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

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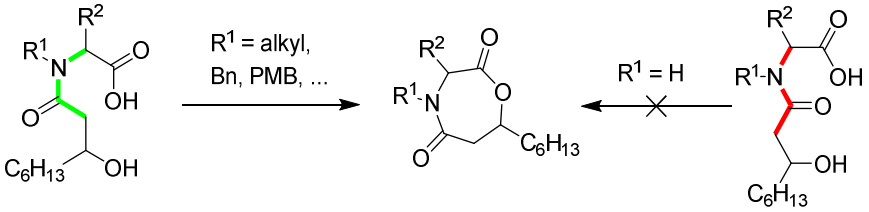
Graphical abstract



Abstract

Several natural products containing a 1,4-oxazepane-2,5-dione-core are known. One example is serratin, isolated from *Serratia marcescens*. Due to 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 towards medium-sized heterocycles cannot be applied. As *N*-acyl amino acids without a third substituent at nitrogen failed to undergo ring-closure, several *N*-protecting groups were evaluated. With the use of the removable PMB-group, a *N*-unsubstituted 1,4-oxazepane-2,5-dione was synthesized. Via the application of pseudo-prolines, *i.e.* serine-derived oxazolidines as another type of protecting group, a compound with the presumed structure of the natural product serratin was obtained. Due to 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 forms a synthetic challenge. A head-to-tail cyclization often fails to yield the desired seven- or eight-membered heterocycles due to a combination of energy and entropy terms. The energy term represents the increase in ring strain and unfavorable interactions needed to overcome when the open chain form approaches the ring-shaped transition state. The entropy term is linked with the probability of the two chain terminals coming close enough to

interact.[1] The resistance towards cyclization is even more profound 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 a high 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 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, 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 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 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]

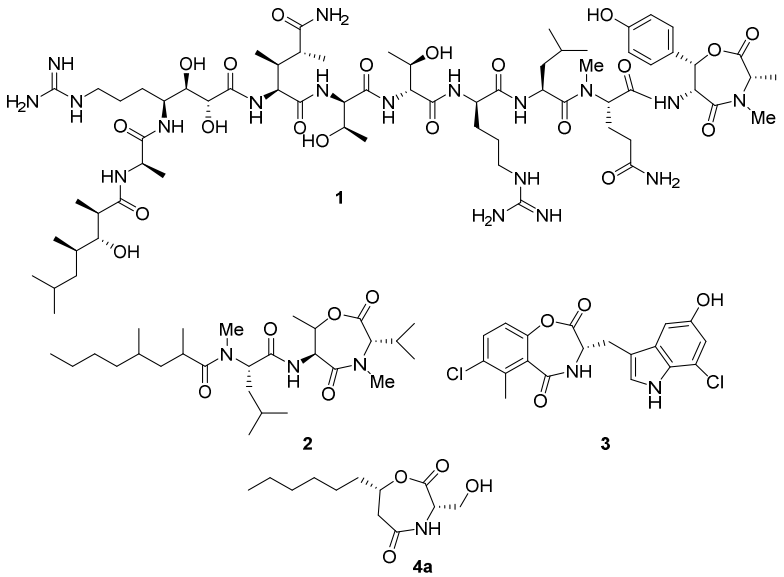


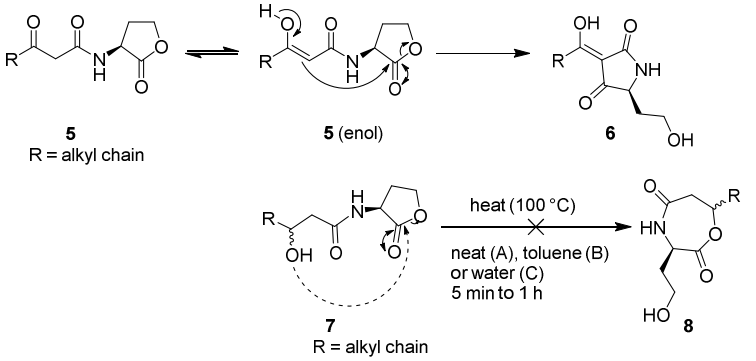
Figure 1: 1,4-Oxazepane-2,5-dione core-containing natural products **1**,[8] **2**,[9] **3**,[10] and **4a**.[11]

Due to 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 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 on the synthesis of the natural product serratin (**4a**).

Results and discussion

Our synthetic efforts were focused in the first instance 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. For *N*-3-oxoacyl-L-homoserine lactones **5**, 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 compouds **6** possess interesting biological properties such as iron chelation and antimicrobial effects.[15] Another type of QS signal molecules, *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). While heating a medium containing the autoinducer **5a** of *A. fischeri* at 100 °C for 5 minutes did not have an effect on the bioluminescence inducing activity of this quorum sensing 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 due to ring-opening.

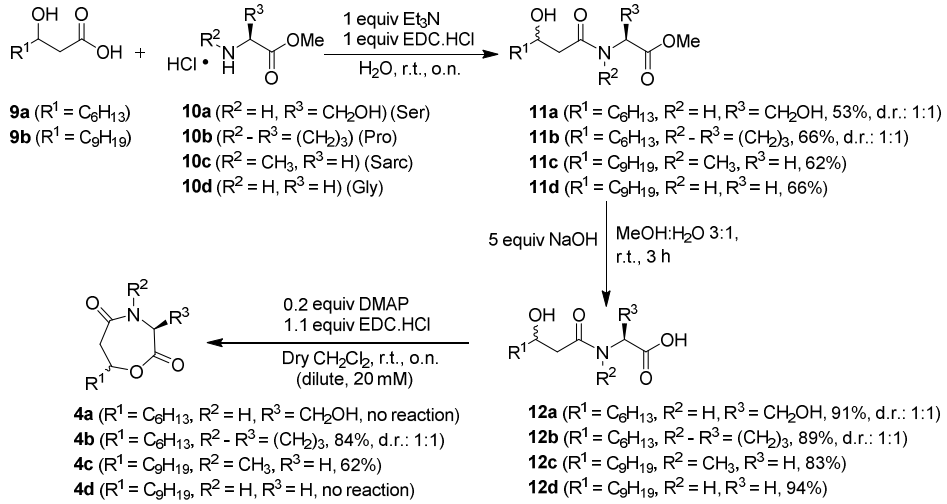


Scheme 1: Described rearrangement of *N*-(3-oxoacyl)-L-homoserine lactones **5** to tetramic acids **6**,[15] and the attempted rearrangement of another type of QS signal molecules, *N*-(3-hydroxyacyl)-L-homoserine lactones **7**, to 1,4-oxazepane-2,5-diones **8**.

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 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, and form the more stable five-membered lactone ring, yielding once again starting material **7b**.

As the lipoamino acid *N*-(3-hydroxydecanoyl)-L-serine, or serratamic acid, has 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**). This compound **12a** was synthesized via a 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC)-mediated coupling reaction of β-hydroxynonanoic acid **9a** with 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 overnight in acetic anhydride also failed to yield any of the desired ring-closed product **4a**.[20]



9a ($R^1 = C_6H_{13}$)
9b ($R^1 = C_9H_{19}$)

10a (R^2 = H, $R^3 = CH_2OH$) (Ser)
10b (R^2 - $R^3 = (CH_2)_3$) (Pro)
10c ($R^2 = CH_3$, R^3 = H) (Sarc)
10d (R^2 = H, R^3 = H) (Gly)

11a ($R^1 = C_6H_{13}$, R^2 = H, $R^3 = CH_2OH$, 53%, d.r.: 1:1)
11b ($R^1 = C_6H_{13}$, R^2 - $R^3 = (CH_2)_3$, 66%, d.r.: 1:1)
11c ($R^1 = C_9H_{19}$, $R^2 = CH_3$, R^3 = H, 62%)
11d ($R^1 = C_9H_{19}$, R^2 = H, R^3 = H, 66%)

12a ($R^1 = C_6H_{13}$, R^2 = H, $R^3 = CH_2OH$, 91%, d.r.: 1:1)
12b ($R^1 = C_6H_{13}$, R^2 - $R^3 = (CH_2)_3$, 89%, d.r.: 1:1)
12c ($R^1 = C_9H_{19}$, $R^2 = CH_3$, R^3 = H, 83%)
12d ($R^1 = C_9H_{19}$, R^2 = H, R^3 = H, 94%)

4a ($R^1 = C_6H_{13}$, R^2 = H, $R^3 = CH_2OH$, no reaction)
4b ($R^1 = C_6H_{13}$, R^2 - $R^3 = (CH_2)_3$, 84%, d.r.: 1:1)
4c ($R^1 = C_9H_{19}$, $R^2 = CH_3$, R^3 = H, 62%)
4d ($R^1 = C_9H_{19}$, R^2 = H, R^3 = H, no reaction)

Scheme 2: Synthesis of *N*-(3-hydroxyacyl) amino acids **12a-d** and ring closure towards 1,4-oxazepane-2,5-diones **4a-d**.

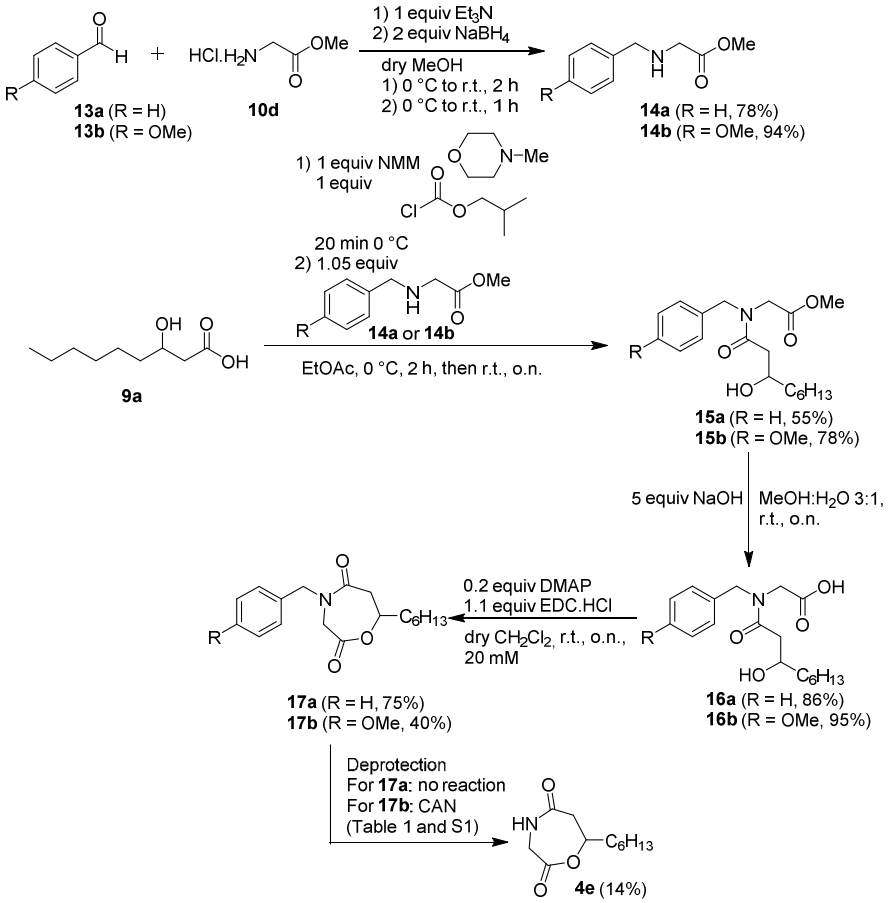
The apparent lack of cyclization of the serine derivative **12a** (Scheme 2), can be explained by the fact that the amide bond strongly prefers a *trans*-conformation, while for the desired cyclization to occur, a *cis*-amide bond is needed. 2D NOESY analysis of methyl ester **11a** revealed that indeed only the *trans*-conformer was present (SI, Figure S1).[21] In the case of larger heterocycles, such as fourteen-membered rings, *trans*- amides can be included and 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 reevaluated (Scheme 2).[20] To our delight, bicyclic structure **4b** was formed in all the cyclization conditions tested.

To evaluate 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 observed in ^1H and ^{13}C NMR ($CDCl_3$, SI Figure S2-A and S3-A).[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 62% yield. In the ^1H and ^{13}C NMR spectrum, no different isomers were observed ($CDCl_3$, SI Figure S2-B and S3-B), 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 high difficulty, a spontaneous, non-enzymatical rearrangement can be excluded for the origin of serratin (**4a**).

From the abovementioned 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 nitrogen should be a removable one. Due to the lability of the desired lactone, many protecting groups, which 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]



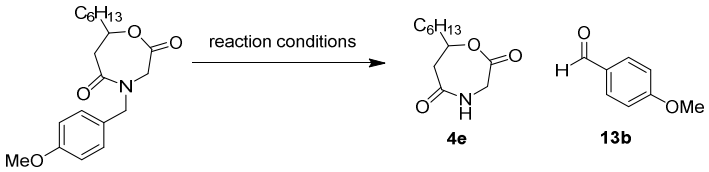
Scheme 3: Synthesis of *N*-benzyl and *N*-PMB-protected seven-membered lactones **17a** and **17b** and CAN-mediated deprotection of **17b** to **4e**.

As the synthesis of the *N*-benzyl-protected seven-membered core-containing compound **17a** was successful, while 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-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]

Table 1: Reaction conditions evaluated to remove the PMB-protecting group of **17b**.[28]



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	$BF_3.OEt_2$, r.t., o.n.	-[d]
11	$BF_3.OEt_2$, 128 °C, 6 h	-[e]

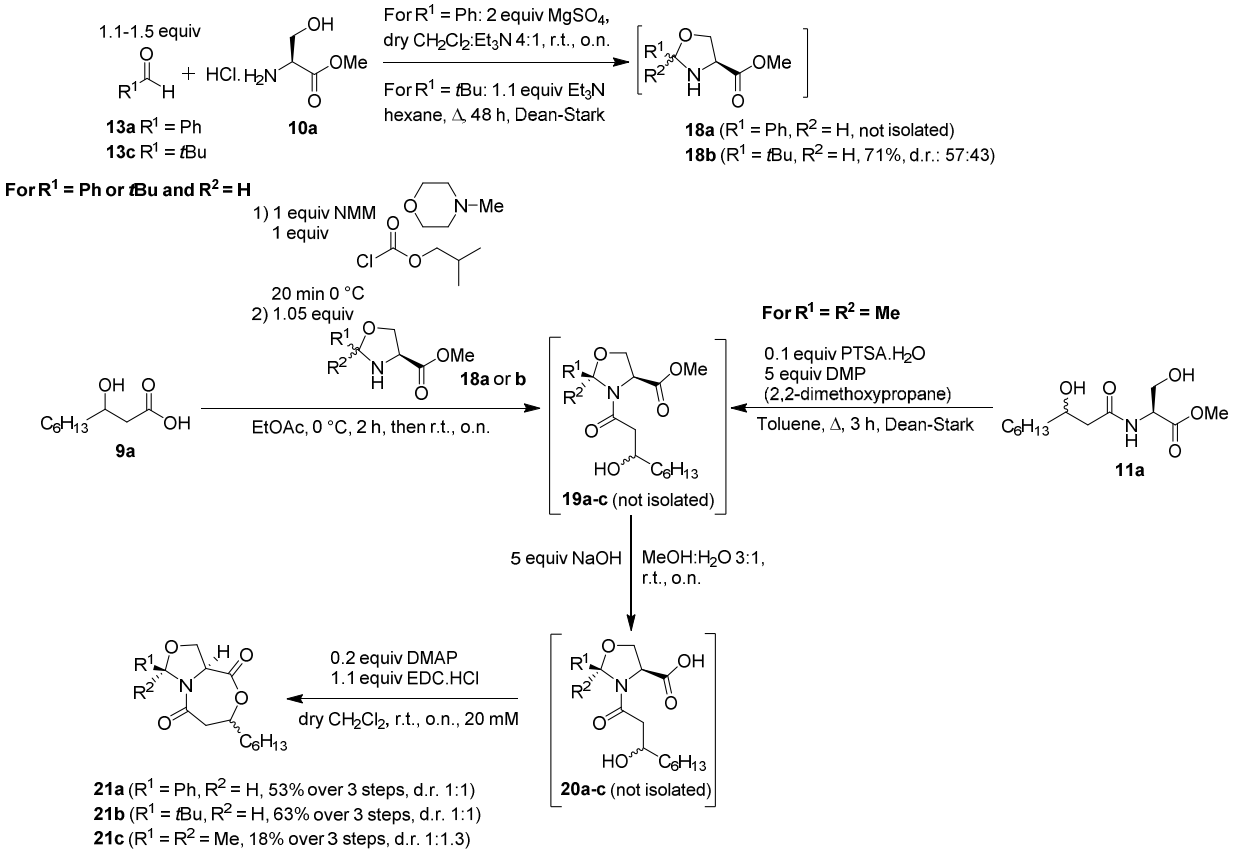
[a] Solvolysis of **17b**. [b] Quantitative data were obtained after extraction of the reaction mixture with ethyl acetate, followed by a washing step with an aqueous saturated sodium bicarbonate solution to remove ring-opened degradation products. The crude yield of the different products was determined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

As the deprotection with 5 equivalents 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. Firstly, the reaction time is too short to allow complete conversion, which is obvious from the recovery of the *N*-PMB-protected lactone **17b**. Secondly, when the product **4e** is formed, lactonolysis can occur by the water present as co-solvent, which is needed for the deprotection. This lactonolysis can also open the starting material **17b**, but this route seems to be slower. Thirdly, reactions with CAN often give rise to a laborious work-up due to the difficult separation of the turbid aquatic 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**), differing only from lactone **4e** 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 post-cyclization modification step, but the introduction of a hydroxymethyl group via reaction of *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 pseudo-prolines (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 alkaline environment and isolated as such. Pseudo-prolines 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 71% yield.[32]



Scheme 4: Synthesis of oxazolidine-containing bicyclic structures **21a-c**.

Several procedures were evaluated for the *N*-acylation of compound **18b** (SI, Table S2). 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 to 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 bicyclic structure **21b** (Scheme 4).

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, while 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.

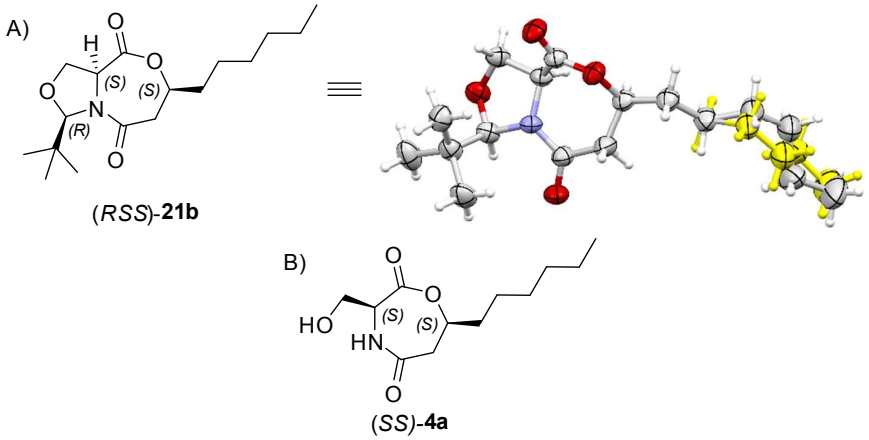


Figure 2: A) Molecular structure of *(RSS)*-**21b**, showing thermal displacement ellipsoid, drawn at the 30% probability level. The positional disorder of the C_6H_{13} alkyl chain is shown in yellow. B) Stereochemistry of serratin (*SS*)-**4a** based upon comparison with theoretical calculations of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

Both diastereomers showed quite different chemical shifts. The crystalline diastereomer (*RSS*)-**21b**, with both substituents in a *cis*-relationship and the *RSS*-stereochemistry showed a signal for *C*H-O at 75.2 ppm ($CDCl_3$) in the ^{13}C NMR spectrum and the attached hydrogen atom C*H*-O showed a multiplet at 4.71-4.83 ppm ($CDCl_3$) in the ^1H NMR spectrum. For the other diastereomer (*RRS*)-**21b**, with a *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 diastereomer (*RSS*)-**21b** the corresponding signals were a dd at 2.85 ppm ($CDCl_3$) and a dd at 2.97 ppm ($CDCl_3$), while for the other diastereomer (*RRS*)-**21b** a d at 2.72 ppm ($CDCl_3$) and a dd at 3.14 ppm ($CDCl_3$) were observed. 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 *C*H-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, it was 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 post-insertion 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

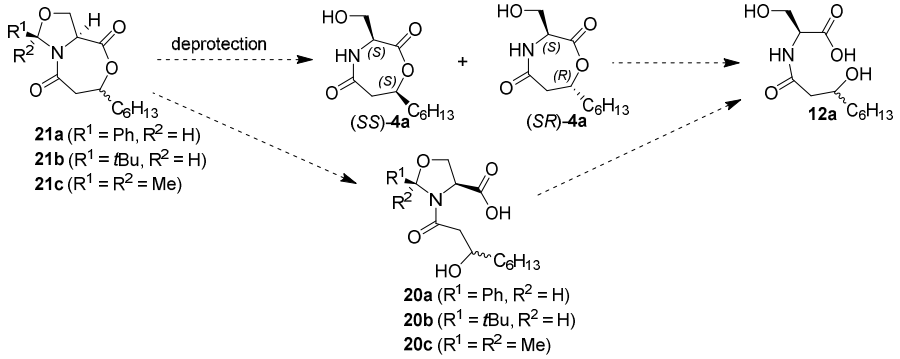
revealed that this compound, obtained after column chromatography, was less pure than the crude compound after work-up due to degradation during purification, it was decided to proceed with the reaction sequence without further purification. Hydrolysis of compound **19c** with NaOH in a water:methanol (ratio 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 *C*H-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 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** got 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, unlike the deprotected compound **4a**, hydrolysis probably preceded deprotection. 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 C). In an alternative procedure, mild acidic conditions for deprotection were evaluated by employing formic acid in a THF:H_2O-mixture (Table 2, entries 3A and B).[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**: while the starting compound had a d.r. of 1:1, an alteration to 1:2.7 was found in the recovered starting material. Treatment with an acidic resin also failed to deliver the desired compound (Table 2, entries 4A and B).[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 ^{1}H 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 4M 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 case of the *t*Bu-compound **21b**, the *cis*-diastereomer (*RSS*)-**21b** got deprotected faster while 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, entry 6A and B). 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-phenyloxazolidine compared to the *cis*-isomers. Once again, no deprotected serratin (**4a**) could be isolated.

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]



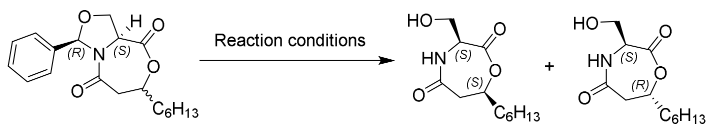
Entry	Reaction conditions	Oxazolidine derivative	Result[a]
1A	0.1 equiv $BiBr_3$, MeCN, r.t., 1 h to o.n.	Ph	-[b]
1B	Idem	*t*Bu	-[b]
1C	Idem	DiMe	-[b]
2A	1 equiv $BiBr_3$, cat. H_2O, MeCN, r.t., 1 h to 48 h	Ph	Conversion of *trans*-diastereomer (*RRS*)-**21a** to **12a**. No isolation of (*SR*)-**4a**. 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 h 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 h 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	4M HCl in dioxane, 0 °C to r.t., 1 h 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 h 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 work-up. [b] No reaction. [c] Deprotection and ring-opening or ring-opening and deprotection. Only recovery of **12a**.

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

Table 3: Reaction conditions evaluated for the hydrogenolytic removal of the 2-phenyloxazolidine moiety of **21a**



21a (d.r.: 1:1) (*SS*)-**4a** (*SR*)-**4a**

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 dia-stereomer, 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.

The (*RSS*)-diastereomer that was deprotected, however, had the correct stereochemistry to deliver serratin (*SS*)-**4a**. In the ^{1}H NMR spectrum ($CDCl_3$), a signal for NH became visible, consistent with successful deprotection. Also the *C*H-O-signal at 73.7 ppm ($CDCl_3$) was 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. Also a big difference for the adjacent CH_2 was apparent: while Luna *et al.* reported two dd at 2.42 and 2.62 ppm ($CDCl_3$), 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 (^{1}H NMR, CD_3OD), the *C*H-O signal at 73.2 ppm (^{13}C NMR, CD_3OD) and the adjacent CH_2 at 2.39 and 2.72 ppm (^{1}H NMR, CD_3OD).[12b] That the actual structure of serratin (**4a**) could be a serratamolide analogue is also hinted by the observed

vicinal coupling constants of the O-CHCH_2C(=O) moiety. While for the compound synthesized in this study vicinal coupling constants of 11.3 Hz 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 Hz 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 Hz 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 two times 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).

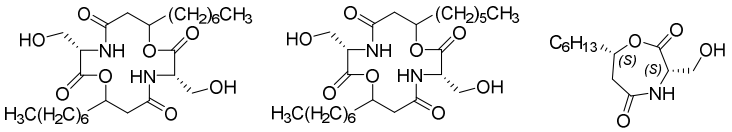


Figure 3: Structure of secondary metabolites Serratamolide A (**22a**), Serratamolide F (**22b**)[12b] and serratin (**4a**)[11] produced by *Serratia* sp.

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 pseudo-proline group was used as a protecting group. Several pseudo-prolines 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. ^{1}H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Bruker Avance III Nano-bay 400 at room temperature. IR spectra were recorded in neat form with a Perkin-Elmer 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 CuKα (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 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 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. Drying over $MgSO_4$, followed by filtration and evaporation of the solvent *in vacuo* gave 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), dissolved in a minimal amount of ethyl acetate, was added at the same temperature and 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. 5 Equiv of NaOH, as a 2M aqueous solution, were added to the methyl ester dissolved in methanol (ratio MeOH:H_2O 3:1). The reaction mixture was left to stir at room temperature for 3 h to overnight, followed by an extraction step with hexane. The aqueous phase was acidified with 2M aqueous HCl and extracted three times with ethyl acetate. After washing with brine, followed by drying ($MgSO_4$) and removal of the drying agent 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. Drying 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). Colorless powder. Melting point: 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. Colorless powder. Melting point: 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. 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 x s), 3.766, 3.772 (0.5H, 2 x 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. Colorless powder. Melting point: 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.

(9a*S*)-3-Hexylhexahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]oxazepine-1,5-dione 4b. This compound was synthesized by 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. Colorless powder. Melting point: 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.

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. Colorless powder. Melting point: 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. Colorless powder. Melting point: 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. Colorless powder. Melting point: 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. Colorless powder. Melting point: 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**. Colorless powder. Melting point: 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. 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. Colorless powder. Melting point 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. Colorless powder. Melting point 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: 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. 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 95% yield. Spectral data were obtained from a mixture of two rotamers in a 2.3:1 ratio. Colorless powder. Melting point: 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. Colorless powder. Melting point: 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. Drying with $MgSO_4$, 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. Colorless powder. Melting point: 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 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**.

(3*R*,7*R*,9a*S*)-3-(*t*Butyl)-7-hexyltetrahydro-3*H*,5*H*,9*H*-oxazolo[4,3-*c*][1,4]oxazepine-5,9-dione (*RRS*)-21b (*trans*-diastereomer). Colorless powder. Melting point: 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.

(3*R*,7*S*,9a*S*)-3-(*t*Butyl)-7-hexyltetrahydro-3*H*,5*H*,9*H*-oxazolo[4,3-*c*][1,4]oxazepine-5,9-dione (*RSS*)-21b (*cis*-diastereomer). Colorless needle-like crystals. Melting point: 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 cooling down, water (20 mL) was added. The aqueous phase was extracted twice with ethyl acetate (2 x 20 mL), the organic phases were combined and washed with brine (20 mL), 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 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.

(9a*S*)-7-Hexyl-3,3-dimethyltetrahydro-3*H*,5*H*,9*H*-oxazolo[4,3-*c*][1,4]oxazepine-5,9-dione 21c. White powder. Melting point: 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).

(3*R*,9a*S*)-7-Hexyl-3-phenyltetrahydro-3*H*,5*H*,9*H*-oxazolo[4,3-*c*][1,4]oxazepine-5,9-dione 21a. Colorless powder. Melting point: 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 a H_2 atmosphere at room temperature for 6 h. Subsequently, the reaction mixture was filtered through celite and the solvent 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).

(3*S*,7*S*)-7-Hexyl-3-(hydroxymethyl)-1,4-oxazepane-2,5-dione (*SS*)**-4a** Colorless powder. Melting point: 81-83 °C. Yield: 22%. R_f = 0.08 (ethyl acetate:petroleum ether 1:1). ^1H 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.

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X-ray data of compound (*RSS)*-**21b** (CIF)
2D NOESY spectrum of **11a**.
Zoom-in of the ^1H and ^{13}C NMR spectra of compound **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 ^1H NMR spectra of 2-phenyloxazolidine protected compound **21a** and compound **21a** recovered after treatment with 5% TFA and treatment with H_2 gas and $Pd(OH)_2/C$.
Spectral data of Serratamolide A (**22a**).
Crystal data for compound (*RSS*)-**21b**.
Copies of ^1H NMR and ^{13}C NMR spectra of compounds **4a-c**, **4e**, **11a-d**, **12a-d**, **15a-b**, **16a-b**, **17a-b** and **21a-c**.

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