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Synthesis of 1,4-Oxazepane-2,5-diones via Cyclization of Rotationally Restricted Amino Acid Precursors and Structural Reassignment of Serratin

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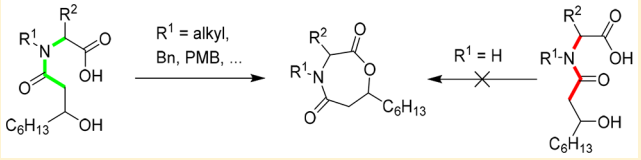
Supporting Information

ABSTRACT: Several natural products containing a 1,4-oxazepane-2,5-dione-core are known. One example is serratin, isolated from *Serratia marcescens*. Because of the presence of a carboxylic amide, which has a preference for a *trans*-conformation, and the presence of a labile lactone in this core, many synthetic methodologies commonly used for the cyclization toward medium-sized heterocycles cannot be applied. As N-acyl amino acids lacking a third substituent at nitrogen failed to undergo ring-closure, several N-protecting groups were evaluated. With the use of the removable PMB-group, an N-unsubstituted 1,4-oxazepane-2,5-dione was synthesized. Via the application of pseudoprolines (i.e. serine-derived oxazolidines as another type of protecting group), a compound with the presumed structure of the natural product serratin was obtained. As a result of the differences in spectral data, the incorrect structural assignment of the natural product serratin was identified. Instead of the predicted seven-membered heterocycle, a symmetrical serratamolide analogue is proposed to be the correct structure of serratin.



INTRODUCTION

The synthesis of medium-sized heterocycles still represents a synthetic challenge. A head-to-tail cyclization often fails to yield the desired seven- or eight-membered heterocycles because of a combination of issues related to energy and entropy. The energy issue is the increase in ring strain and unfavorable interactions needed to be overcome when the open-chain form approaches the ring-shaped transition state. The entropy issue is linked with the probability of the two chain terminals coming close enough to interact.[1] The resistance toward cyclization is even more prevalent when a carboxylic amide bond is present. The preference of an amide for a *trans*-conformation removes both termini of the linear precursor from each other's proximity, impeding cyclization.[2] As medium-sized lactams constitute a class with great potential for drug applications, many synthetic efforts have been devoted to this type of medium-sized heterocycles. N-Substitution of the amide and dilute reaction conditions are often applied,[3] but methods using solid support[4] or those that rely on a Staudinger ligation for ring closure[5] are described as well. Another possibility is the use of pincer auxiliaries, fulfilling both a tethering and templating role.[6]

Although several methods are available for the synthesis of 1,4-diazepane-2,5-diones,[3,5−7] to the best of our knowledge, no general method is known for the synthesis of 1,4-oxazepane-2,5-diones. However, several natural products have been isolated containing this seven-membered core. One example is callipeltin L (**1**) (Figure 1), belonging to a group of antifungal peptides and produced by the marine sponge *Latrunculia* sp.[8] Compound **2**, with a similar lactone core, was isolated from the methanolysis mixture of the marine-immunosuppressant lipopeptide microcolin A and shows relatively potent immunosuppressive activity as well.[9] Also inducamide C (**3**), isolated from a chemically induced mutant strain of *Streptomyces* sp. and exhibiting modest cytotoxicity, contains the same 1,4-oxazepane-2,5-dione core.[10] Finally, a bacterial metabolite was isolated from the Gram-negative bacterium *Serratia marcescens* and was identified as serratin (**4a**), but its biological activities have not been evaluated yet.[11] Bacteria belonging to the *Serratia* genus are known to produce the cyclodepsipeptides serratamolide A−F, which are composed out of similar building blocks as serratin.[12] These macrocyclic compounds do not only possess antimycobacterial activity, but can induce cell-cycle arrest and proapoptotic effects in breast cancer cells.[13]

Because of the instability of the lactone bond, it is often difficult to isolate sufficient amounts of these natural products to fully assess their biological activities. However, the same lactone bond offers the distinct advantage of rendering the

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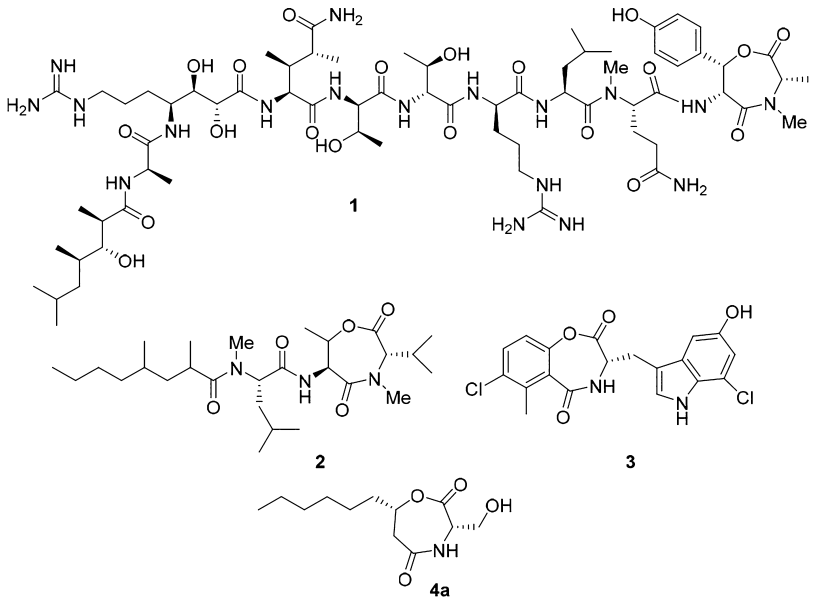
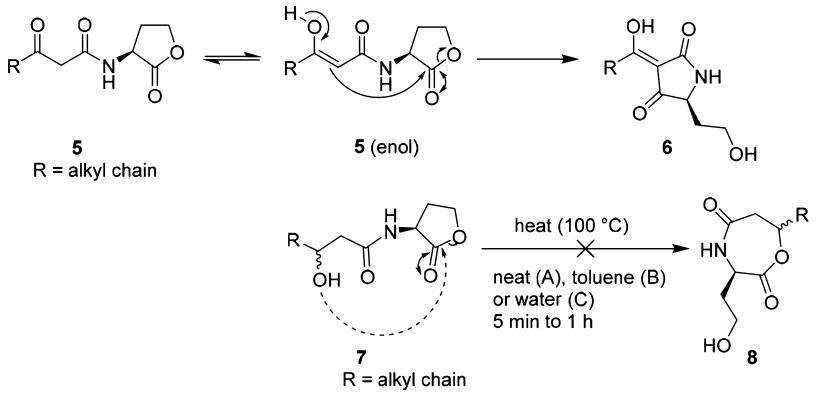


Figure 1. 1,4-Oxazepane-2,5-dione core-containing natural products **1**,[8] **2**,[9] **3**,[10] and **4a**.[11]

Scheme 1. Described Rearrangement of *N*-(3-Oxoacyl)-L-Homoserine Lactones 5 to Tetramic Acids 6,[15] and the Attempted Rearrangement of Another Type of QS Signal Molecule, *N*-(3-Hydroxyacyl)-L-Homoserine Lactones 7, to 1,4-Oxazepane-2,5-diones 8



molecule neutral by masking the carboxylic acid unit, allowing better membrane permeability, whereafter degradation or nucleophilic attack within the cell releases the active molecule.[14]

The goal of this study was to develop a method for the synthesis of 1,4-oxazepane-2,5-diones and to apply this methodology to the synthesis of the natural product serratin (**4a**).

RESULTS AND DISCUSSION

Our synthetic efforts were first focused on the synthesis of the natural product serratin (**4a**), as it contains the targeted seven-membered core. The exact biosynthetic origin of serratin (**4a**) is unknown, so the possibility was evaluated that the seven-membered ring arises from a spontaneous rearrangement of a secondary bacterial metabolite. *N*-3-Oxoacyl-L-homoserine lactones **5** are a type of N-acylated homoserine lactones (AHLs) that Gram-negative bacteria use as signal molecules to regulate different phenotypes in a cell-density controlled manner in a phenomenon called quorum sensing (QS). It is known that these molecules can rearrange via a Claisen-like condensation to tetramic acids **6** (Scheme 1).[15] These compounds **6** possess interesting biological properties such as iron chelation and antimicrobial effects.[15] Another type of QS signal molecule, *N*-(3-hydroxyacyl)-L-homoserine lactones **7**, could participate in a similar rearrangement to 1,4-oxazepane-2,5-diones **8**.[16] This type of reactivity has been suggested by the difference in heat stability of the autoinducers of *Aliivibrio fischeri* (previously designated as *Vibrio fischeri*), *N*-(3-oxohexanoyl)-L-homoserine lactone **5a** (R = Pr), and the autoinducer of *Vibrio harveyi*, *N*-(3-hydroxybutanoyl)-L-homoserine lactone **7a** (R = Me). Heating a medium containing the autoinducer **5a** of *A. fischeri* at 100 °C for 5 min did not have an effect on the bioluminescence-inducing activity of this QS signal molecule. Applying the same treatment on a medium containing the autoinducer **7a** of *V. harveyi*, caused a complete deactivation of the bioluminescence-inducing activity.[17] Not surprisingly, both autoinducers lose their QS stimulating properties at high pH because of ring-opening.

Although rearrangement product **8** possesses a 2-hydroxyethyl group instead of the hydroxymethyl substituent in serratin (**4a**), it was decided to evaluate this route with *N*-(3-hydroxyhexanoyl)-L-homoserine lactone **7b** (R = Pr)[18] by mimicking the reaction conditions (heating at 100 °C for 5

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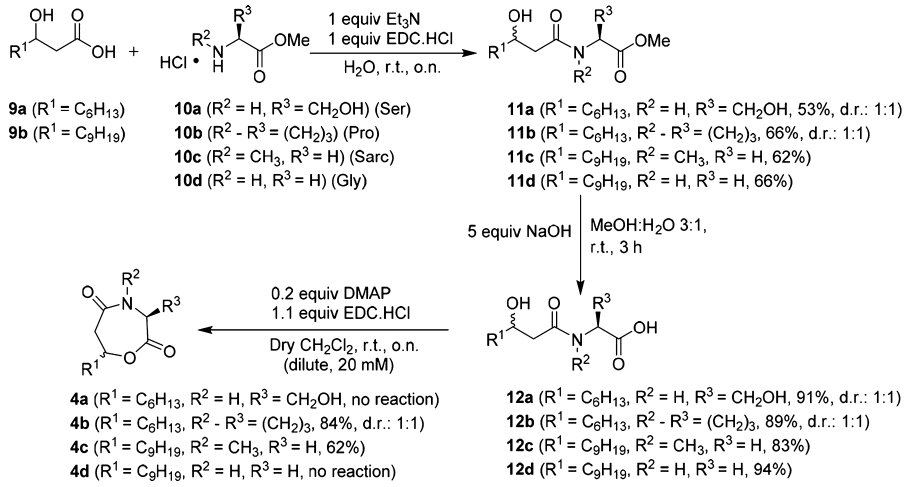
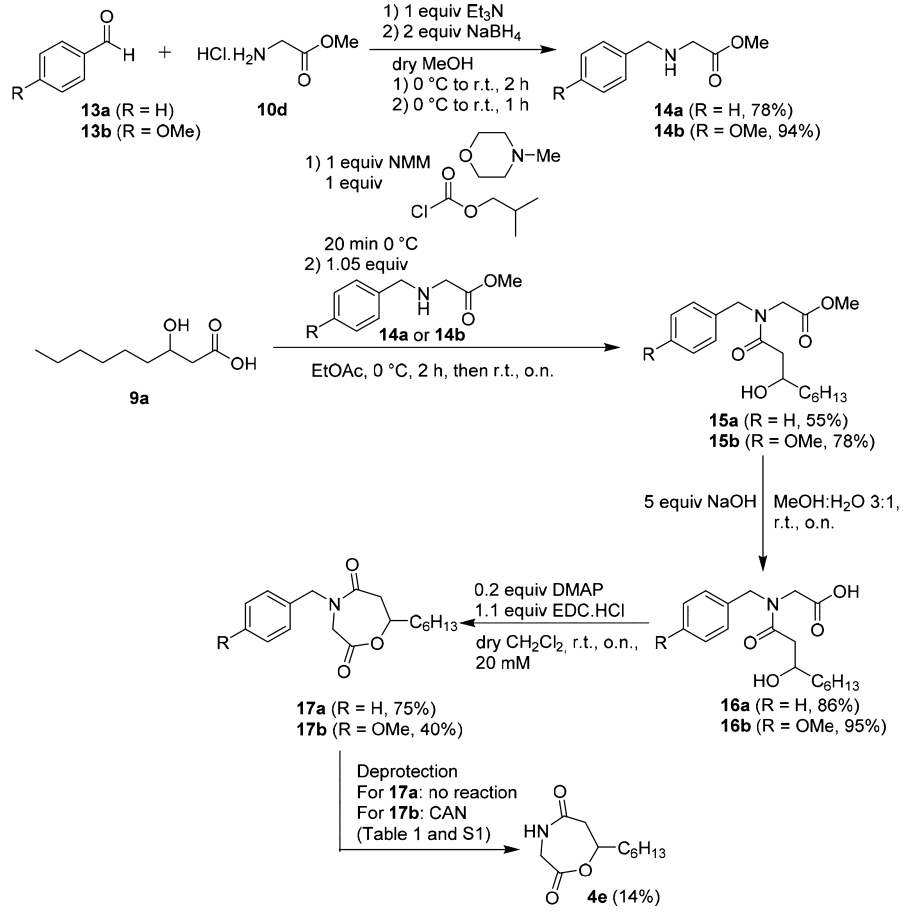
Scheme 2. Synthesis of *N*-(3-Hydroxyacyl) Amino Acids 12a–d and Ring Closure Toward 1,4-Oxazepane-2,5-diones 4a–d



Scheme 3. Synthesis of *N*-Benzyl and *N*-PMB-Protected Seven-Membered Lactones 17a and 17b and CAN-Mediated Deprotection of 17b to 4e



min) described by Eberhard.[17] However, the formation of the desired seven-membered ring **8b** (R = Pr) was never observed (Scheme 1), and the starting material **7b** was fully recovered. When the reaction time was prolonged, elimination and hydrolysis products were observed as well. Reaction conditions suited for the nucleophilic attack of the β-hydroxy group might give rise to compound **8b**, but then the resulting primary hydroxy group could reattack the seven-membered lactone, forming the more stable five-membered lactone ring and once again yielding starting material **7b**.

As the lipoamino acid *N*-(3-hydroxydecanoyl)-L-serine, or serratamic acid, had been isolated from alkaline extracts of *S. marcescens* cultures,[19] presumably formed by the hydrolysis of serratamolides, serratamic acid-analogue **12a** was evaluated as the possible origin of serratin (**4a**). Compound **12a** was synthesized via a 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide (EDC)-mediated coupling reaction of β-hydroxy-

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nonanoic acid **9a** with the serine ester **10a**, followed by alkaline hydrolysis (Scheme 2). For the ring-closure, reaction with 1 equiv of EDC and 1 equiv of Et_3N in water was tested, but no reaction was observed. Repeating this reaction with EDC with a catalytic amount of DMAP in dichloromethane yielded a complex reaction mixture.[20] Stirring the reaction mixture overnight in acetic anhydride also failed to yield any of the desired ring-closed product **4a**.[20]

The apparent lack of cyclization of the serine derivative **12a** (Scheme 2) can be explained by the fact that the amide bond strongly prefers a *trans*-conformation, whereas for the desired cyclization to occur, a *cis*-amide bond is needed. The 2D-NOESY analysis of methyl ester **11a** revealed that only the *trans*-conformer was present (SI, Figure S1).[21] In the case of larger heterocycles, such as 14-membered rings, *trans*-amides can be included. This was used for the synthesis of a serratamolide analogue, but during this synthesis seven-membered rings were never observed.[22] Proline-containing peptides typically contain an elevated amount of *cis*-amide bonds.[23] Therefore, the proline-containing analogue **12b** was synthesized, and the cyclization was re-evaluated (Scheme 2).[20] The bicyclic structure **4b** was formed in all the cyclization conditions tested.

To decide if the imposed rigidity, caused by the cyclic structure of proline, was really necessary for the cyclization, the highest-yielding cyclization conditions were applied to sarcosine derivative **12c** (Scheme 2). The existence of both *cis*- and *trans*-isomers of compound **12c** in solution was apparent by the presence of both conformers being observed in ^1H and ^{13}C NMR ($CDCl_3$, SI Figure S2A and S3A).[24] No such conformers were observed in the ^1H and ^{13}C NMR spectra of derivative **12a**. The cyclic product **4c**, with a similar seven-membered core as callipeltin L (**1**), was obtained in a 62% yield. In the ^1H and ^{13}C NMR spectrum, different isomers were not observed ($CDCl_3$, SI Figure S2B and S3B), which is consistent with the formation of a more rigid, cyclic structure without the possibility of *cis/trans*-isomerization. As a proof of concept, the reaction was repeated with the glycine derivative **12d** under identical reaction conditions, but no cyclization was observed (Scheme 2). As the ring-closing reaction only proceeds with great difficulty, a spontaneous, nonenzymatical rearrangement can be excluded for the origin of serratin (**4a**).

From the above-mentioned results, it is obvious that the *N*-(3-hydroxyacyl) amino acid derivative needs to be forced in the correct conformation for cyclization to occur. This necessity was also observed during the synthesis of 1,4-oxazepan-5-ones.[21] The introduction of a third substituent at nitrogen, as is the case for the proline and sarcosine derivatives **12b** and **12c**, altered the *cis/trans*-ratio and resulted in cyclization. To obtain the natural product serratin (**4a**), this additional group at the nitrogen should be a removable one. As a result of the lability of the desired lactone, many protecting groups that can be applied for the synthesis of seven-membered lactams, cannot be used for this cyclization as the reaction conditions needed for their removal after the cyclization step, will destroy the lactone bond.

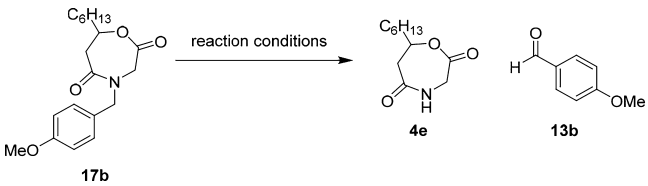
As a benzyl group can be removed via hydrogenolysis, this N-protecting group was evaluated as a possible solution. Reductive amination of benzaldehyde **13a** with methyl glycinate **10d** yielded the N-benzyl-protected methyl ester of glycine **14a**, which was coupled to *β*-hydroxynonanoic acid **9a**. Alkaline hydrolysis followed by cyclization in dilute reaction conditions gave the desired N-benzyl-protected seven-membered ring-containing compound **17a** (Scheme 3).

To remove the N-protecting group, several reaction conditions were tested but none was able to deliver the desired compound **4e** (SI, Table S1).[25] Similar difficulties to remove a benzyl group from a carboxylic amide were also encountered by Williams et al. while debenzylating a diketopiperazine.[26]

As the synthesis of the N-benzyl-protected seven-membered core-containing compound **17a** was successful, whereas the N-deprotection proved to be problematic, the *p*-methoxybenzyl (PMB) protecting group was evaluated as a more-labile protecting group. Reductive amination of glycine methyl ester hydrochloride **10d** with anisaldehyde **13b** gave N-PMB-protected methyl glycinate **14b** in a good yield (Scheme 3).[27] The same N-acylation and cyclization conditions used for the synthesis of the *N*-benzyl derivative **17a** were applied to yield the N-PMB-protected seven-membered ring-containing compound **17b** (Scheme 3).

For the removal of the PMB-protecting group, several reaction conditions were tested (Table 1). Both 2,3-dichloro-

Table 1. Reaction Conditions Evaluated to Remove the PMB-Protecting Group of 17b.[28]



17b

entry	reaction conditions	result
1	2 equiv DDQ, CH_2Cl_2/H_2O 9:1, r.t., 8 h	-[a]
2	5 equiv CAN, MeCN/H_2O 4:1, 0 °C to r.t., 2 h	**4e** (15%)[b]
3	5 equiv CAN, MeCN/H_2O (NaOAc/HOAc buffer, pH 5.2), 0 °C, 2 h	**4e** (18%)[b] and **17b** (41%)[b]
4	10 equiv CAN, MeCN:H_2O 4:1, 0 °C, 1 h	**4e** (30%)[b] and **17b** (6%)[b]
5	**5 equiv CAN, EtOAc/H_2O 4:1, 0 °C, 2 h**	**4e** (36%)[b] and **17b** (28%)[b]
6	10 equiv CAN, EtOAc/H_2O 4:1, 0 °C, 2 h	**4e** (32%)[b] and **17b** (33%)[b]
7	5 equiv CAN, tBuOH/CH_2Cl_2 4:1, r.t., 2 h	-[c]
8	5 equiv CAN, MeCN/H_2O 99:1, r.t., o.n.	**4e** (10%)[b] and **17b** (70%)[b]
9	4 equiv $PhI(OAc)_2$, MeOH, r.t., o.n.	-[a]
10	$BF_3{\cdot}OEt_2$, r.t., o.n.	-[d]
11	$BF_3{\cdot}OEt_2$, 128 °C, 6 h	-[e]

[a]Solvolysis of **17b**. [b]Quantitative data were obtained after the extraction of the reaction mixture with ethyl acetate, followed by a washing step with an aqueous, saturated sodium bicarbonate solution to remove ring-opened degradation products. The crude yield of the different products was determined via integration of the ^1H NMR spectrum. [c]Deprotection followed by solvolysis or solvolysis, followed by deprotection. [d]No reaction. [e]Complex reaction mixture.

5,6-dicyano-1,4-benzoquinone (DDQ) and ceric ammonium nitrate (CAN), the reagents commonly used for PMB-deprotection, were evaluated under different reaction conditions, alongside other reagents.[28]

As the deprotection with 5 equiv of CAN in a solvent mixture of ethyl acetate and water in a 4:1 ratio gave the best result (Table 1, entry 5), this reaction was repeated on a larger scale to give the pure, fully deprotected, seven-membered lactone **4e** in 14% yield after purification via column chromatography (Scheme 3). This rather low yield can be attributed to several factors. First, the reaction time is too short

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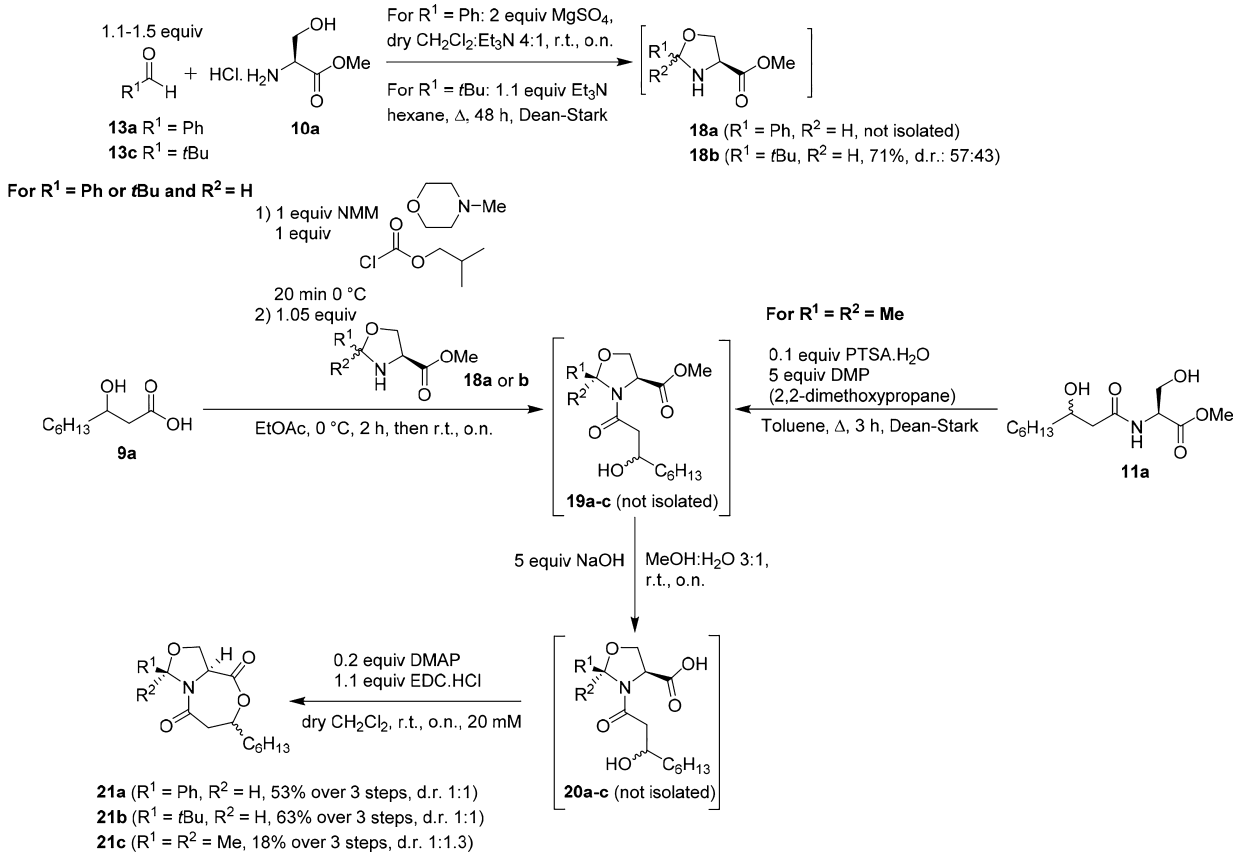
Scheme 4. Synthesis of Oxazolidine-Containing Bicyclic Structures 21a−c



to allow complete conversion, which is obvious from the recovery of the N-PMB-protected lactone **17b**. Second, when the product **4e** is formed, lactonolysis can occur using any present water as cosolvent, which is needed for the deprotection. This lactonolysis can also open the starting material **17b**, but this route seems to be slower. Third, reactions with CAN often give rise to a laborious workup because of the difficult separation of the turbid aqueous phase and the organic phase.

As the synthesis of the deprotected seven-membered core **4e** was successfully completed, the focus was put on the synthesis of serratin (**4a**), which differs from lactone **4e** only by the presence of a hydroxymethyl group. However, when the N-acylation reaction was repeated with methyl *N*-PMB-serinate, O-acylation instead of N-acylation was observed. To avoid this unwanted reaction, the reaction sequence was repeated with *O*-benzylserine, but when the cyclization was attempted in the final step, a complex reaction mixture was obtained instead of the desired heterocycle. This lack of cyclization could be caused by steric factors. A similar observation was made by Imramovský et al. during a coupling reaction of N-benzyloxycarbonyl-protected amino acids with a salicylanilide.[29] When *N*-Cbz-glycine and *N*-Cbz-alanine were used, a seven-membered ring was formed. This type of cyclization was not observed when valine or phenylalanine were used. Another possibility was a postcyclization modification step, but the introduction of a hydroxymethyl group via reaction of the *N*-methyl derivative **4c** as a test substrate with formaldehyde failed in all reaction conditions tested (15 equiv $KHCO_3$, 11 equiv paraformaldehyde, DMF, r.t., o.n.; 1 equiv LDA, dry THF, N_2, −78 °C, 1 h followed by 6 equiv paraformaldehyde, −78 °C, 3 h to r.t., o.n.; 1 equiv LDA, dry THF, N_2, −78 °C, 1 h followed by formaldehyde (g) (formed by dry heating of paraformaldehyde at 170 °C), −78 °C, 3 h to r.t., o.n.)).[30]

Another option for the synthesis of serratin (**4a**) was via the use of pseudoprolines (ΨPro). These oxazolidines are formed via reaction of serine (and threonine) with aldehydes or ketones. These cyclic structures are unstable under acidic conditions, but can be acylated in an alkaline environment and isolated as such. Pseudoprolines are commonly used to alter the solubility of peptides by disrupting secondary structure formation or to facilitate the cyclization of small peptides.[31] Oxazolidine **18b** was synthesized by heating the hydrochloride of the methyl ester of L-serine **10a** with pivaldehyde **13c** and triethylamine with continuous removal of water (Scheme 4). This oxazolidine **18b** was obtained as a 3:2 mixture of diastereomers in a 71% yield.[32]

Several procedures were evaluated for the N-acylation of compound **18b** (SI, Table S2). The formation of the mixed anhydride of *β*-hydroxynonanoic acid **9a** via reaction with isobutyl chloroformate, followed by reaction with the methyl ester of oxazolidine **18b** proved to be the best procedure to obtain compound **19b** (SI, Table S2, entry 4).[33] The N-acylated (2-*t*-butyl)oxazolidine **19b** possessed a C2,C4-*cis*-relation, although the starting oxazolidine **18b** was obtained as a 3:2 diastereomeric mixture. Ring-tautomerism allows equilibration of the more stable product with the *t*Bu-group in a quasi-axial position.[34] Subsequent alkaline hydrolysis of the acylated 2-*t*Bu-oxazolidine **19b**, followed by cyclization in dilute reaction conditions yielded the bicyclic structure **21b** (Scheme 4).

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Bicyclic compound **21b** was obtained as a 1:1 mixture of diastereomers. The diastereomers (*RSS*)-**21b** and (*RRS*)-**21b** were separated via column chromatography followed by recrystallization. One of the two diastereomers remained an amorphous powder, whereas the other one formed needle-like crystals, allowing structure confirmation and stereochemistry determination via X-ray diffraction analysis (Figure 2). The crystals belong to the orthorhombic Sohnke space group $P2_12_12_1$ and hence contain only one enantiomer, being (*RSS*)-**21b** with a *cis*-relationship of the substituents.

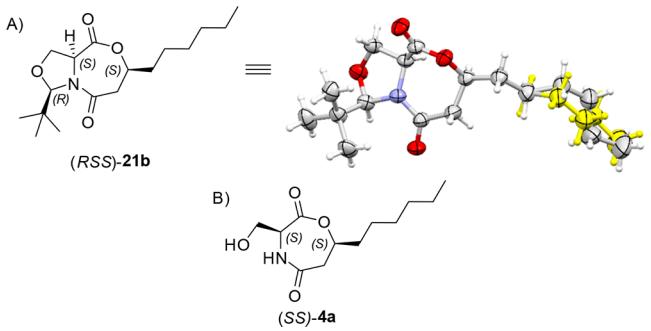

Figure 2. (A) Molecular structure of (*RSS*)-**21b**, showing thermal displacement ellipsoids, drawn at the 30% probability level. The positional disorder of the C_6H_{13} alkyl chain is shown in yellow. (B) Stereochemistry of serratin (*SS*)-**4a** based upon comparison with theoretical calculations of the ^{13}C NMR chemical shift.[11]

Both diastereomers showed quite different chemical shifts. The crystalline diastereomer (*RSS*)-**21b** has both its substituents in a *cis*-relationship. The diastereomer with the *RSS*-stereochemistry showed a signal for CH−O at 75.2 ppm ($CDCl_3$) in the ^{13}C NMR spectrum, and the attached hydrogen atom in CH−O showed a multiplet at 4.71−4.83 ppm ($CDCl_3$) in the ^1H NMR spectrum. For the other diastereomer (*RRS*)-**21b**, with an *RRS*-stereochemistry, the corresponding signals were at 79.7 ppm ($CDCl_3$, ^{13}C NMR) and 4.68−4.79 ppm ($CDCl_3$, ^1H NMR). The signal around 70 ppm in the ^{13}C NMR spectrum is quite characteristic and is present in all 1,4-oxazepane-2,5-diones described in literature (SI, Table S3).[8−11,20,29,35] Another difference was the shift of the CH_2 adjacent to the CH−O moiety. For the diastereomer (*RSS*)-**21b**, the corresponding signals were a dd at 2.85 ppm ($CDCl_3$) and a dd at 2.97 ppm ($CDCl_3$). For the other diastereomer (*RRS*)-**21b**, there was a d at 2.72 ppm ($CDCl_3$) and a dd at 3.14 ppm ($CDCl_3$). For serratin (**4a**), Luna et al. noticed signals for the CH_2 at 2.42 ppm (dd, $CDCl_3$) and 2.62 ppm (dd, $CDCl_3$), and a signal for CH−O at 72.4 ppm ($CDCl_3$) in the ^{13}C NMR spectrum.[11] These values seem to be consistent with our observations for diastereomer (*RSS*)-**21b**.

As the 2-*t*Bu-oxazolidine is a rather stable oxazolidine, we decided to synthesize two different types of oxazolidines as well. The first type was the more labile 2,2-dimethyloxazolidine (Ser($\Psi^{Me,Me}$Pro)), which undergoes rapid deprotection in dilute TFA.[36] Unlike Ser(Ψ^{tBu}Pro) **18b**, this oxazolidine cannot be isolated as such and is commonly introduced via the postinsertion route.[36] Therefore, methyl *N*-(3-hydroxynonanoyl)serinate **11a** was reacted with 2,2-dimethoxypropane (DMP) with continuous removal of water to yield compound **19c** (Scheme 4).[37] As ^1H NMR analysis revealed that this compound, obtained after column chromatography, was less pure than the crude compound after workup because of degradation during purification, it was decided to proceed with the reaction sequence without further purification. Hydrolysis of compound **19c** with NaOH in a water/methanol (1:3) mixture followed by cyclization gave 2,2-dimethyloxazolidine-protected oxazepane-2,5-dione **21c** in a total yield of 18% after purification. Once again, the CH−O and CH_2 of both diastereomers gave very distinct signals in NMR spectroscopy.

For the 2-phenyl-oxazolidine derivative, L-serine methyl ester hydrochloride **10a** was neutralized with Et_3N and allowed to react with benzaldehyde **13a** to produce oxazolidine derivative **18a** (Scheme 4).[38] This compound was N-acylated with *β*-hydroxynonanoic acid **9a,** and the ester functionality was hydrolyzed under alkaline conditions to furnish compound **20a**. The 2-phenyloxazolidine-protected oxazepanedione **21a** was obtained in a 53% total isolated yield after the DMAP-catalyzed cyclization under dilute reaction conditions.

Several reaction conditions were evaluated to deprotect the oxazolidine unit without opening the seven-membered lactone (Table 2). A catalytic amount of bismuth(III) bromide was successfully employed by Cong et al. to deprotect a cyclic N,O-aminal under mild reaction conditions.[39] However, in our case no reaction was observed (Table 2, entry 1A−C). This could be explained by the fact that the reactivity of the oxazolidine ring is dramatically reduced upon amidation.[40] When a catalytic amount of water was added to the reaction mixture, the 2-phenyloxazolidine moiety of the *trans*-diastereomer (*RRS*)-**21a** was deprotected to the ring-opened structure **12a** (Table 2, entry 2B). As traces of the ring-opened oxazolidine-containing product **20a** were detected during the course of the reaction, hydrolysis probably preceded deprotection, unlike with the deprotected compound **4a** . The other diastereomer (*RSS*)-**21a** could be recovered from the crude reaction mixture, albeit in a severely reduced amount. For the two other types of oxazolidines, all stereoisomers seemed to react at a similar pace and only the deprotected and hydrolyzed product **12a** was isolated (Table 2, entries 2A and 2C). In an alternative procedure, mild acidic conditions for deprotection were used by employing formic acid in a THF/H_2O-mixture (Table 2, entries 3A and 3B).[41] In the case of the *t*Bu-containing oxazolidine **21b**, a quick hydrolysis of both diastereomers to **20b** was observed. Interestingly, for the 2-phenyloxazolidine **21a**, the *trans*-diastereomer (*RRS*)-**21a** hydrolyzed significantly faster than the *cis*-diastereomer (*RSS*)-**21a**: whereas the starting compound had a d.r. of 1:1, this changed to 1:2.7 for the recovered starting material. Treatment with an acidic resin also failed to deliver the desired compound (Table 2, entries 4A and 4B).[42] 5% TFA in dichloromethane left the 2-*t*Bu-oxazolidine **21b** intact, even after a reaction time of 48 h (Table 2, entry 5A).[31b] Under the same conditions, the *trans*-diastereomer of the 2,2-dimethyloxazolidine **21c** was successfully deprotected (Table 2, entry 5C). The ^1H NMR of the crude reaction mixture, obtained after washing with a saturated aqueous $NaHCO_3$ solution to remove the TFA and the ring-opened product, revealed the presence of only the *cis*-diastereomer. However, the deprotected *trans*-isomer (*SR*)-**4a** was not detected. When the same treatment was applied on the 2-phenyloxazolidine-protected seven-membered ring **21a** a similar observation was made: the *trans*-diastereomer (*RRS*)-**21a** seemed to react faster, but none of the deprotected serratin (**4a**) could be isolated (Table 2, entry 5B and SI, Figure S5). When 4 M HCl (g) in dioxane was evaluated for the removal of the oxazolidine moiety,[43] a difference in reactivity between the 2-*t*Bu and the 2-phenyloxazolidine moiety was observed: in the

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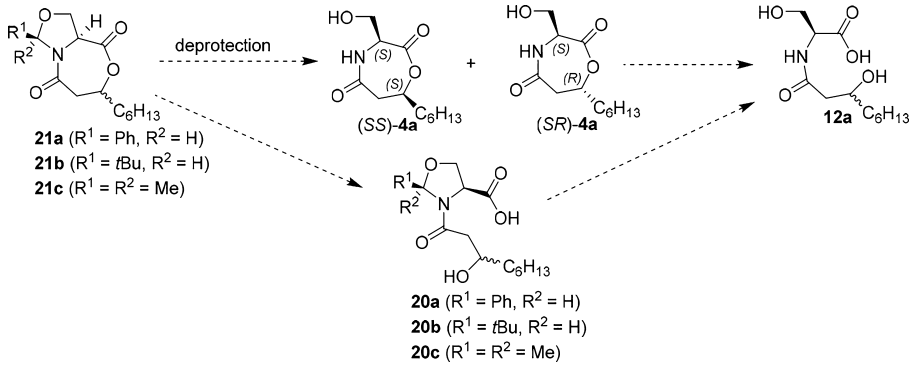
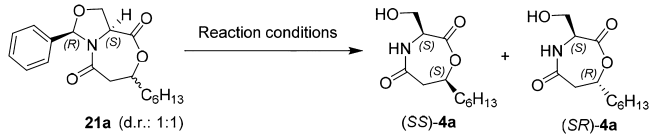
Table 2. Reaction Conditions Evaluated to Achieve the Deprotection of the Different Oxazolidine Moieties of Seven-Membered Rings 21a, 21b, and 21c.[39,41−44]



entry	reaction conditions	oxazolidine derivative	result[a]
1A	0.1 equiv $BiBr_3$, MeCN, r.t., 1 h to o.n.	Ph	-[b]
1B	idem	*t*Bu	-[b]
1C	idem	DiMe	-[b]
2A	1 equiv $BiBr_3$, cat. H_2O, MeCN, r.t., 1 to 48 h	Ph	conversion of *trans*-diastereomer (*RRS*)-**21a** to **12a**; no isolation of (*SR*)-**4a**; no reaction of *cis*-diastereomer (*RSS*)-**21a**
2B	idem	*t*Bu	-[c]
2C	idem	DiMe	-[c]
3A	THF/H_2O/HCOOH 3:1:1, r.t., 1 to 48 h	Ph	ring-opening to **20a**; *trans*-diastereomer (*RRS*)-**21a** reacts faster than (*RSS*)-**21a**
3B	Idem	*t*Bu	ring-opening to **20b**
4A	Amberlyst 15, acetone:H_2O 9:1, r.t., 1 to 24 h	Ph	-[b]
4B	idem	*t*Bu	-[b]
5A	5% TFA in dry CH_2Cl_2, 0 °C, 3 h, then r.t., 48 h	Ph	no reaction of *cis*-diastereomer (*RSS*)-**21a**; deprotection of *trans*-diastereomer (*RRS*)-**21a** to **12a**
5B	idem	*t*Bu	-[b]
5C	idem	DiMe	no reaction of *cis*-diastereomer (*SS*)-**21c**; deprotection of *trans*-diastereomer (*RS*)-**21c** to **12a**
6A	4 M HCl in dioxane, 0 °C to r.t., 1 to 24 h	Ph	formation of **12a**; faster reaction of the *cis*-diastereomer (*RSS*)-**21a**
6B	idem	*t*Bu	formation of **12a**; faster reaction of the *trans*-diastereomer (*RRS*)-**21b**
7A	3 equiv 1,3-propanedithiol, 2% HCl in 2,2,2-trifluoroethanol, r.t., 1 to 24 h	Ph	formation of **12a**; faster reaction of the *trans*-diastereomer (*RRS*)-**21a**
7B	idem	*t*Bu	formation of **12a**; faster reaction of the *trans*-diastereomer (*RRS*)-**21b**

[a]Based on LC−MS analysis during the course of the reaction and ^{1}H NMR analysis of the crude reaction mixture after workup. [b]No reaction. [c]Deprotection and ring-opening or ring-opening and deprotection. Only recovery of **12a**.

Table 3. Reaction Conditions Evaluated for the Hydrogenolytic Removal of the 2-Phenyloxazolidine Moiety of 21a



entry	reaction conditions	result
1	4 atm H_2, 25 wt % Pd/C, EtOAc, r.t., o.n.	-[a]
2	4 atm H_2, 25 wt % Pd/C, MeOH, r.t., o.n.	-[b]
3	4 atm H_2, 25 wt % $Pd(OH)_2$/C, EtOH, r.t., o.n.	-[c]
4	1 atm H_2, 50 wt % $Pd(OH)_2$/C, EtOAc, r.t., 6 h	(*SS*)-**4a** (22%); no reaction of the other diastereomer, recovery of starting material **21a** (67%) with a d.r. of 1:3

[a]No reaction. [b]Solvolysis of starting material **21a**. [c]Deprotection and solvolysis or solvolysis and deprotection.

case of the *t*Bu-compound **21b**, the *cis*-diastereomer (*RSS*)-**21b** was deprotected faster, whereas for the latter compound **21a**, the *trans*-diastereomer (*RRS*)-**21a** was deprotected faster. In both cases, none of the deprotected seven-membered ring **4a** could be isolated (Table 2, entries 6A and 6B). When the reaction time was prolonged, all of the starting material was converted to the deprotected, hydrolyzed compound **12a**. The protocol with 1,3-propanedithiol in acidic trifluoroethanol, developed by Corey,[44] also caused a faster deprotection of the *trans*-diastereomer of both the 2-*t*Bu and the 2-phenyl-oxazolidine compared to the *cis*-isomers. Once again, no deprotected serratin (**4a**) could be isolated.

As deprotection was observed but isolation of serratin (**4a**) failed, either because of deprotection followed by immediate ring-opening or by first ring-opening and then deprotection, another route for the 2-phenyloxazolidine **21a** was evaluated. In

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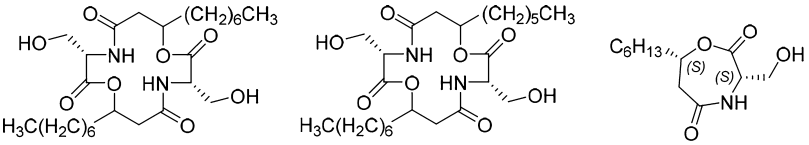

Figure 3. Structure of secondary metabolites Serratamolide A (**22a**), Serratamolide F (**22b**),[12b] and serratin (**4a**)[11] produced by *Serratia* sp.

a first attempt to remove the 2-phenyloxazolidine unit from **21a**, hydrogenolysis with Pd/C in ethyl acetate and in MeOH was evaluated, but no reaction (Table 3, entry 1) or only a limited conversion, combined with degradation (Table 3, entry 2), were obtained. When $Pd(OH)_2/C$ was employed in EtOH, a complete debenzylation was observed, unfortunately combined with ethanolysis of the deprotected product (Table 3, entry 3). When the reaction was repeated in ethyl acetate, deprotection without solvolysis was observed (Table 3, entry 4). Remarkably, both diastereomers behaved differently: only the seven-membered ring (*SS*)-**4a** with both substituents in a *cis*-relationship was obtained and isolated in 22% yield (based on the total amount of starting material). The diastereomeric ratio of the recovered, oxazolidine-containing starting material **21a** had consequently changed from 1:1 to 1:3, favoring the (*RRS*)-diastereomer (SI, Figure S5). This observed selectivity for (*RSS*)-**21a** could be explained by steric factors. The (*RSS*)-isomer of **21a** has the phenyl and alkyl substituent on the same side of the bicyclic ring system (see Figure 2 for (*RSS*)-**21b**), allowing a relatively unhindered interaction of the opposed side with the palladium catalyst. As the (*RRS*)-isomer has the bulky phenyl substituent on one side and the alkyl substituent on the other side, it is expected that such an interaction with the catalyst proceeds with more difficulty.

The (*RSS*)-diastereomer that was deprotected had the correct stereochemistry to deliver serratin (*SS*)-**4a**. In the ^1H NMR spectrum ($CDCl_3$), a signal for NH became visible, which is consistent with successful deprotection. The C*H*−O signal at 73.7 ppm ($CDCl_3$) was also present, indicating that the seven-membered heterocycle was still intact. However, unlike the value around 5.30 ppm ($CDCl_3$) reported by Luna et al. for C*H*−O, a multiplet around 4.73−4.81 ppm ($CDCl_3$) was observed. A big difference for the adjacent CH_2 was also apparent: Luna et al. reported two dd at 2.42 and 2.62 ppm ($CDCl_3$), whereas we detected the corresponding signals at 2.79 and 2.87 ppm ($CDCl_3$).

The values reported by Luna et al. show a lot of similarities with the spectral data of the compound serratamolide A (**22a**) (Figure 3 and SI, Table S4). This antimycobacterial cyclodepsipeptide is produced by *Serratia* sp. and has the C*H*−O signal at 5.33 ppm (^1H NMR, CD_3OD), the CH−O signal at 73.2 ppm (^{13}C NMR, CD_3OD) and the adjacent CH_2 at 2.39 and 2.72 ppm (^1H NMR, CD_3OD).[12b] That the actual structure of serratin (**4a**) could be a serratamolide analogue is also suggested by the observed vicinal coupling constants of the O−C*H*C*H*$_2$C(=O) moiety. Whereas for the compound synthesized in this study, vicinal coupling constants of 11.3 and 3.0 Hz were observed, which corresponds to a conformation as depicted in Figure 2 with one large and one small dihedral angle of the coupling protons. Values of 4.9 and 2.0 Hz were reported by Luna et al.[11] These small vicinal coupling constants were also reported for serratamolide A (**22a**) (5.0 and 2.6 Hz), which correspond with a more flexible structure and smaller dihedral angles (SI, Table S4).[45] Serratamolide A (**22a**) is a symmetrical molecule composed out of two serine units and twice β-hydroxydecanoic acid as the fatty acid moiety. However, the asymmetrical analogue serratamolide F (**22b**) has a β-hydroxydecanoic acid moiety but also a β-hydroxynonanoic acid moiety in its structure.[12b] It is known that during the biosynthesis of cyclic lipopeptides, a relaxed substrate specificity can give rise to the production of several analogues of one main cyclic lipopeptide compound.[12b,46] Therefore, if a symmetrical serratamolide exists with two β-hydroxynonanoic acid tails, the corresponding NMR spectra would contain only a limited number of signals with values nearly identical to those reported by Luna et al. for serratin (**4a**) (SI, Table S4).

CONCLUSION

A method for the synthesis of N-unsubstituted 1,4-oxazepane-2,5-diones is presented. The lability of the lactone moiety excludes the use of many techniques commonly used for the cyclization of medium-sized heterocycles. Therefore, PMB was applied as a protecting group to force the linear amino acid precursor in a correct conformation for cyclization to occur. For serine, the oxazolidine or pseudoproline group was used as a protecting group. Several pseudoprolines and deprotecting reaction conditions were evaluated, but only hydrogenolysis of the 2-phenyloxazlidine moiety with Pearlman's catalyst was able to remove the oxazolidine moiety without opening of the lactone. The application of our methodology led to the identification of the incorrect structural assignment of the natural product serratin, whose spectral data fit better with a serratamolide structure instead of a 1,4-oxazepan-2,5-dione derivative.

EXPERIMENTAL SECTION

General Methods. Solvents and chemicals used were bought from commercial suppliers and used as such, unless stated otherwise. Diethyl ether, toluene, and tetrahydrofuran were dried by distillation over sodium/benzophenone ketyl. Dichloromethane was distilled over calcium hydride. ^1H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Bruker Avance III Nanobay 400 at room temperature. IR spectra were recorded in neat form with a PerkinElmer Spectrum One FTIR spectrometer. High-resolution mass spectra were determined with an Agilent 1100 series HPLC coupled to an Agilent 6210 TOF mass spectrometer, equipped with an ESI/APCI multimode source. Melting points were measured with a Kofler bench, type WME Heizbank of Wagner & Munz. The reaction mixtures were purified by column chromatography on silica gel (Acros, particle size: 0.035−0.070 mm, pore diameter: approximately 6 nm) or by recrystallization. For the structure of (*RSS*)-**21b**, X-ray intensity data were collected at RT on an Agilent Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using ω scans and Cu Kα (λ = 1.54184 Å) radiation. The images were interpreted and integrated with the program CrysAlisPro.[47] Using Olex2,[48] the structure was solved by direct methods using the ShelXS structure solution program and refined by full-matrix least-squares on F^2 using the ShelXL program package.[49] Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and

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isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms (1.5 times for methyl groups).

Synthesis, Hydrolysis, and Cyclization of *N*-(3-Hydroxyacyl) Amino Acids. *General Procedure A: N-Acylation of a Primary Amine.* Triethylamine (1 equiv) was added to a stirred solution of the amino acid methyl ester hydrochloride (1 equiv) in water (5 mL/mmol methyl ester), followed by the addition of the appropriate carboxylic acid (1 equiv) and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (1 equiv). After stirring the solution overnight at room temperature, water (15 mL/mmol methyl ester) was added, and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with saturated aq. $NaHCO_3$ and brine. The mixture was dried over $MgSO_4$, followed by filtration and evaporation of the solvent in vacuo to give the crude product. If necessary, a purification step via column chromatography was included.

General Procedure B: N-Acylation of a Secondary Amine. The N-acylation was executed according to the procedure of Falorni et al. with minor adaptations.[33] Briefly, the appropriate fatty acid (1 equiv) was dissolved in ethyl acetate (2 mL/mmol fatty acid) and cooled to 0 °C, whereafter *N*-methylmorpholine (1 equiv) was added, followed by the dropwise addition of isobutyl chloroformate (1 equiv). The resulting turbid suspension was stirred for 20 min at 0 °C. The secondary amine (1.05 equiv), was dissolved in a minimal amount of ethyl acetate and added at the same temperature. After 2 h, the reaction mixture was allowed to warm to room temperature and stirred overnight. Water was added and the aqueous phase was extracted twice with ethyl acetate. The combined organic phases were washed with a saturated solution of aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and the solvent was removed via rotary evaporation to yield the N-acylated product.

General Procedure C: Hydrolysis. Five equiv of NaOH, as a 2 M aqueous solution, were added to the methyl ester dissolved in methanol ($MeOH/H_2O$; 3:1 ratio). The reaction mixture was left to stir at room temperature between 3 h and overnight, and was followed by an extraction step with hexane. The aqueous phase was acidified with 2 M aqueous HCl and extracted three times with ethyl acetate. The solution was washed with brine, dried over ($MgSO_4$), and the drying agent was removed by filtration. The solvent was removed by rotary evaporation to yield the crude hydrolyzed product which was purified, if applicable, via recrystallization in diethyl ether/hexane.

General Procedure D: Cyclization. The free carboxylic acid was dissolved in dry CH_2Cl_2 to obtain a 20 mM solution whereafter 1.1 equiv of EDC·HCl and 0.2 equiv of DMAP were added. The resulting reaction mixture was stirred overnight at room temperature, after which the solvent was removed in vacuo and the residue redissolved in ethyl acetate/water 1:1. The aqueous phase was extracted twice with ethyl acetate. The organic phases were combined and subsequently washed with a saturated solution of aqueous $NaHCO_3$ and brine. The solution was dried with $MgSO_4$. Filtration and rotary evaporation of the solvent yielded the crude seven-membered ring-containing product, which was purified via column chromatography.

Methyl N-(3-Hydroxynonanoyl)-L-serinate ***11a.*** This compound was synthesized by reacting L-serine methyl ester hydrochloride **10a** (1 equiv, 3.1 g, 20 mmol) with *β*-hydroxynonanoic acid **9a** (1 equiv, 3.48 g, 20 mmol), following general procedure A to yield 2.91 g (10.6 mmol, 53% yield) of compound **11a**. Diastereomers (ratio 1:1) could not be separated via flash chromatography (ethyl acetate/petroleum ether 4:1). This resulted in a colorless powder: mp 65−67 °C; Yield: 53%; R_f = 0.24 (ethyl acetate/petroleum ether 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (3H, t, J = 6.8 Hz), 1.22−1.62 (10H, m), 2.35 (0.5H, dd, J = 14.8 Hz, 9.4 Hz), 2.36 (0.5H, dd, J = 14.7 Hz, 9.3 Hz), 2.467 (0.5H, d, J = 14.7 Hz), 2.474 (0.5H, d, J = 14.7 Hz), 3.54 (0.5H, br s), 3.80 (3H, s), 3.70−4.10 (4.5H, m), 4.64−4.72 (1H, m), 7.02 (0.5H, d, J = 7.7 Hz), 7.08 (0.5H, d, J = 7.7 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.50, 25.53, 31.8, 37.0, 37.1, 43.15, 43.21, 52.77, 52.84, 54.7, 62.7, 68.8, 69.0, 171.1, 171.3, 172.6, 172.9 ppm; MS (ESI): m/z (%): 276 ($M+H^+$, 100); HRMS calcd for $C_{13}H_{25}NO_5H^+$ 276.1805, found 276.1804; IR (neat, cm^{-1}) ν_{max} 1061, 1546, 1622, 1652, 1722, 1742, 2854, 2924, 2952, 3290.

N-(3-Hydroxynonanoyl)-L-serine ***12a.*** This compound was synthesized by hydrolyzing methyl *N*-(3-hydroxynonanoyl)-L-serinate **11a** (1 equiv, 100 mg, 0.36 mmol) according to general procedure C to yield 86 mg (0.33 mmol, 91% yield) of compound **12a**. Diastereomers (ratio 1:1) could not be separated. This resulted in a colorless powder: mp 112−114 °C; Yield: 91%; ^{1}H NMR (400 MHz, CD_3OD): δ = 0.81 (3H, t, J = 6.8 Hz), 1.10−1.45 (10H, m), 2.25−2.35 (2H, m), 3.73 (1H, dd, J = 11.2 Hz), 3.81 (1H, ddd, J = 11.2 Hz, 4.8 Hz, 1.9 Hz), 3.83−3.92 (1H, m), 4.41 (1H, dd, J = 7.8 Hz, 4.0 Hz) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 13.0, 22.3, 25.21, 25.22, 29.0, 31.6, 36.8, 43.1, 43.2, 54.7, 61.48, 61.55, 68.3, 68.4, 172.0, 172.96, 173.02 ppm; MS (ESI): m/z (%): 262 ($M+H^+$, 100), 284 ($M+Na^+$, 40); HRMS calcd for $C_{12}H_{23}NO_5H^+$ 262.1649, found 262.1653; IR (neat, cm^{-1}) ν_{max} 1055, 1204, 1414, 1531, 1614, 1657, 2851, 2920, 3341.

Methyl N-(3-Hydroxynonanoyl)-L-prolinate ***11b.*** This compound was synthesized by reacting L-proline methyl ester hydrochloride **10b** (1 equiv, 1.66 g, 10 mmol) with *β*-hydroxynonanoic acid **9a** (1 equiv, 1.74 g, 10 mmol), following general procedure A. After purification via flash chromatography (ethyl acetate/petroleum ether 1:1), 1.67 g (6.6 mmol, 66% yield) of compound **11b** was obtained. Diastereomers (ratio 1:1) could not be separated via flash chromatography. Both diastereomers existed as a mixture of two rotamers in a 5:1 ratio. This resulted in a colorless oil: Yield: 66%; R_f = 0.12 (ethyl acetate/petroleum ether 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (3H, t, J = 6.5 Hz), 1.21−1.62 (10H, m), 1.88−2.26 (4H, m), 2.26−2.55 (2H, m), 3.45−3.75 (2H, m), 3.74, 3.75 (2.5H, 2*s*), 3.766, 3.772 (0.5H, 2*s*), 3.95−4.10 (1H, m), 4.37 (0.1H, dd, J = 8.6 Hz, 2.5 Hz), 4.41 (0.1H, dd, J = 8.4 Hz, 2.6 Hz), 4.49 (0.4H, dd, J = 8.6 Hz, 3.7 Hz), 4.53 (0.4H, dd, J = 8.4 Hz, 3.5 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.5, 24.5, 24.6, 25.4, 25.5, 29.10, 29.14, 29.2, 29.6, 31.7, 36.4, 36.5, 40.2, 40.6, 40.69, 40.7, 46.1, 46.2, 47.0, 47.1, 52.18, 52.20, 52.5, 52.6, 58.4, 58.5, 59.2, 59.4, 67.7, 68.0, 68.1, 68.3, 171.7, 171.8, 171.9, 172.0, 172.2, 172.3, 172.6 ppm; MS (ESI): m/z (%): 286 ($M+H^+$, 100); HRMS calcd for $C_{15}H_{27}NO_4H^+$ 286.2013, found 286.2012; IR (neat, cm^{-1}) ν_{max} 1038, 1173, 1196, 1300, 1373, 1393, 1435, 1626, 1744, 2859, 2928, 2953, 3438.

N-(3-Hydroxynonanoyl)-L-proline ***12b.*** This compound was synthesized by hydrolyzing methyl *N*-(3-hydroxynonanoyl)-L-prolinate **11b** (1 equiv, 1.43 g, 5 mmol) according to general procedure C to give 1.21 g (4.45 mmol) of compound **12b** in 89% yield. Spectral data were obtained from a mixture of two diastereomers in a 1:1 ratio. Both diastereomers existed as a mixture of two rotamers in a 5:1 ratio. This resulted in a colorless powder: mp 51−53 °C; Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (3H, t, J = 6.4 Hz), 1.23−1.61 (10H, m), 1.88−2.38 (4H, m), 2.38−2.56 (2H, m), 3.45−3.76 (2H, m), 4.03−4.11 (1H, m), 4.37 (0.1H, dd, J = 6.9 Hz, 4.0 Hz), 4.46 (0.1H, dd, J = 7.5 Hz, 3.3 Hz), 4.50−4.58 (0.8H, m), 7.50 (1H, br s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 21.0, 24.5, 24.6, 25.49, 25.51, 28.7, 28.8, 29.2, 31.8, 36.1, 36.4, 36.5, 40.6, 40.7, 40.9, 41.1, 46.4, 47.5, 47.6, 59.02, 58.98, 59.4, 59.5, 68.0, 68.5, 172.2, 172.4, 172.7, 172.8, 174.3 ppm; MS (ESI): m/z (%): 272 ($M+H^+$, 100); HRMS calcd for $C_{14}H_{25}NO_4H^+$ 272.1856, found 272.1865; IR (neat, cm^{-1}) ν_{max} 1045, 1173, 1198, 1240, 1373, 1392, 1628, 1703, 1740, 2889, 2930, 2972, 2982, 3448, 3651.

(9aS)-3-Hexylhexahydro-1H,5H-pyrrolo[2,1-c][1,4]oxazepine-1,5-dione ***4b.*** This compound was synthesized using ring-closing acid **12b** (1 equiv, 0.54 g, 2 mmol) according to general procedure D to give 0.43 g of cyclic compound **4b** in 84% yield after flash chromatography (ethyl acetate/petroleum ether 1:1). Diastereomers (ratio 1:1) could not be separated via flash chromatography. This resulted in a colorless powder: mp 87−89 °C; Yield: 84%; R_f = 0.21 (ethyl acetate/petroleum ether 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (3H, t, J = 6.5 Hz), 1.24−1.55 (8H, m), 1.56−1.80 (2H, m), 1.80−2.02 (2H, m), 2.15−2.24 (1H, m), 2.55−2.64 (1H, m), 2.76 (1H, dd, J = 18.5 Hz, 11.5 Hz), 2.86 (1H, dd, J = 18.5 Hz, 2.4 Hz), 3.58−3.69 (2H, m), 4.67 (1H, dd, J = 7.0 Hz, 7.0 Hz), 4.72−4.82 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.5, 25.2, 28.9, 29.6, 31.6, 35.0, 42.4, 48.3, 55.7, 73.5, 166.9, 169.6 ppm; MS (ESI): m/z (%): 254 ($M+H^+$, 100); HRMS calcd for $C_{14}H_{23}NO_3H^+$ 254.1751, found 254.1763; IR (neat, cm^{-1}) ν_{max} 1223, 1383, 1438, 1616, 1748, 2859, 2902.

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Methyl N-(3-Hydroxydodecanoyl)sarcosinate ***11c***. This compound was synthesized by reacting sarcosine methyl ester hydrochloride **10c** (1 equiv, 1.40 g, 10 mmol) with β-hydroxydodecanoic acid **9b** (1 equiv, 1.74 g, 10 mmol), following general procedure A. After flash chromatography (ethyl acetate/petroleum ether 3:1), 1.87 g (6.2 mmol, 62% yield) of compound **11c** was obtained. Spectral data were obtained from a mixture of two rotamers in a 4:1 ratio. This resulted in a colorless powder: mp 52−54 °C; Yield: 62%; R_f = 0.29 (ethyl acetate/petroleum ether 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ rotamer 1 (major): 0.88 (3H, t, *J* = 6.8 Hz), 1.19−1.61 (16H, m), 2.40 (1H, dd, *J* = 16.5 Hz, 9.4 Hz), 2.55 (1H, dd, *J* = 16.5 Hz, 2.4 Hz), 3.07 (3H, s), 3.75 (3H, s), 3.93 (1H, br d, *J* = 2.8 Hz), 3.98−4.07 (1H, m), 4.09 (1H, d, *J* = 17.3 Hz), 4.19 (1H, d, *J* = 17.4 Hz) ppm; rotamer 2 (minor): 0.88 (3H, t, *J* = 6.8 Hz), 1.19−1.61 (16H, m), 2.25 (1H, dd, *J* = 16.2 Hz, 9.2 Hz), 2.35−2.41 (1H, m), 2.99 (3H, s), 3.79 (3H, s), 3.98−4.07 (2H, m), 3.99 (1H, d, *J* = 18.2 Hz), 4.10 (1H, d, *J* = 18.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ rotamer 1 (major): 14.1, 22.6, 29.3, 29.5, 29.6, 31.9, 36.4, 36.5, 39.5, 49.1, 52.2, 68.7, 169.6, 173.6 ppm; rotamer 2 (minor): 14.1, 22.6, 29.3, 29.5, 29.6, 31.9, 34.7, 36.4, 39.2, 51.3, 52.5, 68.7, 169.1, 173.3 ppm; MS (ESI): *m*/*z* (%): 302 ($M+H^+$, 100); HRMS calcd for $C_{16}H_{31}NO_4H^+$ 302.2326, found 302.2337; IR (neat, cm^{-1}) ν_{max} 1210, 1418, 1471, 1489, 1634, 1746, 2852, 2922, 2954, 3478.

N-(3-Hydroxydodecanoyl)sarcosine ***12c***. This compound was synthesized by hydrolyzing 1.56 g of methyl ester **11c** (1 equiv, 5.2 mmol) according to general procedure C to yield 1.33 g (4.6 mmol, 89% yield) of compound **12c**. Spectral data were obtained from a mixture of two rotamers in a 3:1 ratio. This resulted in a colorless powder: mp 71−73 °C; Yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$): δ rotamer 1 (major): 0.89 (3H, t, *J* = 6.8 Hz), 1.19−1.65 (16H, m), 2.49 (1H, dd, *J* = 16.3 Hz, 9.2 Hz), 2.57 (1H, dd, *J* = 16.2 Hz, 2.7 Hz), 3.10 (3H, s), 3.97−4.21 (3H, m), 7.85 (1H, br s) ppm; rotamer 2 (minor): 0.89 (3H, t, *J* = 6.8 Hz), 1.19−1.65 (16H, m), 2.40−2.50 (2H, m), 3.01 (3H, s), 3.97−4.21 (3H, m), 7.85 (1H, br s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ rotamer 1 (major): 14.1, 22.7, 25.6, 25.7, 29.3, 29.5, 29.6, 31.9, 35.9, 36.3, 36.8, 39.6, 49.5, 68.2, 172.2, 174.1 ppm; rotamer 2 (minor): 14.1, 22.7, 25.6, 25.7, 29.3, 29.5, 29.6, 31.9, 35.9, 36.3, 35.0, 39.2, 51.3, 68.7, 171.3, 173.6 ppm; MS (ESI): *m*/*z* (%): 288 ($M+H^+$, 100); HRMS calcd for $C_{15}H_{29}NO_4H^+$ 288.2169, found 288.2172; IR (neat, cm^{-1}) ν_{max} 1258, 142, 1418, 1497, 1638, 1726, 2849, 2918, 3353.

4-Methyl-7-nonyl-1,4-oxazepane-2,5-dione ***4c***. This compound was synthesized by ring closing acid **12c** (1 equiv, 0.14 g, 0.50 mmol) according to general procedure D. After purification via flash chromatography (ethyl acetate/petroleum ether 2:1), 84 mg (0.31 mmol, 62% yield) of cyclic compound **4c** was obtained. This resulted in a colorless powder: mp 81−83 °C; Yield: 62%; R_f = 0.23 (ethyl acetate/petroleum ether 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (3H, t, *J* = 6.8 H), 1.20−1.80 (16H, m), 2.85 (1H, dd, *J* = 17.5 Hz, 9.5 Hz), 2.91 (1H, dd, *J* = 17.5 Hz, 3.7 Hz), 3.08 (3H, s), 3.96 (1H, d, *J* = 15.8 Hz), 4.53 (1H, d, *J* = 15.8 Hz), 4.63−4.71 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 22.8, 25.2, 29.35, 29.42, 29.57, 29.62, 32.0, 35.7, 37.2, 42.3, 52.7, 76.1, 167.8, 168.9 ppm; MS (ESI): *m*/*z* (%): 270 ($M+H^+$, 100); HRMS calcd for $C_{15}H_{27}NO_3H^+$ 270.2064, found 270.2058; IR (neat, cm^{-1}) ν_{max} 1213, 1339, 1493, 1624, 1736, 2857; 2924.

Methyl N-(3-Hydroxydodecanoyl)glycinate ***11d***. This compound was synthesized by reacting glycine methyl ester hydrochloride **10d** (1 equiv, 1.89 g, 15 mmol) with β-hydroxydodecanoic acid **9b** (1 equiv, 3.24 g, 15 mmol), following general procedure A. After purification via flash chromatography (ethyl acetate/petroleum ether 3:1), 2.83 g (9.9 mmol, 66% yield) of compound **11d** was obtained. This resulted in a colorless powder: mp 77−79 °C; Yield: 66%; R_f = 0.27 (ethyl acetate/petroleum ether 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (3H, t, *J* = 6.9 Hz), 1.19−1.59 (16H, m), 2.32 (1H, dd, *J* = 15.1 Hz, 9.1 Hz), 2.44 (1H, dd, *J* = 15.1 Hz, 2.7 Hz), 3.34 (1H, br d, *J* = 3.6 Hz), 3.77 (3H, s), 3.97−4.05 (1H, m), 4.06−4.14 (2H, m), 6.34 (1H, br s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.4, 25.5, 29.3, 29.55, 29.59, 31.9, 36.9, 41.1, 42.7, 52.5, 68.7, 170.6, 172.7 ppm; MS (ESI): *m*/*z* (%): 288 ($M+H^+$, 100); HRMS calcd for $C_{15}H_{29}NO_4H^+$ 288.2169, found 288.2168; IR (neat, cm^{-1}) ν_{max} = 1221, 1379, 1392, 1434, 1442, 1550, 1643, 1742, 2851, 2919, 2956, 3312.

N-(3-Hydroxydodecanoyl)glycine ***12d***. This compound was synthesized by hydrolyzing methyl ester **11d** (1 equiv, 1.75 g, 6.1 mmol) according to general procedure C to yield 1.35 g (4.9 mmol, 81% yield) of compound **12d**. This resulted in a colorless powder: mp 92−94 °C; Yield: 94%; ^{1}H NMR (400 MHz, CD_3OD): δ = 0.80 (3H, t, *J* = 6.9 Hz), 1.14−1.43 (16H, m), 2.25 (1H, dd, *J* = 14.3 Hz, 7.6 Hz), 2.30 (1H, dd, *J* = 14.3 Hz, 5.3 Hz), 3.78 (1H, d, *J* = 17.8 Hz), 3.85 (1H, d, *J* = 17.8 Hz), 3.84−3.90 (1H, m) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 13.1, 22.3, 25.3, 29.1, 29.3, 31.7, 36.7, 40.4, 43.2, 68.3, 171.7, 173.3 ppm; MS (ESI): *m*/*z* (%): 274 ($M+H^+$, 100), 296 ($M+Na^+$, 28); HRMS calcd for $C_{14}H_{27}NO_4H^+$ 274.2013, found 274.2009; IR (neat, cm^{-1}) ν_{max} 1246, 1262, 1421, 1447, 1556, 1640, 1708, 2849, 2922, 3262, 3326.

Methyl N-Benzyl-N-(3-hydroxynonanoyl)glycinate ***15a***. This compound was synthesized by reacting the methyl ester of *N*-benzyl glycine **14a** (1 equiv, 0.59 g, 3.0 mmol) with β-hydroxynonanoic acid **9a** (1 equiv, 0.52 g, 3.0 mmol), following general procedure B to yield 0.55 g (1.6 mmol, 55% yield) of ester **15a**. Spectral data were obtained from a mixture of two rotamers in a 7:3 ratio. This resulted in a yellow oil: Yield: 55%; ^{1}H NMR (400 MHz, $CDCl_3$): δ rotamer 1 (major): 0.87 (3H, t, *J* = 6.6 Hz), 1.26−1.61 (10H, m), 2.49 (1H, dd, *J* = 16.2 Hz, 9.4 Hz), 2.62 (1H, dd, *J* = 16.2 Hz, 2.4 Hz), 3.73 (3H, s), 3.85−4.15 (4H, m), 4.55−4.77 (2H, m), 7.16−7.41 (5H, m) ppm; rotamer 2 (minor): 0.87 (3H, t, *J* = 6.6 Hz), 1.26−1.61 (10H, m), 2.32 (1H, dd, *J* = 16.3 Hz, 9.3 Hz), 2.45 (1H, dd, *J* = 16.3 Hz, 2.3 Hz), 3.72 (3H, s), 3.85−4.15 (4H, m), 4.55−4.77 (2H, m), 7.16−7.41 (5H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ rotamer 1 (major): 14.1, 22.59, 25.5, 29.3, 31.8, 36.39, 39.4, 46.9, 52.1, 52.2, 68.3, 126.7, 128.4, 129.1, 135.6, 169.7, 173.9 ppm; rotamer 2 (minor): 14.1, 22.61, 25.5, 29.2, 31.8, 36.43, 39.5, 48.2, 49.5, 52.5, 68.2, 127.8, 128.0, 128.7, 136.2, 169.3, 173.4 ppm; MS (ESI): *m*/*z* (%): 336 ($M+H^+$, 100); HRMS calcd for $C_{19}H_{29}NO_4H^+$ 336.2169, found 336.2176; IR (neat, cm^{-1}) ν_{max} 1001, 1175, 1200, 1368, 1406, 1435, 1452, 1634, 1709, 1748, 2857, 2928, 2953, 3451.

N-Benzyl-N-(3-Hydroxynonanoyl)glycine ***16a***. This compound was synthesized by hydrolyzing methyl ester **15a** (1 equiv, 0.50 g, 1.5 mmol) according to general procedure C to give 0.41 g (1.3 mmol) of compound **16a** in 86% yield. Spectral data were obtained from a mixture of two rotamers in a 1.9:1 ratio. This resulted in a colorless powder: mp 91−93 °C; Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$): δ rotamer 1 (major): 0.86−0.91 (3H, m), 1.19−1.68 (10H, m), 2.45−2.65 (2H, m), 3.90−4.21 (3H, m), 4.58 (1H, d, *J* = 16.8 Hz), 4.69 (1H, d, *J* = 16.7 Hz), 7.10−7.41 (5H, m), 7.60 (1H, br s) ppm; rotamer 2 (minor): 0.86−0.91 (3H, m), 1.19−1.68 (10H, m), 2.45−2.65 (2H, m), 3.90−4.21 (3H, m), 4.45−4.55 (1H, m), 4.78−4.86 (1H, m), 7.10−7.41 (5H, m), 7.60 (1H, br s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ rotamer 1 (major): 14.1, 22.61, 25.5, 29.2, 31.8, 36.3, 39.5, 47.1, 52.3, 68.5, 126.8, 128.4, 129.1, 135.2, 172.4, 174.4 ppm; rotamer 2 (minor): 14.1, 22.64, 25.6, 29.2, 31.8, 35.9, 39.5, 48.0, 49.6, 68.7, 127.8, 128.1, 128.8, 136.2, 171.5, 173.6 ppm; MS (ESI): *m*/*z* (%): 322 ($M+H^+$, 100); HRMS calcd for $C_{18}H_{27}NO_4H^+$ 322.2013, found 322.2009; IR (neat, cm^{-1}) ν_{max} 1188, 1213, 1420, 1476, 1626, 1730, 2855, 2927, 3310.

4-Benzyl-7-hexyl-1,4-oxazepane-2,5-dione ***17a***. This compound was synthesized by ring-closing acid **16a** (1 equiv, 0.28 g, 0.86 mmol) according to general procedure D. After purification via flash chromatography (ethyl acetate/petroleum ether 4:1), 0.20 g (0.65 mmol, 75% yield) of cyclic compound **17a** was obtained. This resulted in a colorless powder: mp 53−55 °C; Yield: 75%; R_f = 0.33 (ethyl acetate/petroleum ether 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (3H, t, *J* = 6.8 Hz), 1.21−1.55 (8H, m), 1.58−1.81 (2H, m), 2.90−3.02 (2H, m), 3.94 (1H, d, *J* = 15.9 Hz), 4.31 (1H, d, *J* = 15.9 Hz), 4.49 (1H, d, *J* = 14.7 Hz), 4.67 (1H, tt, *J* = 12.6 Hz, 4.6 Hz), 4.89 (1H, d, *J* = 14.7 Hz), 7.23−7.38 (5H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.5, 25.0, 28.9, 31.6, 35.6, 42.2, 50.2, 52.1, 76.0, 128.1, 128.2, 129.0, 135.9, 167.5, 168.8 ppm; MS (ESI): *m*/*z* (%): 304 ($M+H^+$, 100); HRMS calcd for $C_{18}H_{25}NO_3H^+$ 304.1907, found

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304.1904; IR (neat, cm^{-1}) ν_{max} 1134, 1161, 1233, 1296, 1344, 1423, 1439, 1454, 1638, 1749, 2849, 2920, 2951.

*Methyl N-(3-Hydroxynonanoyl)-N-(4-methoxybenzyl)glycine **15b**.* This compound was synthesized by reacting the methyl ester of *N*-PMB glycine **14b** (1 equiv, 5.23 g, 25 mmol) with *β*-hydroxynonanoic acid **9a** (1 equiv, 4.36 g, 25 mmol), following general procedure B to yield 7.1 g (19.5 mmol, 78% yield) of ester **15a**. Spectral data were obtained from a mixture of two rotamers in a 2:1 ratio. This resulted in a yellow oil: Yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$): δ rotamer 1 (major): 0.85−0.90 (3H, m), 1.21−1.63 (10H, m), 2.50 (1H, dd, J = 16.1 Hz, 9.4 Hz), 2.63 (1H, dd, J = 16.2 Hz, 2.3 Hz), 3.72 (3H, s), 3.83 (3H, s), 3.84−4.03 (2H, m), 4.01−4.11 (1H, m), 4.49−4.69 (2H, m), 6.89 (2H, d, J = 8.6 Hz), 7.11 (2H, d, J = 8.6 Hz) ppm; rotamer 2 (minor): 0.85−0.90 (3H, m), 1.21−1.63 (10H, m), 2.30 (1H, dd, J = 16.3 Hz, 9.1 Hz), 2.43 (1H, dd, J = 16.3 Hz, 2.2 Hz), 3.71 (3H, s), 3.79 (3H, s), 3.84−4.03 (2H, m), 4.01−4.11 (1H, m), 4.49−4.69 (2H, m), 6.85 (2H, d, J = 8.6 Hz), 7.15 (2H, d, J = 8.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ rotamer 1 (major): 14.1, 22.6, 25.5, 29.2, 29.3, 31.8, 36.4, 39.4, 46.6, 51.6, 52.2, 55.33, 68.3, 114.4, 128.2, 129.9, 159.4, 169.7, 173.8 ppm; rotamer 2 (minor): 14.1, 22.6, 25.5, 29.2, 29.3, 31.8, 36.4, 39.5, 47.9, 48.9, 52.5, 55.29, 68.1, 114.1, 127.3, 128.2, 128.6, 159.3, 169.3, 173.4 ppm; MS (ESI): m/z (%): 366 (M+H$^+$, 100); HRMS calcd for $C_{20}H_{31}NO_5H^+$ 366.2275, found 366.2268; IR (neat, cm^{-1}) ν_{max} 1032, 1173, 1200, 1246, 1422, 1437, 1512, 1612, 1632, 1748, 2857, 2928, 2953, 3478.

*N-(3-Hydroxynonanoyl)-N-(4-methoxybenzyl)glycine **16b**.* Methyl ester **15b** (1 equiv, 7.0 g, 19.2 mmol) was hydrolyzed following general procedure C to yield 6.4 g (18.2 mmol) of carboxylic acid **16b** in a 95% yield. Spectral data were obtained from a mixture of two rotamers in a 2.3:1 ratio. This resulted in a colorless powder: mp 70−72 °C; Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$): δ rotamer 1 (major): 0.87−0.93 (3H, m), 1.24−1.71 (10H, m), 2.58 (1H, dd, J = 16.0 Hz, 9.0 Hz), 2.65 (1H, dd, J = 16.0 Hz, 2.5 Hz), 3.83 (3H, s), 4.03 (1H, d, J = 17.4 Hz), 4.11 (1H, d, J = 17.3 Hz), 4.01−4.21 (1H, m), 4.54 (1H, d, J = 16.3 Hz), 4.63 (1H, d, J = 16.3 Hz), 6.92 (2H, d, J = 8.5 Hz), 7.13 (2H, d, J = 8.5 Hz) ppm; rotamer 2 (minor): 0.87−0.93 (3H, m), 1.24−1.71 (10H, m), 2.45−2.54 (2H, m), 3.82 (3H, s), 3.89 (1H, d, J = 18.7 Hz), 3.95 (1H, d, J = 18.7 Hz), 4.01−4.21 (1H, m), 4.54 (1H, d, J = 16.3 Hz), 4.63 (1H, d, J = 16.3 Hz), 4.83 (1H, d, J = 14.8 Hz), 6.87 (2H, d, J = 8.5 Hz), 7.18 (2H, d, J = 8.5 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ rotamer 1 (major): 14.1, 22.6, 25.5, 29.23, 31.8, 36.4, 39.6, 46.9, 51.8, 55.35, 68.4, 114.5, 127.0, 128.3, 159.5, 172.4, 174.3 ppm; rotamer 2 (minor): 14.1, 22.6, 25.6, 29.19, 31.8, 35.8, 39.5, 47.6, 48.9, 55.29, 68.7, 114.2, 128.2, 129.9, 159.3, 171.7, 173.4 ppm; MS (ESI): m/z (%): 352 (M+H$^+$, 100); HRMS calcd for $C_{19}H_{29}NO_5H^+$ 352.2118, found 352.2110; IR (neat, cm^{-1}) ν_{max} 1036, 1175, 1225, 1246, 1398, 1483, 1512, 1620, 1724, 2857, 2920, 3380.

*7-Hexyl-4-(4-methoxybenzyl)-1,4-oxazepane-2,5-dione **17b**.* This compound was synthesized by ring-closing acid **16b** (1 equiv, 6.17 g, 17.5 mmol) according to general procedure D. After purification via flash chromatography (ethyl acetate/petroleum ether 1:1), 2.33 g (7 mmol, 40% yield) of compound **17b** was obtained. This resulted in a colorless powder: mp 54−56 °C; Yield: 40%; R_f = 0.28 (ethyl acetate/petroleum ether 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (3H, t, J = 6.7 Hz), 1.21−1.55 (8H, m), 1.56−1.80 (2H, m), 2.88−3.00 (2H, m), 3.80 (3H, s), 3.94 (1H, d, J = 15.9 Hz), 4.28 (1H, d, J = 15.9 Hz), 4.43 (1H, d, J = 14.6 Hz), 4.64 (1H, tt, J = 12.7 Hz, 4.5 Hz), 4.81 (1H, d, J = 14.6 Hz), 6.87 (2H, d, J = 8.6 Hz), 7.19 (2H, d, J = 8.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.5, 25.0, 28.8, 31.6, 35.6, 42.1, 50.0, 51.4, 55.3, 76.0, 114.3, 127.9, 129.6, 159.4, 167.6, 168.7 ppm; MS (ESI): m/z (%): 334 (M+H$^+$, 100); HRMS calcd for $C_{19}H_{27}NO_4H^+$ 334.2013, found 334.2001; IR (neat, cm^{-1}) ν_{max} 1032, 1175, 1182, 1204, 1223, 1244, 1306, 1325, 1352, 1512, 1628, 1730, 2855, 2926, 2954.

*Removal of the N-PMB Group of **17b**.* N-PMB-protected 1,4-oxazepane-2,5-dione **17b** (1 equiv, 2.3 g, 6.9 mmol) was dissolved in 250 mL of a 4:1 ethyl acetate/water mixture and cooled to 0 °C. Cerium ammonium nitrate (CAN, 5 equiv, 18.9 g, 34.5 mmol) was added, and after 2 h, 150 mL of a saturated solution of aqueous $NaHCO_3$ was added. After a slow-phase separation, the aqueous phase was extracted twice with 150 mL of ethyl acetate. The combined organic phases were washed once with brine. The solution was dried with $MgSO_4$, and filtration and removal of the solvent in vacuo yielded the crude seven-membered ring, which was purified immediately via column chromatography (ethyl acetate/petroleum ether 1:1), to yield 200 mg of compound **4e** as a colorless powder (14% yield).

*7-Hexyl-1,4-oxazepane-2,5-dione **4e**.* This compound is a colorless powder: mp 62−64 °C; Yield: 14%; R_f = 0.15 (ethyl acetate/petroleum ether 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (3H, t, J = 6.5 Hz), 1.22−1.61 (8H, m), 1.61−1.83 (2H, m), 2.83 (2H, d, J = 6.8 Hz), 3.85 (1H, dd, J = 15.3 Hz, 7.4 Hz), 4.40 (1H, d, J = 15.3 Hz), 4.72 (1H, quint., J = 6.5 Hz), 6.18 (1H, d, J = 7.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.5, 25.1, 28.8, 31.6, 35.1, 41.7, 44.5, 74.7, 167.9, 170.5 ppm; MS (ESI): m/z (%): 214 (M+H$^+$, 100); HRMS calcd for $C_{11}H_{19}NO_3H^+$ 214.1438, found 214.1438; IR (neat, cm^{-1}) ν_{max} 1090, 1113, 1348, 1422, 1447, 1489, 1551, 1638, 1707, 1738, 2849, 2924, 2953, 3256.

*Synthesis of 2-t-Butyl-oxazolidine-Protected Oxazepane-2,5-dione **21b**.* 2-*t*Bu-Oxazolidine **18b** (1.05 equiv, 0.75 g, 4.0 mmol) was N-acylated according to general procedure B. The N-acylated 2-*t*Bu-oxazolidine **19b** was immediately subjected to a hydrolysis and cyclization reaction according to general procedures C and D. The crude oxazepane-2,5-dione **21b**, present as a 1:1 mixture of diastereomers, was purified via column chromatography (Reveleris X2 automated flash chromatography instrument: gradient increase over 5 column volumes (CV) from 100% hexane to 90% hexane and 10% ethyl acetate, hold 5 CV, gradient increase over 10 CV to 50% hexane/50% ethyl acetate, hold 2 CV, then 2 CV 100% ethyl acetate) followed by recrystallization in diethyl ether/hexane to successfully separate both diastereomers and to give 0.28 g (0.91 mmol, 24% yield) of (*RRS*)-**21b**, 0.33 g (1.1 mmol, 28% yield) of (*RSS*)-**21b** and 0.13 g (0.42 mmol, 11% yield) of a mixture of (*RRS*)/(*RSS*)-**21b**.

*(3R,7R,9aS)-3-(t-Butyl)-7-hexyltetrahydro-3H,5H,9H-oxazolo[4,3-c][1,4]oxazepine-5,9-dione (RRS)-**21b** (trans-diastereomer).* This compound is a colorless powder: mp 94−96 °C; Yield: 24%; R_f = 0.29 (ethyl acetate/petroleum ether 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (3H, t, J = 6.8 Hz), 0.95 (9H, s), 1.19−1.55 (8H, m), 1.63−1.84 (2H, m), 2.72 (1H, d, J = 16.6 Hz), 3.14 (1H, dd, J = 16.5 Hz, 11.2 Hz), 4.44 (1H, dd, J = 9.1 Hz, 9.1 Hz), 4.52 (1H, dd, J = 9.3 Hz, 8.3 Hz), 4.68−4.79 (2H, m), 5.36 (1H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.5, 24.5, 25.9, 28.9, 31.6, 37.2, 38.7, 42.6, 59.4, 69.2, 79.7, 96.2, 166.3, 171.7 ppm; MS (ESI): m/z (%): 312 (M+H$^+$, 100); HRMS calcd for $C_{17}H_{28}NO_4^-$ 310.2024, found 310.2016; IR (neat, cm^{-1}) ν_{max} 1119, 1179, 1215, 1231, 1362, 1369, 1381, 1680, 1703, 1711, 2870, 2930, 2970, 2980.

*(3R,7S,9aS)-3-(t-Butyl)-7-hexyltetrahydro-3H,5H,9H-oxazolo[4,3-c][1,4]oxazepine-5,9-dione (RSS)-**21b** (cis-diastereomer).* This compound appeared to be colorless needle-like crystals: mp 96−98 °C; Yield: 28%; R_f = 0.28 (ethyl acetate/petroleum ether 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (3H, t, J = 6.8 Hz), 0.95 (9H, s), 1.21−1.58 (8H, m), 1.61−1.89 (2H, m), 2.85 (1H, dd, J = 17.7 Hz, 9.8 Hz), 2.97 (1H, dd, J = 17.6 Hz, 2.6 Hz), 4.36 (1H, dd, J = 9.2 Hz, 8.0 Hz), 4.62 (1H, dd, J = 9.2 Hz, 9.2 Hz), 4.71−4.83 (2H, m), 5.44 (1H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.5, 24.5, 26.4, 28.8, 31.5, 35.5, 38.9, 42.5, 55.1, 68.6, 75.2, 97.0, 167.6, 168.5 ppm; MS (ESI): m/z (%): 312 (M+H$^+$, 100); HRMS calcd for $C_{17}H_{28}NO_4^-$ 310.2024, found 310.2028; IR (neat, cm^{-1}) ν_{max} 1076, 1125, 1175, 1211, 1233, 1354, 1364, 1375, 1396, 1649, 1738, 2889, 2924, 2970, 2982.

*Synthesis of 2,2-Dimethyloxazolidine-Protected Oxazepane-2,5-dione **21c**.* To methyl *N*-(3-hydroxynonanoyl)serinate **11a** (1 equiv, 0.55 g, 2 mmol) dissolved in dry toluene (20 mL) under a nitrogen atmosphere, were sequentially added 2,2-dimethoxypropane (DMP) (5 equiv, 1.2 mL, 10 mmol) and *p*-toluenesulfonic acid monohydrate (0.1 equiv, 40 mg, 0.2 mmol). The mixture was heated to reflux with a Dean−Stark apparatus for 3 h to remove water. After the mixture was cooled down, water (20 mL) was added. The aqueous phase was extracted twice with ethyl acetate (2 × 20 mL), and the organic phases were combined and washed with brine (20 mL). The mixture was

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dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. The crude oxazolidine **19c** was hydrolyzed and cyclized according to the general procedures C and D to yield compound **21c** (0.10 g, 0.36 mmol) in an 18% total yield after column chromatography (Reveleris X2 automated flash chromatography instrument: 5 column volumes (CV) 100% hexane, gradient increase over 15 CV to 50% hexane/50% ethyl acetate, hold 2 CV, then 2 CV 100% ethyl acetate). Diastereomers (ratio 1:1.3) could not be separated via flash chromatography.

(9aS)-7-Hexyl-3,3-dimethyltetrahydro-3H,5H,9H-oxazolo[4,3-c]-[1,4]oxazepine-5,9-dione ***21c.*** The compound is a white powder: mp 88−90 °C; Yield: 18%; R_f = 0.21 (ethyl acetate/petroleum ether 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer 1 (major): 0.91 (3H, t, J = 6.8 Hz), 1.25−1.82 (10H, m), 1.61 (3H, s), 1.64 (3H, s), 2.63 (1H, dd, J = 15.1 Hz, 2.2 Hz), 3.06 (1H, dd, J = 15.1 Hz, 11.7 Hz), 4.23−4.33 (1H, m), 4.59−4.67 (1H, m), 4.70−4.81 (2H, m) ppm; diastereomer 2 (minor): 0.91 (3H, t, J = 6.8 Hz), 1.25−1.82 (10H, m), 1.62 (3H, s), 1.69 (3H, s), 2.80 (1H, dd, J = 18.5 Hz, 10.8 Hz), 2.88 (1H, dd, J = 18.5 Hz, 2.8 Hz), 4.23−4.33 (1H, m), 4.51 (1H, dd, J = 9.6 Hz, 7.6 Hz), 4.59−4.67 (1H, m), 4.70−4.81 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ diastereomer 1 (major): 14.0, 22.5, 23.5, 24.5, 24.9, 25.1, 28.8, 28.9, 31.6, 34.8, 37.5, 43.1, 59.7, 65.8, 79.8, 96.6, 164.8, 167.9 ppm; diastereomer 2 (minor): 14.0, 22.5, 23.8, 24.5, 25.1, 25.3, 28.8, 28.9, 31.6, 34.8, 37.5, 43.4, 54.6, 65.7, 73.8, 98.3, 166.9, 167.1 ppm; MS (ESI): m/z (%): 284 ($M+H^+$, 100); HRMS calcd for $C_{15}H_{25}NO_4H^+$ 284.1856, found 284.1860; IR (neat, cm^{-1}) ν_{max} 1072, 1085, 1155, 1209, 1233, 1252, 1335, 1381, 1418, 1632, 1667, 1703, 1742, 2889, 2916, 2932, 2972, 2982.

Synthesis of 2-Phenyloxazolidine-Protected Oxazepane-2,5-dione ***21a.*** To a stirred solution of L-serine methyl ester hydrochloride **10a** (1 equiv, 3.1 g, 20 mmol) in 60 mL of anhydrous CH_2Cl_2 and 15 mL Et_3N at room temperature was added 4.8 g of anhydrous $MgSO_4$ (2 equiv, 40 mmol), followed by freshly distilled benzaldehyde **13a** (1.1 equiv, 2.24 mL, 22 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight, filtered, and the filtrate was concentrated under reduced pressure. The resulting 2-phenyloxazolidine **18a** was N-acylated analogously to the *t*Bu-derivative **18b**, followed by hydrolysis and cyclization (procedures C and D) to give the oxazepane-2,5-dione **21a**, as a 1:1 mixture of diastereomers in 53% overall yield (3.5 g, 10.6 mmol). Diastereomers (ratio 1:1) could not be separated via flash chromatography (ethyl acetate/petroleum ether 3:1).

(3R,9aS)-7-Hexyl-3-phenyltetrahydro-3H,5H,9H-oxazolo[4,3-c]-[1,4]oxazepine-5,9-dione ***21a.*** The compound is a colorless powder: mp 96−98 °C; Yield: 53% R_f = 0.14 (ethyl acetate/petroleum ether 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer 1: 0.88−0.95 (3H, m), 1.28−1.90 (10H, m), 2.75 (1H, d, J = 15.8 Hz), 3.17 (1H, dd, J = 15.8 Hz, 11.2 Hz), 4.35−4.44 (1H, m), 4.47−4.54 (1H, m), 4.75−4.83 (1H, m), 4.85−4.97 (1H, m), 6.50 (1H, s), 7.27−7.31 (1H, m), 7.35−7.42 (4H, m) ppm; diastereomer 2: 0.88−0.95 (3H, m), 1.28−1.90 (10H, m), 2.91 (2H, d, J = 6.8 Hz), 4.35−4.44 (1H, m), 4.47−4.54 (1H, m), 4.75−4.83 (1H, m), 4.85−4.97 (1H, m), 6.52 (1H, s), 7.27−7.31 (1H, m), 7.35−7.42 (4H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ diastereomer 1: 14.0, 22.5, 24.5, 28.8, 28.9, 31.57, 31.58, 35.1, 37.4, 41.9, 59.0, 68.1, 79.9, 89.9, 126.1, 128.7, 129.2, 137.2, 165.4, 169.3 ppm; diastereomer 2: 14.0, 22.5, 24.5, 28.8, 28.9, 31.57, 31.58, 35.1, 37.4, 42.1, 54.2, 67.1, 74.2, 91.7, 126.3, 126.8, 129.1, 137.0, 166.0, 167.5 ppm; MS (ESI): m/z (%): 332 ($M+H^+$, 100); HRMS calcd for $C_{19}H_{25}NO_4H^+$ 332.1856, found 332.1868; IR (neat, cm^{-1}) ν_{max} 1061, 1117, 1184, 1221, 1389, 1425, 1655, 1676, 1703, 1724, 2857, 2926, 2953.

Debenzylation of ***21a.*** 500 mg (1 equiv, 1.5 mmol) of 2-phenyloxazolidine **21a** (d.r. 1:1) was dissolved in 30 mL of ethyl acetate, whereafter 250 mg of $Pd(OH)_2/C$ (20 wt % loading) was added, and the reaction mixture was stirred under an H_2 atmosphere at room temperature for 6 h. Subsequently, the reaction mixture was filtered through Celite, and the solvent was removed in vacuo. The crude mixture was purified via column chromatography (ethyl acetate/petroleum ether 1:1 to 100% ethyl acetate) to yield 82 mg (0.32 mmol, 22% yield) of deprotected compound **4a**, alongside with 334 mg (1 mmol) of recovered 2-phenyloxazolidine **21a** (d.r. 1:3).

(3S,7S)-7-Hexyl-3-(hydroxymethyl)-1,4-oxazepane-2,5-dione (SS)- ***4a.*** The compound is a colorless powder: mp 81−83 °C; Yield: 22%; R_f = 0.08 (ethyl acetate/petroleum ether 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (3H, t, J = 6.7 Hz), 1.23−1.57 (8H, m), 1.58−1.83 (2H, m), 2.60−2.66 (1H, m), 2.79 (1H, dd, J = 18.7 Hz, 3.0 Hz), 2.87 (1H, dd, J = 18.6 Hz, 11.3 Hz), 3.89 (1H, ddd, J = 12.3 Hz, 8.3 Hz, 4.3 Hz), 4.06 (1H, ddd, J = 12.0 Hz, 5.0 Hz, 5.0 Hz), 4.46−4.51 (1H, m), 4.73−4.81 (1H, m), 6.45 (1H, br s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.5, 25.1, 28.8, 31.5, 34.9, 41.7, 52.8, 61.1, 73.7, 169.5, 171.6 ppm; MS (ESI): m/z (%): 244 ($M+H^+$, 100); HRMS calcd for $C_{12}H_{21}NO_4H^+$ 244.1543, found 244.1543; IR (neat, cm^{-1}) ν_{max} 1013, 1028, 1072, 1084, 1134, 1186, 1231, 1329, 1391, 1429, 1624, 1742, 2853, 2916, 2953, 3098, 3206.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00790.

2D NOESY spectrum of **11a**; zoom-in of the ^{1}H and ^{13}C NMR spectra of compounds **12c** and **4c**; reaction conditions evaluated for the N-debenzylation of compound **17a**; reaction conditions evaluated for the N-acylation of 2-*t*Bu-oxazolidine **18b**; spectral data of 1,4-oxazepane-2,5-diones reported in literature; overlay of the ^{1}H NMR spectra of 2-phenyloxazolidine-protected compound **21a**, and compound **21a** recovered after treatment with 5% TFA, H_2 gas, and $Pd(OH)_2/C$; spectral data of Serratamolides **22**; crystal data for compound (*RSS*)-**21b**; copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **4a−c**, **4e**, **11a−d**, **12a−d**, **15a−b**, **16a−b**, **17a−b**, and **21a−c**. (PDF)

X-ray data of compound (*RSS*)-**21b** (CIF)

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Notes

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■ DEDICATION

Dedicated to Prof. Al Padwa on the occasion of his 80th birthday.

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