5h**, alanine **5i**, serine **5j**, and threonine **5k**−**m** gave the corresponding rearrangement products **6b**−**m** in moderate to good yields. These results suggest that the course of the reaction is not influenced by the structural properties of the tetramate cores but rather by those of the acyl groups on the

Scheme 1. Synthesis of Penicillenol A_1[8]



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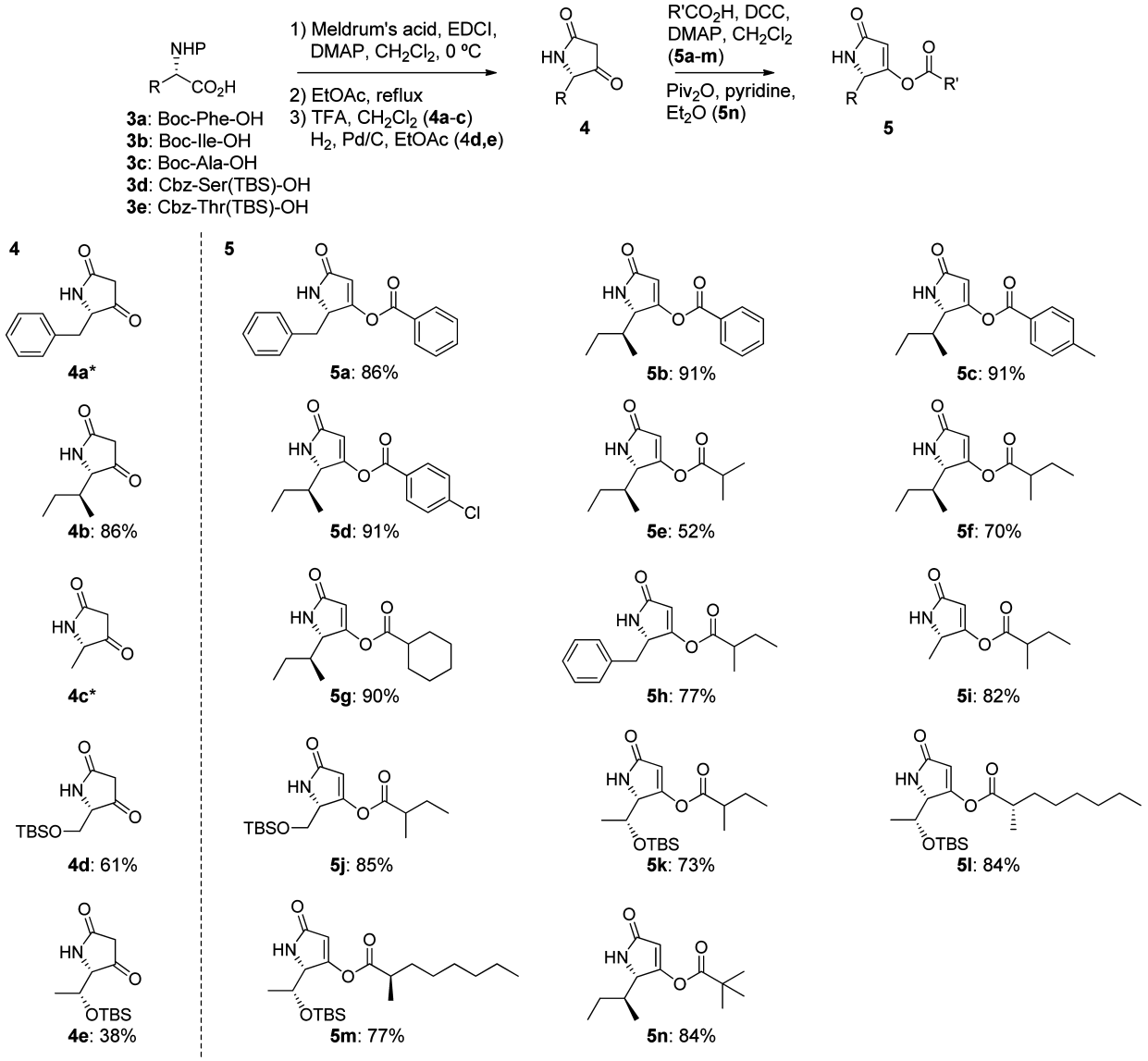
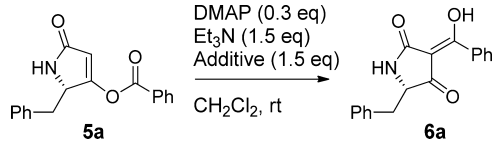


Figure 3. Preparation of 4-*O*-acyltetramic acids **5**. Isolated yields of products are indicated below each entry. *See ref 11.

Table 1. *O*- to *C*-Acyl Rearrangement of 5a in the Presence of Various Metal Salts



entry	additive	time/h	yield/%[a]
1		24	10
2	LiBr	8	43
3	NaCl	24	46
4	NaI	4	70
5	$MgBr_2$	24	29
6	KF	24	44
7	$CaCl_2$	3	71
8	$CeCl_3$	7	55
9	$FeCl_3$	24	0[b]

[a]Isolated yields. [b]**5a** was not recovered.

oxygen atoms. As for stereochemical integrity of the reaction products, it should be noted that small amounts of the epimeric C5 diastereomers were in situ generated for the cases of the substituted benzoyl series **6b–d**, as revealed by the ^{1}H NMR analysis. Apparently, the occurrence of the epimerization can be understood in terms of pathways involving deprotonation of the C5–H and enolization to form planar structures of the relevant enolates. Through inspection of the stereochemical control for the product formation, a higher degree of epimerization was observed as an increase in the reaction time. Actually, prolongation of the reaction time to ensure complete consumption of the reactants led to increases in the relative ratios of the epimeric isomers over the desired ones, where **5c** representing the typical example gave a ratio of 70:30 (**6c**/epimer) for 16 h as compared with 78:22 for 1 h along with **5b** (83:17 for 3 h) and **5d** (87:13 for 3 h). On the other hand, the series of 4-*O*-alkylcarbonyl tetramic acids **5e–m** underwent fast reactions that completed within 1 h, affording the enantiomerically pure products. In such cases, the epimerization was exclusively avoided, probably because of substantially much slower rates as compared to the *O*- to *C*-acyl rearrangement processes. In this regard, we found that a noticeable epimerization of the recovered substrate took place

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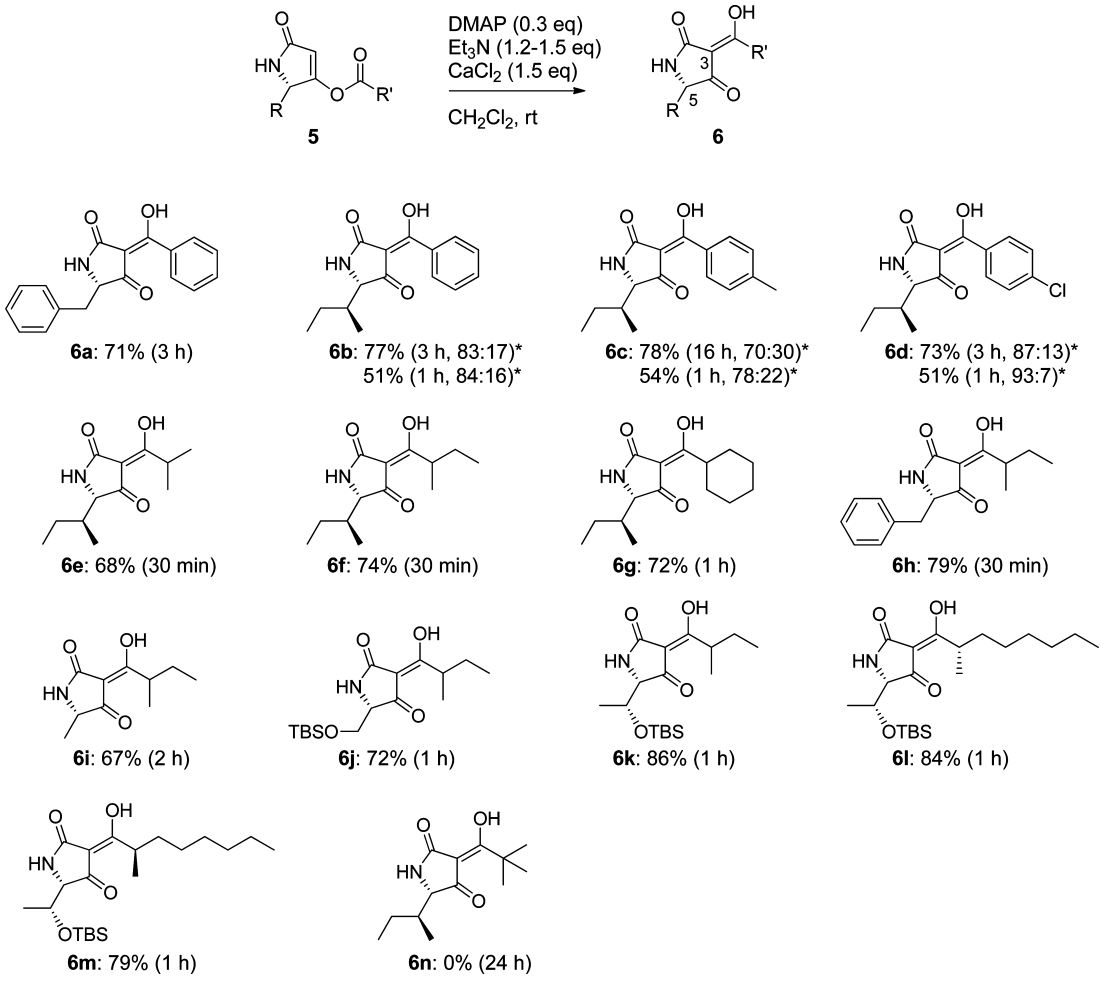

Figure 4. Acyl rearrangement of 4-*O*-acyltetramic acids in the presence of $CaCl_2$. Isolated yields are indicated below each entry. *Reaction time and diastereomeric ratio determined by ^{1}H NMR are indicated in parentheses.

at a rate of 96:4 (**5b**/epimer) when the enantiomerically pure **5b** was treated with Et_3N (1.5 equiv) and in the presence of $CaCl_2$ (1.5 equiv) in CH_2Cl_2 at room temperature,[14] as observed by ^{1}H NMR, while no epimerization of the product occurred when **6b** was treated under the same conditions (Figure 5). These findings confirm that the formation of

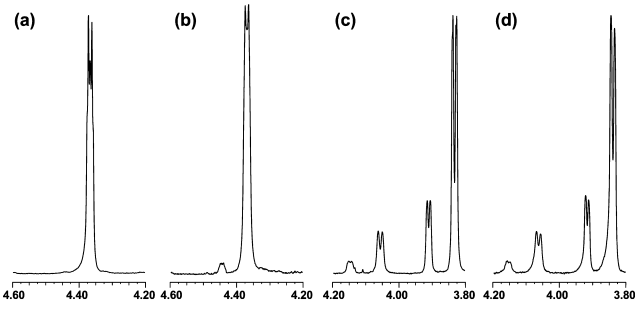

Figure 5. Comparison of ^{1}H NMR spectra on H5 of **5b** or **6b** (300 MHz, $CDCl_3$, δ in ppm). (a) **5b**, (b) **5b** after treatment with Et_3N (1.5 equiv) and $CaCl_2$ (1.5 equiv) in CH_2Cl_2 at room temperature, (c) **6b**, and (d) **6b** after treatment with Et_3N (1.5 equiv) and $CaCl_2$ (1.5 equiv) in CH_2Cl_2 at room temperature.

3-acyltetramic acids competes with the epimerization proceeding at comparable rates. From the above considerations, we can conclude that the metal salts serve a dual purpose of suppressing the epimerization under the conditions employed as well as enhancing the product formation.[15]

As our continuing interest in the context of the present studies, we considered that a properly designed 3-acyltetramic acid obtained through the *O*- to *C*-acyl rearrangement would serve as a substrate pertinent to achieving the total synthesis of natural products such as penicillenols, which have been isolated from the culture broth of a fungus *Penicillium* sp. as cytotoxic agents.[2f] In our previous work, the total synthesis of penicillenol A_1 **1** and its C9-epimer has been completed by employing **6l**,**m**, respectively.[8] Following the above synthetic strategy, we considered that the synthesis of penicillenol A_2, a C5-epimer of penicillenol A_1, would be achieved using D-allothreonine as a starting chiral source. Thus, we turned to synthesize this natural product to demonstrate the versatility of this synthetic methodology for a generous supply of 3-acyltetramic acids (Scheme 2). The synthesis started with a 56:44 mixture of L-threonine and D-allothreonine, which could be prepared by isomerization of L-threonine.[16] When this material was allowed to react under conditions identical to that for **4e**, a 61:39 inseparable diastereomeric mixture of **9** was obtained. Subsequent condensation of this material with (*S*)-2-methyloctanoic acid[17] afforded a mixture consisting of **10** and its diastereoisomeric counterpart **5m**, which could be separated by silica gel column chromatography. The enantiomerically

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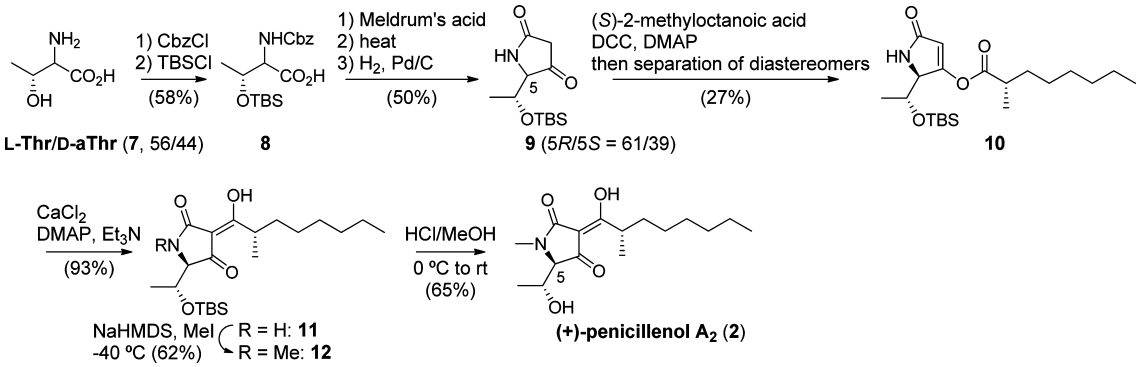
Scheme 2. Total Synthesis of Penicillenol A_2



pure **10** underwent the *O*- to *C*-acyl rearrangement followed by *N*-methylation to produce **12** in 58% yield over two steps. At the final step, the TBS group of **12** could be removed by exposure to methanolic HCl (2%) to give **2** in 65% yield as a 90:10 mixture of *Z*:*E* isomers.

Identification of this product was performed by spectroscopic analyses and optical rotatory measurements. As a consequence, ^{1}H NMR, ^{13}C NMR, and IR spectroscopic data of **2** appeared to be fully consistent with those of the natural penicillenol A_2, although the optical rotation of **2** $\{[\alpha]_D^{22}$ +49.2 (*c* 0.137, MeOH)} showed a significant difference to that reported in the literature[2f] $\{[\alpha]_D^{25}$ +386.7 (*c* 0.135, MeOH)}.[18] Unfortunately, other data to be discussed were unavailable except that the optical rotations of both penicillenols fluctuated significantly because of their low solubilities in MeOH.[19] Further measurements of the synthetic sample of **1** and **2** in $CHCl_3$ allowed us to reevaluate the optical activities, giving constant values of $[\alpha]_D^{23}$ −47.6 (*c* 0.918) for **1** and $[\alpha]_D^{22}$ +27.8 (*c* 0.864) for **2**. Although an obvious reason for the observed difference in the $[\alpha]_D$ values remains unclear at present, we are reasonably confident with the complete spectroscopic characterization that the synthetic approach described above should ensure completion of the first total synthesis of penicillenol A_2 with the complete structure and absolute stereochemistry.[20]

CONCLUSION

The synthesis of 3-acyltetramic acids via *O*- to *C*-acyl rearrangement has been systematically investigated. We demonstrated that the presence of metal salts significantly improved the product yields to produce the desired 3-acyltetramic acids, and a variety of substituents were found to be well tolerated. Coupled with our preceding report on the success in synthesizing penicillenol A_1, this synthetic method has been demonstrated to allow for completing the first total synthesis of penicillenol A_2.

EXPERIMENTAL SECTION

(*S*)-5-((*S*)-*sec*-Butyl)-4-oxo-2-pyrrolidone (4b). To a solution of Meldrum's acid (1.20 g, 8.33 mmol) and protected amino acid **3c** (1.76 g, 7.61 mmol) in dichloromethane (50 mL) at 0 °C were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (1.75 g, 9.13 mmol) and DMAP (1.39 g, 11.4 mmol). After stirring for 5 h at room temperature, the reaction mixture was poured into EtOAc (150 mL) and extracted. The organic layer was washed with brine and 5% aqueous $NaHSO_4$ solution, dried over Na_2SO_4, and filtered. The filtrate was refluxed for 1 h until completion of the reaction (monitored by TLC) and concentrated under reduced pressure. The residue was treated with 1:1 TFA/dichloromethane (2.0 mL) for 1 h. After removal of the solvent by evaporation, the crude product was purified by column chromatography (silica gel, hexane/EtOAc = 1/1) to give **4b** (1.01 g, 86%) as a white powder: dp 94−100 °C; $[\alpha]_D^{27}$ −71.7 (*c* 1.04, $CHCl_3$); IR (KBr) 3178 (N−H), 3098 (N−H), 2936 (C−H), 1772 (C═O), 1694 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (brs, 1H), 3.92 (d, *J* = 4.2 Hz, 1H), 2.97 (s, 2H), 1.89 (m, 1H), 1.46−1.26 (m, 2H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8 (*C*), 172.5 (*C*), 69.1 (CH), 41.6 (CH), 37.6 (CH), 24.2 (CH_2), 15.1 (CH_3), 11.4 (CH_3). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.02; H, 8.58; N, 8.64.

(*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-4-oxo-2-pyrrolidone (4d). To a solution of Meldrum's acid (951 mg, 6.60 mmol) and protected amino acid **3d** (2.12 g, 6.00 mmol) in dichloromethane (30 mL) at 0 °C were added EDCI (1.38 g, 7.20 mmol) and DMAP (1.10 g, 9.00 mmol). After stirring for 2 h at room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was washed with 5% aqueous $NaHSO_4$ solution, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated to give the crude mixture. This material was dissolved in EtOAc (90 mL), and the solution was refluxed for 1 h until completion of the reaction (monitored by TLC) and concentrated under reduced pressure. A suspension containing the residue and Pd/C (31.2 mg) in EtOH (9.0 mL) was stirred under hydrogen atmosphere for 2 h. The reaction mixture was filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH = 40:1) to give **4d** (891 mg, 61%) as a pale yellow solid: dp 78−84 °C; $[\alpha]_D^{27}$ −53.7 (*c* 1.03, $CHCl_3$); IR (KBr) 3200 (N−H), 3104 (N−H), 2930 (C−H), 1778 (C═O), 1690 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (brs, 1H), 4.01 (brt, *J* = 3.3 Hz, 1H), 3.92 (dd, *J* = 3.3, 10.5 Hz, 1H), 3.77 (dd, *J* = 2.4, 10.5 Hz, 1H), 2.91 (s, 2H), 0.84 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5 (*C*), 172.3 (*C*), 66.0 (CH_2), 63.0 (CH), 41.4 (CH_2), 25.6 (CH_3), 18.0 (CH_3), −5.8 (CH_3), −5.9 (CH_3). Anal. Calcd for $C_{11}H_{21}NO_3Si$: C, 54.29; H, 8.70; N, 5.76. Found: C, 54.44; H, 8.43; N, 5.93.

(*S*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-4-oxo-2-pyrrolidone (4e). To a solution of Meldrum's acid (1.50 g, 10.3 mmol) and protected amino acid **3e** (3.45 g, 9.39 mmol) in dichloromethane (35 mL) at 0 °C were added DCC (2.13 g, 10.3 mmol) and DMAP (1.49 g, 12.2 mmol). After stirring for 10 h at 0 °C, the reaction mixture was filtered through a pad of Celite, and the residue was washed with CH_2Cl_2. The filtrate was washed with 5% aqueous $NaHSO_4$ solution and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated to give the crude mixture. The solution of this material in EtOAc (200 mL) was refluxed for 5 h until completion of the reaction (monitored by TLC). After removal of the solvent by evaporation, the suspension containing the residue and Pd/C (500 mg) in EtOAc (50 mL) was stirred under hydrogen atmosphere for 12 h. The mixture was filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane/EtOAc = 3/1−2/1−1/1) to give **4e** (911 mg, 38%, 3 steps) as a white

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powder: dp 122−124 °C; $[\alpha]_D^{29}$ −84.8 (*c* 1.10, $CHCl_3$); IR (NaCl) 3199 (N−H), 3111 (N−H), 1777 (C═O), 1709 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (brs, 1H), 4.21 (dq, *J* = 2.7, 6.6 Hz, 1H), 3.80 (brd, *J* = 2.6 Hz, 1H), 2.90 (s, 2H), 1.24 (d, *J* = 6.6 Hz, 3H), 0.82 (s, 9H), 0.04 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8 (*C*), 172.9 (*C*), 70.2 (*CH*), 68.1 (*CH*), 41.3 (CH_2), 25.5 (CH_3), 20.3 (CH_3), 17.7 (*C*), −4.5 (CH_3), −5.4 (CH_3). Anal. Calcd for $C_{12}H_{23}NO_3Si$: C, 55.99; H, 9.01; N, 5.44. Found: C, 55.66; H, 8.75; N, 5.59.

General Procedure for the Preparation of the 4-*O*-Acyltetramic Acids. To a solution of carboxylic acid (1.1−1.4 equiv) in dichloromethane at 0 °C were added DCC (1.2−1.9 equiv) and DMAP (0.2−0.3 equiv). After stirring for 5 min at the same temperature, **4** (1.0 equiv) was added. It was stirred at room temperature until completion of the reaction (monitored by TLC). The reaction mixture was filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate was washed with saturated aqueous NH_4Cl solution and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product afforded 4-*O*-acyltetramic acid **5**.

(*S*)-2-Benzyl-5-oxo-2,5-dihydro-1*H*-3-pyrrolyl Benzoate (5a). The crude product was rinsed with Et_2O (5 mL) to give **5a** (40.1 mg, 86%) as a white powder: dp 113−115 °C; $[\alpha]_D^{30}$ −34.3 (*c* 0.978, $CHCl_3$); IR (KBr) 3193 (N−H), 3075 (N−H), 2895 (C−H), 1752 (C═O), 1696 (C═O), 1612 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.67 (m, 1H), 7.51 (m, 2H), 7.32−7.22 (m, 5H), 6.55 (s, 1H), 6.21 (s, 1H), 4.59 (dd, *J* = 5.1, 8.1 Hz, 1H), 3.22 (dd, *J* = 5.1, 13.5 Hz, 1H), 2.91 (dd, *J* = 8.1, 13.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 (*C*), 165.8 (*C*), 162.2 (*C*), 136.0 (*C*), 134.5 (*C*), 130.3 (*CH*), 129.2 (*CH*), 128.9 (2*CH*), 128.0 (*CH*), 127.2 (*CH*), 108.0 (*CH*), 100.6 (*CH*), 59.0 (*CH*), 38.7 (CH_2). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 74.02; H, 5.45; N, 5.17.

(*S*)-2-((*S*)-*sec*-Butyl)-5-oxo-2,5-dihydro-1*H*-3-pyrrolyl Benzoate (5b). The crude product was purified by column chromatography (silica gel, hexane/EtOAc/AcOH = 66/33/1) to give **5b** (106 mg, 91%) as a white powder: dp 106−114 °C; $[\alpha]_D^{27}$ +1.97 (*c* 1.05, $CHCl_3$); IR (KBr) 3198 (N−H), 3072 (N−H), 2935 (C−H), 1765 (C═O), 1682 (C═O), 1616 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (m, 2H), 7.93 (brs, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 6.28 (s, 1H), 4.38 (brd, *J* = 3.0 Hz, 1H), 1.97 (m, 1H), 1.44 (m, 1H), 1.24 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4 (*C*), 165.5 (*C*), 162.3 (*C*), 134.4 (*C*), 130.2 (*CH*), 128.9 (*CH*), 128.2 (*CH*), 108.7 (*CH*), 63.1 (*CH*), 36.3 (*CH*), 23.1 (CH_2), 15.8 (CH_3), 11.9 (CH_3). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.84; H, 6.56; N, 5.55.

(*S*)-2-((*S*)-*sec*-Butyl)-5-oxo-2,5-dihydro-1*H*-3-pyrrolyl 4-Methylbenzoate (5c). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 3/1−1/1) to give **5c** (113 mg, 91%) as a white powder: dp 112−117 °C; $[\alpha]_D^{27}$ −2.51 (*c* 1.05, $CHCl_3$); IR (KBr) 3241 (N−H), 3092 (N−H), 2930 (C−H), 1751 (C═O), 1690 (C═O), 1616 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.34−7.30 (m, 2H), 6.25 (s, 1H), 4.36 (brd, *J* = 3.3 Hz, 1H), 2.46 (s, 3H), 1.96 (m, 1H), 1.44 (m, 1H), 1.26 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1 (*C*), 165.6 (*C*), 162.3 (*C*), 145.6 (*C*), 130.3 (*CH*), 129.7 (*CH*), 125.5 (*C*), 108.6 (*CH*), 63.0 (*CH*), 36.4 (*CH*), 23.1 (CH_2), 21.7 (CH_3), 15.9 (CH_3), 11.9 (CH_3). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 69.92; H, 7.00; N, 5.12.

(*S*)-2-((*S*)-*sec*-Butyl)-5-oxo-2,5-dihydro-1*H*-3-pyrrolyl 4-Chlorobenzoate (5d). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 1/1) to give **5d** (120 mg, 91%) as a white powder: dp 88−92 °C; $[\alpha]_D^{29}$ −3.6 (*c* 1.03, $CHCl_3$); IR (KBr) 3249 (N−H), 2931 (C−H), 1770 (C═O), 1696 (C═O), 1656 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.79 (brs, 1H), 7.51 (m, 2H), 6.27 (s, 1H), 4.37 (brd, *J* = 3.0 Hz, 1H), 1.95 (m, 1H), 1.48−1.20 (m, 2H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1 (*C*), 165.3 (*C*), 161.5 (*C*), 141.2 (*C*), 131.5 (*CH*), 129.4 (*CH*), 126.6 (*C*), 108.9 (*CH*), 63.0 (*CH*), 36.4 (*CH*), 23.1 (CH_2), 15.8 (CH_3), 11.9 (CH_3). Anal. Calcd for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49; N, 4.77. Found: C, 61.14; H, 5.76; N, 4.82.

(*S*)-2-((*S*)-*sec*-Butyl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl Isobutyrate (5e). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 1/1) to give **5e** (52.9 mg, 52%) as a white powder: dp 88−92 °C; $[\alpha]_D^{25}$ +45.9 (*c* 0.880, $CHCl_3$); IR (KBr) 3234 (N−H), 3103 (N−H), 2935 (C−H), 1778 (C═O), 1687 (C═O), 1652 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (brs, 1H), 6.08 (s, 1H), 4.21 (t, *J* = 1.5 Hz, 1H), 2.74 (sep, *J* = 6.9 Hz, 1H), 1.85 (m, 1H), 1.39−1.13 (m, 8H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2 (*C*), 172.6 (*C*), 165.5 (*C*), 108.2 (*CH*), 62.8 (*CH*), 36.1 (*CH*), 34.4 (*CH*), 22.9 (CH_2), 18.5 (CH_3), 18.4 (CH_3), 15.8 (CH_3), 11.8 (CH_3). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.26; H, 8.83; N, 6.59.

(*S*)-2-((*S*)-*sec*-Butyl)-5-oxo-2,5-dihydro-1*H*-3-pyrrolyl 2-Methylbutanoate (5f). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 1/1) to give **5f** (48.0 mg, 70%) as a white powder: dp 95−99 °C; IR (KBr) 3233 (N−H), 3100 (N−H), 2936 (C−H), 1778 (C═O), 1686 (C═O), 1652 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (brs, 2H), 6.09−6.08 (m, 2H), 4.20 (brt, *J* = 1.5 Hz, 2H), 2.57 (m, 2H), 1.84 (m, 2H), 1.74 (m, 2H), 1.59 (m, 2H), 1.38−1.13 (m, 4H), 1.25 (d, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 6H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7 (*C*), 172.4 (*C*), 172.3 (*C*), 165.7 (2*C*), 108.3 (*CH*), 63.2 (*CH*), 41.5 (*CH*), 41.4 (*CH*), 36.3 (*CH*), 36.2 (*CH*), 26.6 (CH_2), 26.4 (CH_2), 23.0 (CH_2), 22.9 (CH_2), 16.4 (CH_3), 16.1 (CH_3), 16.0 (CH_3), 12.0 ($2CH_3$), 11.5 (CH_3), 11.4 (CH_3). Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 64.92; H, 8.49; N, 5.80.

(*S*)-2-((*S*)-*sec*-Butyl)-5-oxo-2,5-dihydro-1*H*-3-pyrrolyl Cyclohexanecarboxylate (5g). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 1/1) to give **5g** (124 mg, 90%) as a white powder: dp 112 −117 °C; $[\alpha]_D^{28}$ +33.1 (*c* 1.02, $CHCl_3$); IR (KBr) 3235 (N−H), 3104 (N−H), 2932 (C−H), 1773 (C═O), 1692 (C═O), 1652 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (brs, 1H), 6.06 (s, 1H), 4.19 (t, *J* = 1.5 Hz, 1H), 2.49 (m, 1H), 2.00−1.12 (m, 13H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4 (*C*), 171.5 (*C*), 165.6 (*C*), 108.1 (*CH*), 62.9 (*CH*), 43.2 (*CH*), 36.1 (*CH*), 28.6 (CH_2), 28.4 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 22.8 (CH_2), 15.9 (CH_3), 11.8 (CH_3). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.64; H, 8.36; N, 5.58.

(*S*)-2-Benzyl-5-oxo-2,5-dihydro-1*H*-3-pyrrolyl 2-Methylbutanoate (5h). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 1/1−1/2) to give **5h** (65.0 mg, 77%) as a white powder: dp 70−76 °C; $[\alpha]_D^{29}$ −41.9 (*c* 0.515, $CHCl_3$); IR (KBr) 3234 (N−H), 2974 (C−H), 1773 (C═O), 1685 (C═O), 1644 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.26 (m, 6H), 7.20−7.18 (m, 4H), 6.37 (brs, 2H), 6.02 (s, 2H), 4.40 (dd, *J* = 4.2, 5.7 Hz, 2H), 3.16 (dd, *J* = 4.2, 13.7 Hz, 2H), 2.76 (dd, *J* = 5.7, 13.7 Hz, 2H), 2.62−2.54 (m, 2H), 1.72 (m, 2H), 1.59 (m, 2H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.25 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 7.4 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7 (*C*), 172.2 (*C*), 165.8 (*C*), 136.2 (*C*), 129.1 (*CH*), 128.9 (*CH*), 127.3 (*CH*), 107.6 (*CH*), 58.9 (2*CH*), 41.2 (2*CH*), 38.5 (CH_2), 26.4 ($2CH_2$), 16.1 ($2CH_2$), 14.1 (CH_3), 11.3 (CH_2). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 69.92; H, 6.61; N, 5.30.

(*S*)-2-Methyl-5-oxo-2,5-dihydro-1*H*-3-pyrrolyl 2-Methylbutanoate (5i). The crude product was purified by column chromatography (silica gel, $CHCl_3$/MeOH = 30/1) to give **5i** (71.5 mg, 82%) as a white powder: dp 58−65 °C; IR (KBr) 3233 (N−H), 3108 (N−H), 2937(C−H), 1776 (C═O), 1687 (C═O), 1651 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (brs, 2H), 6.03 (s, 2H), 4.25 (q, *J* = 6.6 Hz, 2H), 2.59 (m, 2H), 1.75 (m, 2H), 1.60 (m, 2H), 1.37 (d, *J* = 6.6 Hz, 6H), 1.26 (d, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.98

(t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (*C*), 172.2 (*C*), 172.1 (*C*), 167.5 (2*C*), 106.3 (2*C*), 53.7 (2CH), 41.1 (CH), 41.0 (CH), 26.3 (CH_2), 26.2 (CH_2), 17.3 (CH_3), 16.0 (CH_3), 15.9 (CH_3), 11.1 (2CH_3). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.53; H, 7.54; N, 7.23.

(*S*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-5-oxo-2,5-dihydro-1*H*-2-pyrrolyl 2-Methylbutanoate (5j). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 1/1) to give **5j** (46.0 mg, 85%) as a pale yellow oil: IR (KBr) 3173 (N−H), 3086 (N−H), 2927(C−H), 1778 (C═O), 1698 (C═O), 1656 (C═C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (brs, 1H), 6.28 (brs, 1H), 6.08 (s, 2H), 4.25 (m, 2H), 3.93 (dd, J = 3.3, 10.1 Hz, 2H), 3.60 (dd, J = 7.5, 10.1 Hz, 2H), 2.57 (m, 2H), 1.75 (m, 2H), 1.58 (m, 2H), 1.22 (d, J = 6.9 Hz, 6H), 0.94 (t, J = 7.5 Hz, 6H), 0.86 (s, 18H), 0.04 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 (*C*), 172.1 (2*C*), 163.5 (2*C*), 108.4 (CH), 63.1 (CH_2), 60.0 (2CH), 41.1 (2CH), 26.3 (2*C*), 25.5 (CH_3), 18.1 (CH_2), 16.1 (CH_3), 16.0 (CH_3), 11.2 (2CH_3), −5.7 (CH_3), −5.8 (CH_3). Anal. Calcd for $C_{16}H_{29}NO_4Si$: C, 58.68; H, 8.93; N, 4.28. Found: C, 58.51; H, 8.58; N, 4.67.

(*S*)-2-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-5-oxo-2,5-dihydro-1*H*-3-pyrrolyl 2-Methylbutanoate (5k). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 3/1) to give **5k** (77.1 mg, 73%) as a pale yellow oil: IR (KBr) 3219 (N−H), 3085 (N−H), 2932 (C−H), 1779 (C═O), 1697 (C═O), 1623 (C═C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (brs, 2H), 6.06 (s, 2H), 4.10−4.00 (m, 4H), 2.52 (m, 2H), 1.76 (m, 2H), 1.54 (m, 2H), 1.26−1.20 (m, 12H), 0.94 (t, J = 7.5 Hz, 6H), 0.82 (s, 18H), 0.03 (s, 6H), −0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1 (*C*), 172.2 (*C*), 164.1 (2*C*), 108.5 (CH), 67.5 (CH), 67.4 (CH), 64.0 (CH), 41.3 (CH), 41.2 (CH), 26.3 (CH_2), 26.2 (CH_2), 25.5 (CH_3), 20.6 (2*C*), 17.8 (CH_3), 16.1 (CH_3), 16.0 (CH_3), 11.3 (CH_3), −4.4 (CH_3), −5.2 (CH_3) −5.3 (CH_3). Anal. Calcd for $C_{17}H_{31}NO_4Si$: C, 59.79; H, 9.15; N, 4.10. Found: C, 59.53; H, 8.95; N, 4.38.

(*S*)-2-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-5-oxo-2,5-dihydro-1*H*-3-pyrrolyl (*S*)-2-Methyloctanoate (5l). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 3/1−1/1) to give **5l** (97.7 mg, 84%) as a colorless oil: $[\alpha]_D^{24}$ +30.6 (*c* 0.660, $CHCl_3$); IR (NaCl) 3219 (N−H), 3088 (N−H), 1776 (C═O), 1701 (C═O), 1624 (C═C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (brs, 1H), 6.07 (d, J = 0.9 Hz, 1H), 4.05−3.97 (m, 2H), 2.58 (m, 1H), 1.71 (m, 1H), 1.49 (m, 1H), 1.34−1.22 (m, 11H), 1.22 (d, J = 7.2 Hz, 3H), 0.87 (t, J = 6.0 Hz, 3H), 0.83 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (*C*), 172.4 (*C*), 164.0 (*C*), 108.6 (CH), 67.5 (CH), 64.0 (CH), 39.8 (CH), 33.4 (CH_2), 31.5 (CH_2), 29.0 (CH_2), 26.9 (CH_2), 25.5 (CH_3), 22.4 (CH_2), 20.7 (CH_3), 17.8 (CH_3), 16.5 (CH_3), 13.9 (*C*), −4.4 (CH_3), −5.2 (CH_3). Anal. Calcd for $C_{21}H_{39}NO_4Si$: C, 63.43; H, 9.89; N, 3.52. Found: C, 63.69; H, 9.54; N, 3.74.

(*S*)-2-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-5-oxo-2,5-dihydro-1*H*-3-pyrrolyl (*R*)-2-Methyloctanoate (5m). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 3/1−1/1) to give **5l** (88.6 mg, 77%) as a colorless oil: $[\alpha]_D^{24}$ +3.5 (*c* 0.769, $CHCl_3$); IR (NaCl) 3226 (N−H), 3083 (N−H), 1777 (C═O), 1699 (C═O), 1624 (C═C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (brs, 1H), 6.07 (s, 1H), 4.03−3.96 (m, 2H), 2.58 (m, 1H), 1.72 (m, 1H), 1.49 (m, 1H), 1.34−1.24 (m, 11H), 1.23 (d, J = 6.9 Hz, 3H), 0.89−0.82 (m, 12H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 (*C*), 172.3 (*C*), 164.1 (*C*), 108.6 (CH), 67.7 (CH), 64.0 (CH), 39.9 (CH), 33.2 (CH_2), 31.5 (CH_2), 29.0 (CH_2), 26.9 (CH_2), 25.5 (CH_3), 22.4 (CH_3), 20.7 (CH_3), 17.8 (CH_3), 16.6 (CH_3), 13.9 (*C*), −4.4 (CH_3), −5.2 (CH_3). Anal. Calcd for $C_{21}H_{39}NO_4Si$: C, 63.43; H, 9.89; N, 3.52. Found: C, 63.16; H, 9.65; N, 3.55.

(*S*)-2-((*S*)-*sec*-Butyl)-5-oxo-2,5-dihydro-1*H*-3-pyrrolyl Pivalate (5n). To a solution of tetramic acid **4b** (80.0 mg, 0.515 mmol) in Et_2O (1.7 mL) were added Piv_2O (144 mg, 0.773 mmol) and pyridine (61.1 mg, 0.772 mmol). The solution was stirred at room temperature for 17 h until completion of the reaction (monitored by TLC). The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane/EtOAc = 1/1) to give **5n** (104 mg, 84%) as a yellow powder: dp 127−133 °C; $[\alpha]_D^{27}$ +17.5 (*c* 1.32, $CHCl_3$); IR (NaCl) 3199 (N−H), 3077 (N−H), 2935(C−H), 1772 (C═O), 1682 (C═O), 1619 (C═C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (s, 1H), 4.22 (brt, J = 1.5 Hz, 1H), 1.85 (m, 1H), 1.40−1.07 (m, 2H), 1.30 (s, 9H), 1.04 (d, J = 6.9 Hz, 3H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2 (*C*), 174.0 (*C*), 165.6 (*C*), 108.1 (CH), 62.8 (CH), 39.5 (*C*), 36.2 (CH), 26.7 (CH_3), 23.0 (CH_2), 15.9 (CH_3), 11.8 (CH_3). Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.13; H, 8.66; N, 6.02.

General Procedure for the Preparation of the 3-Acyltetramic Acids. To a solution of 4-*O*-acyltetramic acid **5** (1.0 equiv) in dichloromethane were added $CaCl_2$ (1.5 equiv), DMAP (0.3 equiv), and Et_3N (1.2−1.5 equiv). After the suspension was stirred until completion of the reaction (monitored by TLC), the reaction was quenched by addition of 3% aqueous HCl, and the resulting mixture was extracted with EtOAc. The organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product afforded 3-acyltetramic acid **6**.

(*S*)-5-Benzyl-3-(α-hydroxybenzylidene)-4-oxo-2-pyrrolidone (6a). The crude product was washed with MeOH (5 mL) to give **6a** (64.5 mg, 71%) as a white powder: dp 168−169 °C; IR (KBr) 3213 (O−H), 3062 (N−H), 1702 (C═O), 1685 (C═O), 1669 (C═C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (m, 2H), 7.64−7.48 (m, 3H), 7.35−7.21 (m, 5H), 6.86 (brs, 0.97H, *Z*-isomer), 6.21 (brs, 0.03H, *E*-isomer), 4.28 (dd, J = 2.7, 8.4 Hz, 0.03H, *E*-isomer), 4.05 (dd, J = 3.6, 10.1 Hz, 0.97H, *Z*-isomer), 3.32 (dd, J = 3.6, 13.8 Hz, 1H), 2.71 (dd, J = 10.1, 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2 (*C*), 181.4 (*C*), 177.1 (*C*), 136.5 (*C*), 133.9 (*C*), 131.7 (CH), 129.7 (CH), 129.2 (CH), 128.9 (CH), 128.2 (CH), 127.2 (CH), 99.5 (*C*), 62.9 (*CH*), 38.3 (CH_2). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 74.08; H, 5.09; N, 5.00.

(*S*)-5-((*S*)-*sec*-Butyl)-3-(α-hydroxybenzylidene)-4-oxo-2-pyrrolidone (6b). The crude product was purified by column chromatography (silica gel, hexane/EtOAc/AcOH = 83/16/1) to give **6b** (78.9 mg, 77%, **6b**/5-epimer = 83/17) as an orange oil: IR (KBr) 3256 (O−H), 1685 (C═O), 1660 (C═O), 1596 (C═C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 7.2 Hz, 2H), 7.60 (m, 1H), 7.51 (m, 2H), 7.00 (brs, 1H), 4.16 (brs, 0.04H, 5-epimer, *E*-isomer), 4.06 (brd, J = 3.6 Hz, 0.14H, *E*-isomer), 3.92 (brd, J = 2.7 Hz, 0.13H, 5-epimer, *Z*-isomer), 3.84 (brd, J = 3.3 Hz, 0.69H, *Z*-isomer), 2.03 (m, 1H), 1.48−1.16 (m, 2H), 1.10−0.96 (m, 3H), 0.94−0.82 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4 (*C*), 180.5 (*C*), 177.8 (*C*), 133.8 (*C*), 131.8 (CH), 130.7 (CH), 129.7 (2CH), 128.2 (CH), 128.0 (CH), 100.6 (*C*), 66.4 (CH), 65.1 (CH), 37.1 (CH), 36.6 (CH), 26.8 (CH_2), 23.4 (2CH_2), 15.7 (CH_3), 15.4 (CH_3), 12.8 (CH_3), 11.6 (CH_3). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.19; H, 6.38; N, 5.44.

(*S*)-5-((*S*)-*sec*-Butyl)-3-(α-hydroxy-4-methylbenzylidene)-4-oxo-2-pyrrolidone (6c). The crude product was purified by column chromatography (silica gel, hexane/EtOAc/AcOH = 66/33/1) to give **6c** (70.0 mg, 78%, **6c**/5-epimer = 70/30) as a yellow oil: IR (KBr) 3235 (O−H), 1699 (C═O), 1657 (C═O), 1613 (C═C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23−8.13 (m, 2H), 7.35−7.29 (m, 2H), 6.83 (s, 1H), 4.13 (brd, J = 3.0 Hz, 0.01H, 5-epimer, *E*-isomer), 4.04 (brd, J = 4.2 Hz, 0.11H, *E*-isomer), 3.90 (brd, J = 3.3 Hz, 0.29H, 5-epimer, *Z*-isomer), 3.82 (brd, J = 3.3 Hz, 0.59H, *Z*-isomer), 2.43 (s, 3H), 2.11−1.96 (m, 1H) 1.51−1.19 (m, 2H), 1.06−0.80 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6 (*C*), 181.8 (*C*), 181.7 (*C*), 176.7 (*C*), 176.4 (*C*), 137.2 (*C*), 137.1 (*C*), 130.8 (2*C*), 129.3 (2CH), 125.4 (2CH), 125.1 (2CH), 102.1 (*C*), 100.6 (*C*), 66.6 (CH), 65.4 (CH), 37.0 (CH), 36.5 (CH), 26.7 (CH_2), 23,6 (CH_2), 19.6 (CH_3), 15.5 (CH_3), 12.9 (CH_3), 11.6 (2CH_3). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 69.92; H, 6.79; N, 5.21.

(*S*)-5-((*S*)-*sec*-Butyl)-3-(α-hydroxy-4-chlorobenzylidene)-4-oxo-2-pyrrolidone (6d). The crude product was purified by column chromatography (silica gel, hexane/EtOAc/AcOH = 66/33/1) to give **6d** (83.1 mg, 73%, **6d**/5-epimer = 87/13) as a yellow powder: dp 91−101 °C; IR (KBr) 3222 (O−H), 3075 (N−H), 1707 (C═O), 1661

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(C═O), 1590 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.30−8.20 (m, 2H), 7.58 (brs, 1H), 7.47 (d, J = 8.7 Hz, 2H), 4.18 (brd, J = 2.7 Hz, 0.03H, *S*-epimer, *E*-isomer), 4.09 (brd, J = 3.6 Hz, 0.16H, *E*-isomer), 3.93 (brd, J = 2.7 Hz, 0.11H, *S*-epimer, *Z*-isomer), 3.85 (brd, J = 2.7 Hz, 0.70H, *Z*-isomer), 2.04 (m, 1H), 1.10−0.96 (m, 3H), 0.94−0.81 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5 (2*C*), 179.0 (2*C*), 177.7 (*C*), 140.1 (*CH*), 132.1 (*C*), 131.4 (*CH*), 131.1 (*CH*), 130.2 (*C*), 128.8 (*CH*), 128.5 (*CH*), 128.4 (*CH*), 100.7 (*C*), 66.5 (*CH*), 65.2 (*CH*), 63.7 (*CH*), 37.1 (*CH*), 37.0 (*CH*), 26.7 (CH_2), 23.8 (CH_2), 23.4 (CH_2), 15.7 (CH_3), 15.3 (CH_3), 12.8 (CH_3), 11.6 (CH_3), 11.5 (CH_3). Anal. Calcd for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49; N, 4.77. Found: C, 61.13; H, 5.45; N, 4.59.

(*S*)-5-((*S*)-*sec*-Butyl)-3-(1-hydroxy-2-methylpropylidene)-4-oxo-2-pyrrolidone (6e). The crude product was purified by column chromatography (silica gel, hexane/EtOAc/AcOH = 90/9/1) to give **6e** (34.4 mg, 68%) as an orange powder: dp 83−89 °C; $[\alpha]_D^{29}$ −58.1 (*c* 1.03, $CHCl_3$); IR (KBr) 3207 (O−H), 3064 (N−H), 1715 (C═O), 1655 (C═O), 1610 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12 (brs, 0.82H, *Z*-isomer), 6.70 (brs, 0.18H, *E*-isomer), 3.96 (brd, J = 3.9 Hz, 0.18H, *E*-isomer), 3.78 (brd, J = 3.6 Hz, 0.82H, *Z*-isomer), 3.74−3.62 (m, 1H), 1.95 (m, 1H), 1.45−1.19 (m, 8H), 1.02 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7 (*C*), 195.0 (*C*), 193.2 (*C*), 176.3 (*C*), 100.3 (*C*), 66.8 (*CH*), 63.3 (*CH*), 37.0 (*CH*), 36.9 (*CH*), 31.8 (*CH*), 31.0 (*CH*), 23.9 (CH_2), 23.5 (CH_2), 18.4 ($2CH_3$), 15.3 (CH_3), 11.6 (CH_3), 11.5 (CH_3). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.65; H, 8.11; N, 6.62.

(*S*)-5-((*S*)-*sec*-Butyl)-3-(1-hydroxy-2-methylbutylidene)-4-oxo-2-pyrrolidone (6f). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 1/1) to give **6f** (35.5 mg, 74%) as a pale yellow oil: IR (KBr) 3236 (O−H), 1690 (C═O), 1658 (C═O), 1609 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07 (brs, 0.8H, *Z*-isomer), 6.73 (brs, 0.2H, *E*-isomer), 3.95 (d, J = 3.6 Hz, 0.2H, *E*-isomer), 3.78 (d, J = 2.7 Hz, 0.8H, *Z*-isomer), 3.57 (m, 1H), 1.97 (m, 1H), 1.74 (m, 1H), 1.54 (m, 1H), 1.38 (m, 1H), 1.26 (m, 2H), 1.21−1.17 (m, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.95−0.87 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4 (2*C*), 192.7 (*C*), 192.5 (*C*), 176.4 (*C*), 176.3 (*C*), 101.6 (*C*), 101.6 (*C*), 101.4 (*C*), 67.0 (*CH*), 63.5 (*CH*), 37.6 (*CH*), 37.4 (*CH*), 26.9 (CH_2), 26.6 (CH_2), 23.6 (CH_2), 23.5 (CH_2), 16.6 (CH_3), 16.4 (CH_3), 15.7 ($2CH_3$), 11.6 ($2CH_3$), 11.5 ($2CH_3$). Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.64; H, 9.00; N, 6.09.

(*S*)-5-((*S*)-*sec*-Butyl)-3-(cyclohexyl(hydroxy)methylene)-4-oxo-2-pyrrolidone (6g). The crude product was purified by column chromatography (silica gel, hexane/EtOAc/AcOH = 83/16/1) to give **6g** (89.6 mg, 72%) as an orange oil: $[\alpha]_D^{30}$ −54.5 (*c* 0.966, $CHCl_3$); IR (KBr) 3235 (O−H), 1706 (C═O), 1657 (C═O), 1608 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (brs, 0.8H, *Z*-isomer), 7.31 (brs, 0.2H, *E*-isomer), 3.95 (d, J = 3.3 Hz, 0.2H, *E*-isomer), 3.78 (d, J = 2.7 Hz, 0.8H, *Z*-isomer), 3.46−3.37 (m, 1H), 1.98 (m, 1H), 1.79−1.21 (m, 12H), 1.00 (d, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 0.6H, *E*-isomer), 0.89 (t, J = 7.5 Hz, 2.4H, *Z*-isomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0 (*C*), 192.5 (*C*), 176.4 (*C*), 100.4 (*C*), 67.0 (*CH*), 41.4 (*CH*), 40.8 (*CH*), 37.0 (CH_2), 36.9 (CH_2), 28.6 ($4CH_2$), 25.4 ($2CH_2$), 25.3 ($2CH_2$) 23.9 (CH_2), 23.5 (CH_2), 15.6 (CH_3), 15.3 (CH_3), 11.6 (CH_3), 11.5 (CH_3). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.62; H, 8.34; N, 5.52.

(*S*)-5-Benzyl-3-(1-hydroxy-2-methylbutylidene)-4-oxo-2-pyrrolidone (6h). The crude product was purified by column chromatography (silica gel, toluene/EtOAc = 3/1) to give **6h** (54.3 mg, 79%) as a yellow oil: IR (KBr) 3234 (O−H), 1706 (C═O), 1659 (C═O), 1608 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.19 (m, 5H), 5.72 (brs, 0.9H, *Z*-isomer), 5.47 (brs, 0.1H, *E*-isomer), 4.18 (dd, J = 3.6, 9.0 Hz, 0.1H, *E*-isomer), 4.02 (dd, J = 3.5, 10.1 Hz, 0.9H, *Z*-isomer), 3.55 (m, 2H), 3.26 (m, 1H), 2.69 (m, 1H), 1.68 (m, 1H), 1.53 (m, 1H), 1.21−1.16 (m, 3H), 0.96−0.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2 (*C*), 193.5 (*C*), 175.6 (*C*), 136.5 (*C*), 136.3 (*C*), 129.3 (*CH*), 129.2 (*CH*), 128.8 (2*CH*), 127.1 (*CH*), 100.5 (*C*), 100.4 (*C*), 63.4 (*CH*), 63.3 (*CH*), 38.1 (*CH*), 38.0 (*CH*), 37.6 ($2CH_2$), 33.8 (CH_2), 29.6 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 23.8 (CH_2), 23.4 (CH_2), 16.5 (CH_3), 16.4 (CH_3), 11.5 ($2CH_3$). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.24; H, 7.23; N, 5.26.

(*S*)-3-(1-Hydroxy-2-methylbutylidene)-5-methyl-4-oxo-2-pyrrolidone (6i). The crude product was purified by column chromatography (silica gel, $CHCl_3$/MeOH = 80/1−50/1−30/1) to give **6i** (47.1 mg, 67%) as a yellow oil: IR (KBr) 3259 (O−H), 1685 (C═O), 1656 (C═O), 1618 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.19 (brs, 0.8H, *Z*-isomer), 6.09 (brs, 0.2H, *E*-isomer), 4.06 (q, J = 7.2 Hz, 0.2H, *E*-isomer), 3.89 (dq, J = 2.1, 6.9 Hz, 0.8H, *Z*-isomer), 3.64 (m, 0.2H, *E*-isomer), 3.55 (m, 0.8H, *Z*-isomer), 1.73 (m, 1H), 1.55 (m, 1H), 1.41 (d, J = 6.9 Hz, 0.6H, *E*-isomer), 1.37 (d, J = 6.9 Hz, 2.4H, *Z*-isomer), 1.22−1.18 (m, 3H), 0.97−0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6 (*C*), 193.6 (*C*), 175.6 (*C*), 99.8 (*C*), 57.7 (*CH*), 54.4 (*CH*), 38.0 (*CH*), 37.6 (*CH*), 29.6 (CH_2), 26.7 (CH_2), 17.4 (CH_3), 16.5 (CH_3), 11.5 ($2CH_3$). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.57; H, 7.27; N, 7.20.

(*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-3-(1-hydroxy-2-methylbutylidene)-4-oxo-2-pyrrolidone (6j). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 1/1) to give **6j** (28.0 mg, 72%) as an orange oil: IR (KBr) 3438 (N−H), 3234 (O−H), 1708 (C═O), 1661 (C═O), 1607 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (brs, 0.9H, *Z*-isomer), 6.18 (brs, 0.1H, *E*-isomer), 4.10−3.45 (m, 4H), 1.71 (m, 1H), 1.53 (m, 1H), 1.21−1.16 (m, 3H), 0.95−0.88 (m, 3H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.1 (*C*), 192.0 (*C*), 176.2 (*C*), 100.1 (*C*), 64.1 (*CH*), 63.2 (CH_2), 61.2 (CH_2), 37.7 (*CH*), 26.6 (*C*), 25.6 (CH_3), 18.0 (CH_2), 16.5 (CH_3), 11.5 (CH_3), −5.7 ($2CH_3$). Anal. Calcd for $C_{16}H_{29}NO_4Si$: C, 58.68; H, 8.93; N, 4.28. Found: C, 58.50; H, 8.56; N, 4.23.

(*S*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-3-(1-hydroxy-2-methylbutylidene)-4-oxo-2-pyrrolidone (6k). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 1/2) to **6k** (63.4 mg, 86%) as a yellow oil: IR (KBr) 3449 (N−H), 3239 (O−H), 1709 (C═O), 1660 (C═O), 1608 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (brs, 0.8H, *Z*-isomer), 7.13 (brs, 0.2H, *E*-isomer), 4.17 (m, 2H), 3.79 (m, 0.2H, *E*-isomer), 3.62 (m, 0.8H, *Z*-isomer), 3.48 (m, 2H), 1.67 (m, 2H), 1.48 (m, 2H), 1.30−1.10 (m, 12H), 0.92−0.77 (m, 24H), 0.05--0.05 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8 (*C*), 193.5 (*C*), 192.2 (*C*), 176.6 (*C*), 101.5 (*C*), 101.1 (*C*), 68.0 (*CH*), 67.6 (*CH*), 65.2 (*CH*), 37.7 (*CH*), 37.3 (*CH*), 27.0 (*C*), 25.9 (CH_2), 25.5 ($2CH_3$), 21.1 (CH_3), 21.0 (CH_3), 17.7 (CH_3), 16.8 (CH_3), 16.0 (CH_3), 11.7 (CH_3), 11.4 (CH_3), −4.4 ($2CH_3$), −5.3 (CH_3), −5.4 (CH_3). Anal. Calcd for $C_{17}H_{31}NO_4Si$: C, 59.79; H, 9.15; N, 4.10. Found: C, 59.72; H, 9.12; N, 4.49.

(*S*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-3-((*S*)-1-hydroxy-2-methyloctylidene)-4-oxo-2-pyrrolidone (6l). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 3/1) to give **6l** (37.7 mg, 84%) as a colorless oil: $[\alpha]_D^{17}$ −64.1 (*c* 0.636, $CHCl_3$); IR (NaCl) 3235 (N−H), 3068 (N−H), 1694 (C═O), 1660 (C═O), 1615 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (brs, 0.8H, *Z*-isomer), 5.67 (brs, 0.2H, *E*-isomer), 4.14 (m, 1H), 3.78 (dd, J = 0.6, 3.9 Hz, 0.2H, *E*-isomer), 3.70 (m, 1H), 3.61 (dd, J = 0.6, 4.2 Hz, 0.8H, *Z*-isomer), 3.59 (m, 1H), 1.66 (m, 1H), 1.47 (m, 1H), 1.32−1.22 (m, 8H), 1.28 (d, J = 6.3 Hz, 3H), 1.19 (d, J = 6.9 Hz, 0.6H, *E*-isomer), 1.16 (d, J = 6.6 Hz, 2.4H, *Z*-isomer), 0.86 (t, J = 7.0 Hz, 3H), 0.82 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6 (*C*), 192.5 (*C*), 176.6 (*C*), 104.4 (*C*), 101.3 (*C*), 68.0 (*CH*), 67.6 (*CH*), 67.4 (*CH*), 65.2 (*CH*), 36.1 (*CH*), 35.9 (*CH*), 34.0 (CH_2), 33.5 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 27.1 (CH_2), 25.5 (CH_3), 22.5 (CH_2), 21.1 (CH_3), 20.9 (CH_3), 17.7 (*C*), 16.9 (CH_3), 16.5 (CH_3), 13.9 (CH_3), −4.4 (CH_3), −5.4 (CH_3). Anal. Calcd for $C_{21}H_{39}NO_4Si$: C, 63.43; H, 9.89; N, 3.52. Found: C, 63.08; H, 9.55; N, 3.69.

(*S*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-3-((*R*)-1-hydroxy-2-methyloctylidene)-4-oxo-2-pyrrolidone (6m). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 3/1) to give **6m** (35.7 mg, 79%) as a colorless oil: $[\alpha]_D^{23}$ −86.8 (*c* 1.13, $CHCl_3$); IR (NaCl) 3236 (N−H), 3068 (N−H),

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1694 (C═O), 1660 (C═O), 1614 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (brs, 0.75H, *Z*-isomer), 5.73 (brs, 0.25H, *E*-isomer), 4.14 (m, 0.25H, *E*-isomer), 4.12 (m, 0.75H, *Z*-isomer), 3.77 (dd, *J* = 0.6, 3.9 Hz, 0.25H, *E*-isomer), 3.70 (m, 0.25H, *E*-isomer), 3.60 (d, *J* = 4.5 Hz, 0.75H, *Z*-isomer), 3.54 (m, 0.75H, *Z*-isomer), 1.68 (m, 1H), 1.45 (m, 1H), 1.32−1.24 (m, 8H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 2.25H, *Z*-isomer), 1.17 (d, *J* = 6.9 Hz, 0.75H, *E*-isomer), 0.87 (t, *J* = 7.2 Hz, CH_3), 0.82 (s, 6.75H, *Z*-isomer), 0.80 (s, 2.25H, *E*-isomer), 0.05 (s, 2.25H, *Z*-isomer), 0.04 (s, 0.75H, *E*-isomer), 0.01 (s, 2.25H, *Z*-isomer), −0.02 (s, 0.75H, *E*-isomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4 (*C*), 195.2 (*C*), 193.3 (*C*), 192.8 (*C*), 176.5 (*C*), 169.4 (*C*), 104.6 (*C*), 100.9 (*C*), 100.6 (*C*), 68.0 (CH), 67.5 (CH), 65.2 (CH), 39.4 (CH), 36.3 (CH), 35.9 (CH_2), 33.6 (CH_2), 32.9 (CH_2), 31.6 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.3 (CH_2), 27.2 (CH_2), 25.5 (CH_3), 22.5 (CH_2), 21.1 (CH_3), 20.8 (CH_3), 17.7 (*C*), 17.2 (CH_3), 17.0 (CH_3), 13.9 (CH_3), −4.4 ($2CH_3$), −5.2 (CH_3), −5.5 (CH_3). Anal. Calcd for $C_{21}H_{39}NO_4Si$: C, 63.43; H, 9.89; N, 3.52. Found: C, 63.35; H, 9.89; N, 3.52.

(3*R*)-2-Benzyloxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)-butanoic Acid (8). To a solution of a 56:44 mixture of L-threonine and D-allothreonine (1.00 g, 12.6 mmol) in saturated aqueous $NaHCO_3$ solution (35 mL) was added carbobenzoxy chloride (CbzCl) (2.15 g, 12.6 mmol) at room temperature. After stirring for 18 h at the same temperature, the reaction mixture was poured into water. The aqueous layer was washed with Et_2O, acidified with concentrated HCl, and extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. To a solution of the residue (1.73 g) in DMF (27 mL) were added imidazole (1.16 g, 17.1 mmol), DMAP (100 mg, 0.819 mmol), and TBSCl (2.27 g, 15.0 mmol) at room temperature. After stirring for 18 h at the same temperature, the reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed with 3% aqueous HCl and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was roughly purified by column chromatography (silica gel, hexane/EtOAc = 1/1) to afford the crude sample of **8**. To a solution of the crude product in a 1:1 mixture of water and methanol (6.0 mL) was added an aqueous solution of K_2CO_3 (900 mg, in 2.0 mL). After stirring for 3 h, the solution was acidified to pH 3 with 3 M aqueous HCl. The reaction mixture was poured into EtOAc and extracted. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 1/1) to afford a diastereomeric mixture of **8** (1.80 g, 58%, 2*S*/2*R* = 56/44): IR (NaCl) 3400 (N−H), 3091 (O−H), 3067 (N−H), 1755 (C═O), 1691 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.29 (m, 10H), 5.50 (brd, *J* = 8.7 Hz, 1H), 5.47 (brd, *J* = 9.3 Hz, 1H), 5.12−5.10 (m, 4H), 4.46 (m, 1H), 4.33−4.30 (m, 2H), 4.13 (m, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5 (*C*), 156.7 (*C*), 136.1 (*C*), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (2CH), 69.7 (CH), 68.5 (CH), 67.3 (CH_2), 67.1 (CH_2), 59.8 (CH), 59.3 (CH), 25.6 (CH_3), 25.5 (CH_3), 20.2 (CH_3), 19.6 (CH_3), 17.8 (*C*), 17.7 (*C*), −4.7 ($2CH_3$), −5.3 (CH_3), −5.4 (CH_3). Anal. Calcd for $C_{18}H_{29}NO_5Si$: C, 58.83; H, 7.95; N, 3.81. Found: C, 58.87; H, 7.67; N, 3.58.

5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-4-oxo-2-pyrrolidone (9). To a solution of Meldrum's acid (777 mg, 5.39 mmol) and **8** (1.80 g, 4.90 mmol) in dichloromethane (25 mL) at 0 °C were added EDCI (1.13 g, 5.88 mmol) and DMAP (838 mg, 6.86 mmol). After stirring for 16 h at room temperature, the reaction mixture was poured into EtOAc (70 mL) and extracted. The organic layer was washed with 5% aqueous $NaHSO_4$ solution and brine, dried over Na_2SO_4, and filtered. The filtrate was refluxed for 2 h until completion of the reaction (monitored by TLC) and concentrated under reduced pressure. The residue was roughly purified by column chromatography (silica gel, $CHCl_3$/MeOH = 10/1) to give the crude product (1.90 g) as a yellow oil. A suspension containing the crude product and Pd/C (100 mg) in EtOAc (10 mL) was stirred under hydrogen atmosphere for 4 h. The reaction mixture was filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane/EtOAc = 3/1−2/1−1/1−1/2) to give **9** (636 mg, 50%, 3 steps, 5*R*/5*S* = 61/39) as a white powder: IR (NaCl) 3201 (N−H), 3108 (N−H), 1768 (C═O), 1702 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (brs, 1H, 5*S*-isomer), 7.41 (brs, 1H, 5*R*-isomer), 4.21 (dq, *J* = 2.7, 6.6 Hz, 1H, 5*S*-isomer), 4.06 (dq, *J* = 2.4, 6.3 Hz, 1H, 5*R*-isomer), 3.90 (brs, 1H, 5*R*-isomer), 3.80 (brd, *J* = 2.6 Hz, 1H, 5*S*-isomer), 2.91 (s, 2H, 5*S*-isomer), 2.89 (brs, 2H, 5*R*-isomer), 1.24 (d, *J* = 6.6 Hz, 3H, 5*S*-isomer), 1.23 (d, *J* = 6.3 Hz, 3H, 5*R*-isomer), 0.84 (s, 9H, 5*R*-isomer), 0.81 (s, 9H, 5*S*-isomer), 0.06 (s, 3H, 5*R*-isomer), 0.05 (s, 3H, 5*R*-isomer), 0.04 (s, 3H, 5*S*-isomer), −0.03 (s, 3H, 5*S*-isomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8 (*C*), 205.6 (*C*), 172.8 (*C*), 172.3 (*C*), 70.2 (CH), 69.6 (CH), 69.2 (CH), 68.1 (CH), 41.8 (CH_2), 41.3 (CH_2), 25.6 (CH_3), 25.5 (CH_3), 20.3 (CH_3), 18.5 (CH_3), 17.7 (2C), −4.5 (CH_3), −5.0 (CH_3), −5.1 (CH_3), −5.4 (CH_3). Anal. Calcd for $C_{12}H_{23}NO_3Si$: C, 55.99; H, 9.01; N, 5.44. Found: C, 56.34; H, 8.80; N, 5.81.

(*R*)-2-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-5-oxo-2,5-dihydro-1*H*-3-pyrrolyl (*S*)-2-Methyloctanoate (10). The crude product was purified by column chromatography (silica gel, hexane/toluene/EtOAc = 1/1/1, CH_2Cl_2/$CHCl_3$/MeOH = 10/10/1) to give **10** (127 mg, 27%) as a colorless oil: $[\alpha]_D^{24}$ +29.7 (*c* 1.37, $CHCl_3$); IR (NaCl) 3207 (N−H), 3091 (N−H), 1778 (C═O), 1701 (C═O), 1621 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.05 (brs, 1H), 5.69 (brs, 1H), 4.32 (d, *J* = 3.3 Hz, 1H), 4.16 (m, 1H), 2.63 (m, 1H), 1.70 (m, 1H), 1.53 (m, 1H), 1.34−1.24 (m, 8H), 1.24 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.91−0.88 (m, 12H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1 (*C*), 172.1 (*C*), 163.1 (*C*), 108.6 (CH), 67.6 (CH), 63.2 (CH), 39.8 (CH), 33.6 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 27.0 (CH_2), 25.7 (CH_3), 22.6 (CH_3), 17.9 (CH_3), 16.6 (CH_3), 16.2 (CH_3), 14.0 (*C*), −4.7 (CH_3), −5.0 (CH_3). Anal. Calcd for $C_{21}H_{39}NO_4Si$: C, 63.43; H, 9.89; N, 3.52. Found: C, 63.63; H, 9.52; N, 3.83.

(*R*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-3-((*S*)-1-hydroxy-2-methyloctylidene)-4-oxo-2-pyrrolidone (11). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 3/1−1/1) to give **11** (40.1 mg, 93%) as a colorless oil: $[\alpha]_D^{20}$ +68.8 (*c* 0.904, $CHCl_3$); IR (NaCl) 3229 (N−H), 3069 (N−H), 1716 (C═O), 1660 (C═O), 1610 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (brs, 0.85H, *Z*-isomer), 6.06 (brs, 0.15H, *E*-isomer), 4.26 (m, 1H), 4.07 (d, *J* = 3.3 Hz, 0.15H, *E*-isomer), 3.94 (d, *J* = 3.3 Hz, 0.85H, *Z*-isomer), 3.71 (m, 0.15H, *E*-isomer), 3.60 (m, 0.85H, *Z*-isomer), 1.67 (m, 1H), 1.46 (m, 1H), 1.30−1.21 (m, 8H), 1.19 (d, *J* = 6.9 Hz, 0.45H, *E*-isomer), 1.17 (d, *J* = 6.9 Hz, 2.55H, *Z*-isomer), 1.10 (d, *J* = 6.3 Hz, 0.45H, *E*-isomer), 1.03 (d, *J* = 6.0 Hz, 2.55H, *Z*-isomer), 0.88−0.86 (m, 12H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4 (*C*), 192.9 (*C*), 176.4 (*C*), 101.4 (*C*), 68.3 (CH), 67.5 (CH), 36.1 (CH), 33.8 (CH_2), 33.6 (CH_2), 31.6 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.1 (CH_2), 25.6 (CH_3), 22.5 (CH_2), 17.8 (*C*), 17.4 (CH_3), 16.9 (CH_3), 16.7 (CH_3), 14.0 (CH_3), −4.7 (CH_3), −5.0 (CH_3). Anal. Calcd for $C_{21}H_{39}NO_4Si$: C, 63.43; H, 9.89; N, 3.52. Found: C, 63.23; H, 9.50; N, 3.84.

(*R*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-3-((*S*)-1-hydroxy-2-methyloctylidene)-1-methyl-4-oxo-2-pyrrolidone (12). To a solution of **11** (57.5 mg, 0.145 mmol) in THF (2.0 mL) was added NaHMDS (1.09 M solution in THF, 0.29 mL, 0.32 mmol) at −78 °C. After stirring for 20 min at −78 °C, MeI (0.090 mL, 1.5 mmol) was added to the mixture. The resulting mixture was warmed to −40 °C and stirred for 10 h. It was quenched with 5% aqueous tartaric acid solution (5 mL) and extracted with EtOAc. Combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 10/1−7/1−5/1−1/1) to give **12** (37.0 mg, 62%) as a colorless oil: $[\alpha]_D^{20}$ +32.9 (*c* 0.371, $CHCl_3$); IR (NaCl) 1712 (C═O), 1653 (C═O), 1619 (C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.32 (dq, *J* = 2.4, 6.3 Hz, 1H), 3.80 (d, *J* = 2.1 Hz, 0.1H, *E*-isomer), 3.71 (d, *J* = 2.4 Hz, 0.9H, *Z*-isomer), 3.57 (m, 1H), 3.08 (s, 2.7H, *Z*-isomer), 3.03

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(s, 0.3H, *E*-isomer), 1.65 (m, 1H), 1.44 (m, 1H), 1.29−1.20 (m, 8H), 1.16 (d, J = 6.6 Hz, 3H), 1.05 (d, J = 6.3 Hz, 3H), 0.88−0.85 (m, 12H), 0.097 (s, 3H), 0.088 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1 (*C*), 191.7 (*C*), 174.4 (*C*), 101.1 (*C*), 72.4 (*CH*), 69.0 (*CH*), 36.0 (*CH*), 33.7 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 28.3 (CH_3), 27.1 (CH_2), 25.6 (CH_3), 22.5 (CH_2), 17.8 (*C*), 17.4 (CH_3), 17.0 (CH_3), 13.9 (CH_3), −4.8 (CH_3), −5.2 (CH_3). Anal. Calcd for $C_{22}H_{41}NO_4Si$: C, 64.19; H, 10.04; N, 3.40. Found: C, 64.57; H, 9.66; N, 3.79.

(+)-Penicillenol A_2 (2). A solution of **12** (37.0 mg, 0.0899 mmol) in 2% HCl−MeOH (3.0 mL) was stirred at 0 °C for 1 h. The mixture was warmed to room temperature and stirred for an additional 1.5 h. After removal of the solvent under vacuum, the residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH = 40/1). A solution of isolated material in EtOAc (10 mL) was washed with 5% aqueous tartaric acid (10 mL) and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give **2** (17.4 mg, 65%) as a colorless oil: $[\alpha]_D^{22}$ +49.2 (*c* 0.137, MeOH, averaged value for 10 measurements); $[\alpha]_D^{22}$ +27.8 (*c* 0.864, $CHCl_3$); IR (NaCl) 3413 (O−H), 2960 (C−H), 2928 (C−H), 2857 (C−H), 1711 (C═O), 1651 (C═O), 1615 (C═C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (dq, J = 3.3, 6.3 Hz, 1H), 3.84 (d, J = 3.0 Hz, 0.1H, *E*-isomer), 3.75 (d, J = 3.3 Hz, 0.9H, *Z*-isomer), 3.58 (m, 1H), 3.11 (s, 2.7H, *Z*-isomer), 3.06 (s, 0.3H, *E*-isomer), 1.66 (m, 1H), 1.46 (m, 1H),1.33−1.23 (m, 8H), 1.21 (d, J = 6.6 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4 (*C*), 192.4 (*C*), 174.6 (*C*), 100.8 (*C*), 71.5 (*CH*), 68.2 (*CH*), 36.0 (*CH*), 33.7 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 28.4 (CH_3), 27.0 (CH_2), 22.4 (CH_2), 17.5 (CH_3), 17.0 (CH_3), 13.9 (CH_3); Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.67; H, 8.83; N, 4.50.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all the new 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.

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(18) One may expect that (*E*)-isomer included in the product mixture may cause a decrease in the optical rotation value. However, this interpretation can be substantially ruled out, considering that the literature data should be obtained with a mixture of the geometrically isomeric penicillenols generated in situ by inevitable equilibration that we observed in the ^{1}H NMR spectrum of the $CDCl_3$ solution. For tautomeric equilibrium of 3-acyltetramic acids in solutions, see: (a) Yamaguchi, T.; Saito, K.; Tsujimoto, T.; Yuki, H. *Bull. Chem. Soc.*

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(19) In fact, we observed that the optical rotation values ranged irregularly between +41.0 and +55.2 for 10 measurements performed on this compound.

(20) The structural and stereochemical integrity of the synthetic penicillenol A_2 were unequivocally confirmed by ^{1}H and ^{13}C NMR. For more details on these observations and those for penicillenol A_1, see the Supporting Information.

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