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Total synthesis and structural validation of cyclodepsipeptides solonamide A and B

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ABSTRACT

Microorganisms are an attractive source of new natural products with antimicrobial properties, and the marine environment constitutes a prolific resource of bioactive microorganisms. During a global research expedition (Galathea III), two depsipeptides, solonamide A and solonamide B, were isolated from the marine bacterium *Photobacterium halotolerance* and were found to inhibit virulence gene expression in the serious human pathogen, *Staphylococcus aureus*. They act by interfering with the *agr* quorum sensing system and show resemblance to the endogenous *S. aureus* quorum sensing peptide, autoinducing peptide I (AIP-I). To enable more comprehensive studies, we embarked on the chemical synthesis of solonamides A and B. The key synthetic steps were formation of the (*R*)-β-hydroxy-fatty-acids by stereo-selective aldol reactions and a cyclative macrolactamization, which proceeded under highly dilute conditions. Thus, the first total syntheses of the solonamides corroborated the originally assigned structures, and by changing the stereochemistry of the auxiliary in the aldol steps we gained access to the natural products as well as their β^3-epimers.

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1. Introduction

The Gram-positive bacterium *Staphylococcus aureus* is a major human pathogen worldwide, being the leading cause of a variety of infections, such as pneumonia, bacteremia, and endocarditis.[1–5] The pathogenicity of *S. aureus* is largely attributed to its ability to produce a variety of toxins and virulence factors, including those believed to induce immune responses and spread within the body.[6–8] In many cases, infections can be treated successfully using conventional antibiotics, however, strains with resistance to known antibiotics have emerged.[9] Therefore, development of new therapeutic approaches that suppress *S. aureus* pathogenicity through mechanisms that are non-bactericidal, like anti-virulence approaches, could provide new options for treating infections caused by resistant strains.[10,11] A promising example of such an approach is targeting of quorum sensing (QS) pathways.[12–14] Quorum sensing inhibitors (QSI) are not intended to kill or inhibit the growth of a pathogen, but rather target the expression or the activity of virulence factors,[10,15–17] which have been speculated to circumvent resistance development if non-essential to the microbe. In a recent search for compounds that reduce virulence gene expression in *S. aureus*, two promising depsipeptides, solonamides A and B, were discovered (Fig. 1).[18] Both of these macrocycles were shown to inhibit virulence of *S. aureus* by interfering with the *agr* quorum sensing system,[19] and access to these compounds through total synthesis was therefore desirable. In this present study, we report the first total syntheses of the solonamides, which confirm the initial structural assignment of both natural product cyclodepsipeptides.

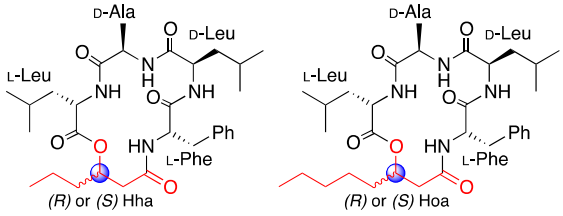

Fig. 1. Structures of target compounds.

2. Results and discussion

The solonamides were proposed to be macrocyclic depsipeptides containing four D- or L-amino acids and a β-hydroxy acid, the

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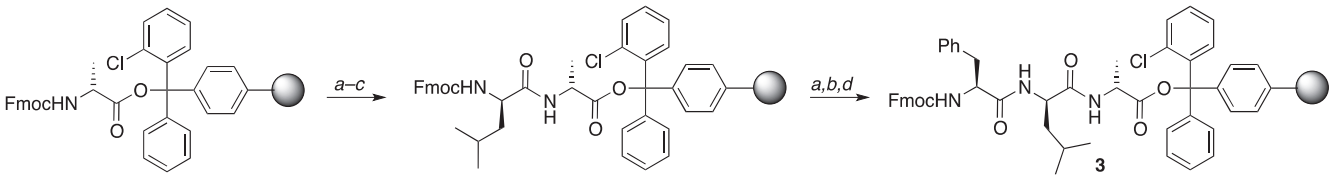
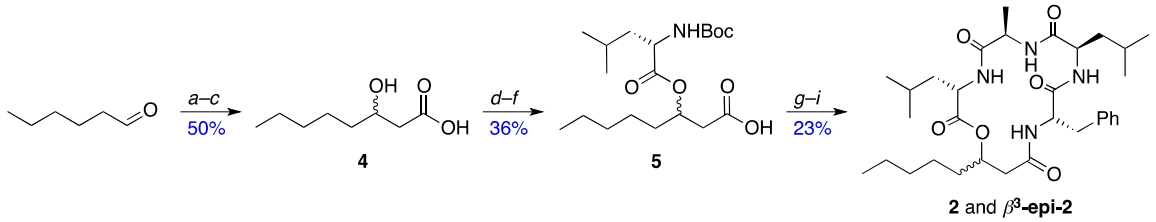
only difference between the two natural products being the length of the hydrocarbon side chain in the β-hydroxy acid moiety (Fig. 1).

We decided to first prepare a pair of diastereomeric macrocycles using commercially available α-amino acids and a racemic β-hydroxy acid with the hydrocarbon length of solonamide B. This would allow us to address the stereochemical assignment of the α-amino acids as well as the disconnection/cyclization point in the macrocycle.



Scheme 1. Solid-phase synthesis of peptide **3**. *Reagents and conditions*: (a) piperidine–DMF (1:4); (b) DBU–piperidine–DMF (2:2:96); (c) Fmoc-D-Leu-OH (3 equiv), HATU (2.95 equiv), 2,6-lutidine (6 equiv), DMF; (d) Fmoc-L-Phe-OH (3 equiv), HATU (2.95 equiv), 2,6-lutidine (6 equiv), DMF.



Scheme 2. Synthesis of diastereomeric mixture of solonamide B and β^3-*epi*-solonamide B. *Reagents and conditions*: (a) $SnCl_2$ (0.1 equiv), ethyl diazoacetate (1 equiv), CH_2Cl_2; (b) Bu_4NBH_4 (8 equiv), AcOH, MeOH; (c) LiOH (1.5 equiv, 1 M in H_2O), THF; (d) BnBr (1.1 equiv), $CsCO_3$ (0.6 equiv), DMF; (e) Boc-L-Leu-OH (1.2 equiv), DIC (2 equiv), DMAP (0.1 equiv), CH_2Cl_2; (f) Pd/C (0.1%/w/w, 0.1 equiv), H_2 (1 atm), EtOH; (g) C-terminally 2-chlorotrityl-resin-bound H-L-Phe-D-Leu-D-Ala (**3**), HATU (2 equiv), ^{i}Pr$_2$EtN (4 equiv), DMF; (h) TFA–CH_2Cl_2 (1:1); (i) HATU (2 equiv), ^{i}Pr$_2$EtN (4 equiv), DMF (0.5 mM), room temperature, 16 h.

Our strategy for this initial synthesis was thus based on assembly of two building blocks; resin-bound tripeptide H-L-Phe-D-Leu-D-Ala-OH (**3**; Scheme 1) prepared on a 2-chlorotrityl linker by standard Fmoc chemistry and a dimer (**5**) containing the ester ('depsi') bond, which was obtained by coupling of Boc-L-leucine and (±)-β-hydroxyoctanoic acid (Hoa; **4**) (Scheme 2). Incorporation of the ester bond in the building block rather than having to rely on a macrolactonization in the final cyclization step was chosen as this has been shown to be difficult and low yielding in similar syntheses.[20] An efficient three-step route afforded the racemic β-hydroxyoctanoic acid from hexanal and ethyl diazoacetate, first giving ethyl β-ketooctanoate under conditions reported by Holmquist and Roskamp.[21] An initial yield of 47% in this step was improved to 90% by using excess of hexanal. Next, the ketone was reduced using excess Bu_4NBH_4 to give the ethyl β-hydroxy-octanoate in 80% yield, whereas alternative reducing agents $NaBH_4$, $LiBH_4$ or $NaBH(OAc)_3$ proved inefficient for this transformation. Finally, hydrolysis of the ethylester gave the desired acid **4** in good overall yield. The carboxylate was then benzyl protected selectively and Boc-L-leucine was coupled to the hydroxy group followed by catalytic hydrogenation to give building block **5** in 36% overall yield for three steps. Coupling of **5** to resin **3** afforded a resin-bound pentamer, which upon cleavage and direct macrocyclization under dilute conditions using HATU as the coupling reagent[22–26] gave a mixture of **2** and diastereoisomer β^3-***epi*-2** (Scheme 2). The crude mixture of compounds was subjected to preparative reversed-phase HPLC applying multiple injections due to the poor solubility of these 'lipo'-depsipeptides.[27] We succeeded in isolating two macrocyclic depsipeptides, which upon characterization by NMR and HRMS as well as comparison with a ^{1}H NMR spectrum of authentic solonamide B proved to be compound **2** and the diastereoisomer β^3-***epi*-2** (Fig. 2). Synthetic solonamide B (**2**) was obtained in 13% yield (from resin **3**) and its epimer in 10%, which was found to be a satisfactory yield for coupling and macrolactamization. The complete overlap observed between the natural product (blue spectrum) and one of the synthetic isomers (black spectrum) show that the original stereochemical assignment of all α-amino acids were correct. Thus, after validation of the stereochemistry of the α-amino acids, the stereochemical identity of the β-hydroxy acid also needed validation through chemical synthesis.

To achieve stereoselective total syntheses, we therefore prepared the hydroxy acids by aldol reactions using chiral auxiliaries (Scheme 3). We decided to obtain both enantiomers of both hydroxy acids, and thus first prepared the *tert*-butylglycine-derived Evans' auxiliary, (*S*)-4-(*tert*-butyl)oxazolidin-2-one.[28] However, this did not give rise to satisfactory diastereoselectivity in our hands. Next, (*R*)- and (*S*)-4-benzylthiazolidine-2-thione were used as auxiliaries in aldol reactions with butanal or hexanal (Scheme 3A and B). Commercially available (*S*)-4-benzylthiazolidine-2-thione (**6**) was acetylated to give **7**, which furnished the aldol adducts **8** and **9** in diastereoselectivities of 6:1–3:1 (Scheme 3A). Removal of the auxiliary by hydrolysis afforded β-hydroxy acids (***S*)-10** and (***S*)-11**, for which the stereochemistry was confirmed by comparison of specific optical rotations to literature values. The (*R*)-4-benzylthiazolidine-2-thione auxiliary was prepared from D-phenylalanine by reduction to **12** (D-phenylalaninol), which was then refluxed in the presence of CS_2 under basic aqueous conditions to give (*R*)-4-benzylthiazolidine-2-thione in good yield. Acetylation to give compound **13** was followed by aldol reactions with butanal or hexanal and cleavage of the auxiliary by hydrolysis as described vide supra (Scheme 3B). The stereochemistry of β-hydroxy acids (***R*)-10** and (***R*)-11** were also validated by comparison of optical rotation to literature values, showing that the acids had the expected configurations.

During purification of the aldol adducts by column chromatography, partial hydrolysis was observed presumably due to the slight acidity of the silica. This resulted in somewhat lowered yields and purification difficulties due to co-elution of free auxiliary; however, subsequent hydrolysis and purification afforded the pure β-hydroxy acids.

With the β-hydroxy acids in hand, we prepared dimeric building blocks **18** and **19** for synthesis of the natural products and building

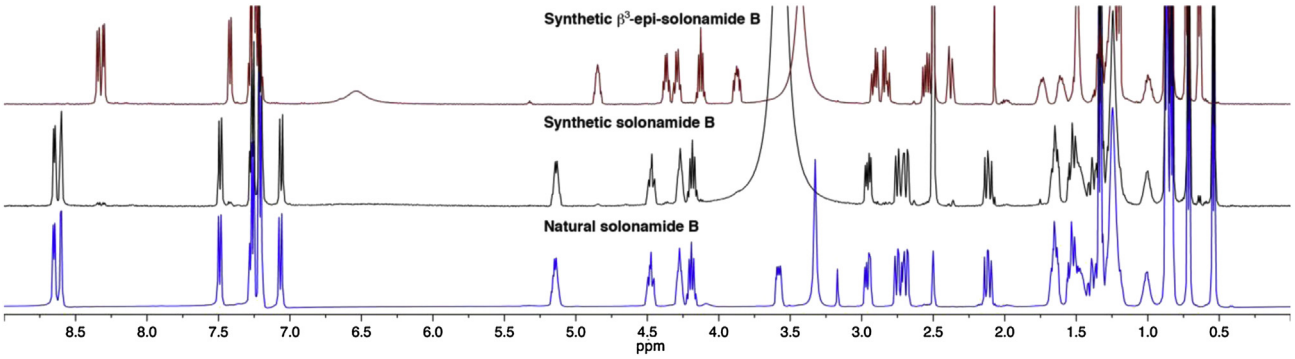
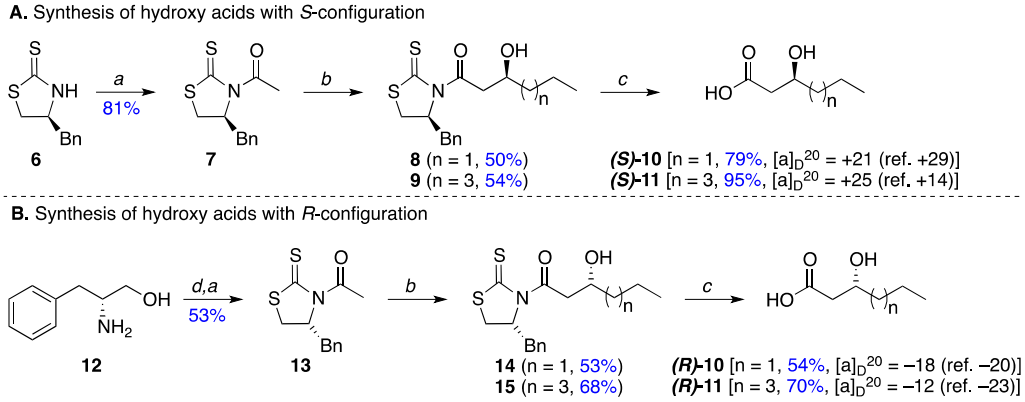


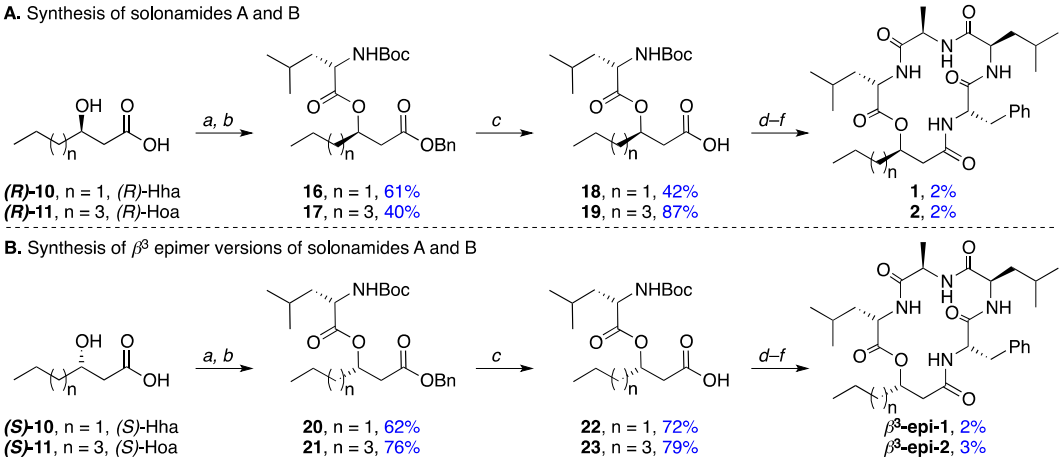
Fig. 2. Overlays of NMR spectra of synthetic materials with that of the natural solonamide B isolated from cell culture. Synthetic solonamide B from this experiment contains ~4% of β^3-*epi*-solonamide B. Solonmaide B and all additional compounds obtained from the stereoselective syntheses below were purified to >98% HPLC and NMR purity.



Scheme 3. Stereoselective synthesis of hydroxy acids Hha (**10**) and Hoa (**11**). *Reagents and conditions*: (a) AcCl (1.5 equiv), DMAP (0.1 equiv), NEt_3 (1.5 equiv), CH_2Cl_2; (b) butanal or hexanal (1 equiv), $TiCl_4$ (1.8 equiv), ^{i}PrEtN (1.8 equiv), CH_2Cl_2; (c) LiOH (4 equiv, 1 M, H_2O), THF; (d) $NaBH_4$ (2.3 equiv), I_2 (1 equiv), CH_2Cl_2; (e) CS_2 (5 equiv), KOH (5 M).

blocks **22** and **23** for synthesis of the corresponding β^3-epimers. Three-step sequences afforded the dimer building blocks containing Boc-protected amines to enable concomitant N-terminal deprotection during cleavage of linear pentamers from the resin in the later stage of syntheses. Thus, benzylester protection, coupling of Boc-L-Leu-OH, and hydrogenation furnished the desired four dimers in good yields (Scheme 4).

Coupling of each to the resin-bound tripeptide (**3**) followed by cleavage/deprotection and macrolactamization of the crude linear precursors afforded **1** and **2** (Scheme 4A) as well as β^3-***epi*-1** and β^3-***epi*-2** (Scheme 4B). Spectral data of **1** and **2** were in complete agreement with those originally reported for the solonamides isolated from natural sources, thus unequivocally validating the original assignment of the structures of solonamides A and B.



Scheme 4. Synthesis of solonamides A and B as well as their β^3-epimers using enantiomerically pure β-hydroxy acids. *Reagents and conditions*: (a) BnBr (1.1 equiv), $CsCO_3$ (0.6 equiv), DMF; (b) Boc-L-Leu-OH (1.2 equiv), DIC (2 equiv), DMAP (0.1 equiv), CH_2Cl_2; (c) Pd/C (10% w/w), H_2 (1 atm), EtOH; (d) resin-bound H-L-Phe-D-Leu-D-Ala-OH (**3**), HATU (2 equiv), ^{i}PrEtN (4 equiv), DMF; (e) TFA–CH_2Cl_2, 1:1; (f) HATU (2 equiv), ^{i}PrEtN (4 equiv), DMF (0.1 mM).

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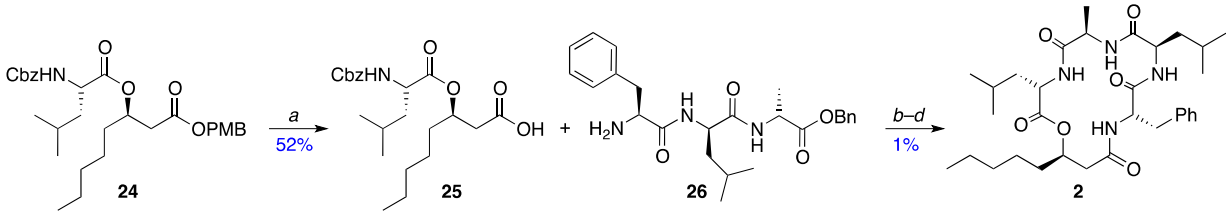
Furthermore, synthetic material for further biological testing was obtained. However, although the cyclizations proceeded with full conversion of linear precursors according to LC–MS analyses, the isolated yields were relatively low. Since the identity of linear resin-bound trimer (**3**), which was a common intermediate, had been checked, we saw only three possible explanations, or a combination thereof, for the low yields achieved. Although the linear peptides were fully converted during macrocyclization, unindentified byproducts were present in the crude pointing to difficulties during the preceding dimer coupling or side reactions during cleavage. The final reason for the low isolated yields could be incompatibility of ***epi*-2**). This was surprising as the carboxylic acid and not the hydroxy group was activated in the coupling to give the dimer building block. Thus, to test if the epimerization had occurred during protecting group manipulation in the dimer (**25**) synthesis, we coupled the β-hydroxy acid directly on to the resin (**3**) followed by coupling of Boc-L-leucine. Unfortunately, a test cleavage of this linear pentamer also revealed 4 compounds with the same mass, which was puzzling since cleavage of the tripeptide precursor only showed one peak in the LC-MS. Applying the follow-up solution-phase synthesis approach, we were unfortunately not able to improve the overall yields of macrocyclic peptides.



Scheme 5. Alternative solution-phase synthesis of solonamide B (**2**). *Reagents and conditions*: (a) TFA–CH_2Cl_2 (1:1), Et_3SiH (10 equiv); (b) PyBOP (1.2 equiv), ^{i}PrEtN (1.2 equiv), DMF; (c) Pd/C (0.1% w/w, 0.1 equiv), H_2 (1 atm), EtOH; (d) HATU (2 equiv), *i*PrEtN (4 equiv), DMF.

highly lipophilic compounds with aqueous reversed-phase purification, and the macrocycles in this study were poorly soluble in both water and acetonitrile. In general, we were able to recover more material when attempting purification by column chromatography, however, this did not provide the final compounds in satisfying purity for biological testing, and thus HPLC purification was applied despite potential loss of material. In the future, we therefore envision that purification by normal-phase preparative HPLC may enable improved isolated yields of these compounds.

Nevertheless, we also decided to address the possible inefficiencies in the synthetic approach discussed above, and hence devised an alternative solution-phase strategy. This would circumvent cleavage issues and reveal putative problems with the peptide coupling applied to assemble the linear pentamer. Thus, a tripeptide (**26**) was prepared in solution and dimer (**25**) was synthesized from (***R*)-11** applying a different protecting group strategy than described above. The hydroxy acid was first PMB-protected, then coupled to Cbz-L-Leu-OH, finally deprotected under acidic conditions to afford dimer **23** in 52% yield. A selection of coupling reagents (i.e., DIC, EDC, HATU, and PyBOP) was tested for condensation of **25** and **26**, and PyBOP gave the best purity (Scheme 5). Unfortunately, purification at this stage proved to be difficult as well, since column chromatography provided the linear pentamer in impure form after attempts with several eluent systems. Therefore we chose to continue with the crude pentamer and hydrogenation proceeded smoothly to give the linear precursor ready for macrocyclization. It was decided to perform this important step using two different strategies; (*A*) by slow addition of the linear peptide to a solution of Hünig's base and HATU using a syringe pump as described by Ganesan and co-workers for similar macrocyles;[29] and (*B*) by using dilute conditions (0.5–1 mM) as described above. LC–MS analyses of the two reaction mixtures did not show significant difference between the cyclizations and no oligomerization/dimerization were observed. However, upon purification using preparative reversed-phase HPLC, four peaks were isolated and analyzed, proving to be compounds **2** and **β^3-*epi*-2** along with two additional isomers with the same mass as solonamide B and similar proton NMR spectra. This indicated that the compound had epimerized in two positions leading to four diastereoisomers, two of which could be identified as **2** and its homologue epimerized at the –*CH*OCO– chiral center in the (*R*)-β-hydroxy acid residue (**β^3-**

Finally, the biological activity of our synthetic solonamide A and B was verified and compared to the samples obtained by isolation from culture. An agar diffusion assay was conducted[18] that monitored the expression of the *S. aureus* virulence genes *hla* (encoding α-hemolysin) and *spa* (encoding Protein A) for both synthetic and natural solonamides along with linear solonamide B as negative control. Correlating with *agr* inhibition, we observed an increased expression of *spa* and decreased expression of *hla* with the same potency for the synthetic and natural solonamides, thus verifying that the synthetic solonamides retain biological activity (Fig. 3).

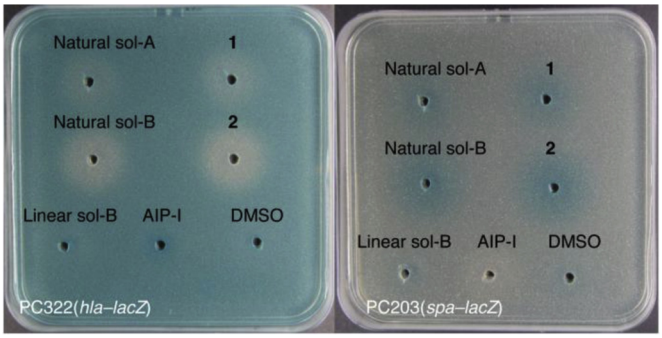


Fig. 3. Biological validation of the synthetic material compared with the natural isolates. Agar plates containing the *hla-lacZ* (PC322) or *spa-lacZ* (PC203) reporter strains from *S. aureus* were subjected to DMSO (20 μL) containing the noted compound (0.5 mg/mL). Vehicle (DMSO), linear solonamide B, and autoinducing peptide I (AIP-I) were applied as controls.

3. Conclusion

In summary, we report the first total syntheses of macrocyclic depsipeptide marine natural products solonamides A and B, which validate the original structural assignments unequivocally. Our synthetic efforts furthermore enabled preparation of unnatural synthetic analogues, which were epimerized at the β^3-position of the β-hydroxy acid residue, by simply changing the stereochemistry of

the chiral auxiliaries used to prepare the β-hydroxy acids. A scale-up strategy based entirely on solution-phase chemistry proved to be more challenging than expected due to epimerization problems at several stereocenters, but the most important challenge related to these targets remain to be the final purification step.

4. Experimental section

4.1. General

All chemicals and solvents were analytical grade and used without further purification. Vacuum liquid chromatography (VLC) was performed on silica gel 60 (particle size 0.015–0.040 mm). Flash chromatography was performed on silica gel 60 (particle size 0.035–0.070 mm). UPLC-MS analyses were performed on a Phenomenex Kinetex column (1.7 μm, 50×2.10 mm) using a Waters Acquity ultra high-performance liquid chromatography (UPLC) system. Gradient A with eluent I (0.1% HCOOH in water) and eluent II (0.1% HCOOH in acetonitrile) rising linearly from 0% to 95% of II during t=0.00–5.20 min was applied at a flow rate of 0.6 mL/min. Preparative reversed-phase HPLC purification was performed on a C18 Phenomenex Luna column (5 μm, 100 Å, 250 mm×20 mm) using an Agilent 1260 LC system equipped with a diode array UV detector and an evaporative light scattering detector (ELSD). Gradient B with eluent III (water–MeCN–TFA, 95:5:0.1) and eluent IV (0.1% TFA in acetonitrile) rising linearly from 45% to 95% of IV during t=5–35 min, then isocratically at 95% from t=35–55 min was applied at a flow rate of 20 mL/min. Analytical HPLC was performed on a C18 phenomenex Luna column (3 μm, 100 Å, 150 mm×4.60 mm) using an Agilent 1100 series system equipped with a diode array UV detector. Gradient C using eluent III and eluent IV rising linearly from 0% to 95% of IV during t=2–20 min was applied at a flow rate of 1 mL/min. High-resolution LC–DAD–MS was performed on an Agilent 1100 system equipped with a photodiode array detector (DAD) and coupled to an LCT orthogonal time-of-flight mass spectrometer (Waters-Micromass, Manchester, UK) with Z-spray electrospray ionization (ESI). Optical rotation was measured on a Perkin Elmer Polarimeter with DMSO, $CHCl_3$ or CH_2Cl_2 as the solvents. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury 300 instrument (^{1}H NMR and ^{13}C NMR were recorded at 300 and 75 MHz, respectively). 1D and 2D NMR spectra were recorded on a varian INOVA 500 MHz instrument at 500 MHz for ^{1}H and 125 MHz for ^{13}C or on a Bruker Ascend 400 MHz at 400 MHz for ^{1}H and 100 MHz for ^{13}C. All spectra were recorded at 298 K. Correlation spectroscopy (COSY) spectra was recorded with a relaxation delay of 1.5 s before each scan, a spectral width of 6k×6k, collecting 8 FIDs and 1k×512 datapoints. Heteronuclear single quantum coherence (HSQC) spectra were recorded with a relaxation delay of 1.5 s before each scan, a spectral width of 6k×25k, collecting 16 FIDs and 1k×128 datapoints. Heteronuclear 2-bond correlation (H2BC) spectra were recorded with a relaxation delay of 1.5 s before each scan, a spectral width of 4k×35k, collecting 16 FIDs at 295 K and 1k×256 datapoints. Heteronuclear multiple-bond correlation (HMBC) spectra were recorded with a relaxation delay of 1.5 s before each scan, a spectral width of 6k×35k, collecting 32 FIDs and 1k×256 datapoints. Rotating frame Overhauser effect (ROESY) spectra were recorded with a relaxation delay of 2 s before each scan, a spectral width of 4k×4k, collecting 8 FIDs at 295 K, 1k×256 datapoints, and a mixing time of 100 ms or 200 ms. Chemical shifts are reported in parts per million relative to deuterated solvent peaks as internal standards (δ_H DMSO-d_6 2.50 ppm; δ_C DMSO-d_6 39.52 ppm; δ_H $CDCl_3$ 7.26 ppm; δ_C $CDCl_3$ 77.16 ppm). Coupling constants (J) are given in hertz (Hz). Multiplicities of ^{1}H NMR signals are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

4.2. Solid-phase peptide synthesis of 2-chlorotrityl-resin-bound tripeptide (H-L-Phe-D-Leu-D-Ala-O-Trt(Cl)-resin) (3)

Polystyrene 2-chlorotrityl chloride resin was added to a fritted syringe and swelled in dry CH_2Cl_2. A solution of Fmoc-D-Ala-OH (1.2 g, 4 mmol, 2.5 equiv) and ^{i}PrEtN (1.4 mL, 8 mmol, 5 equiv) in dry CH_2Cl_2 were added to the resin and the loading step was allowed to proceed on a rocking table for 1 h. After washing with CH_2Cl_2 (×3), the resin was capped with CH_2Cl_2–MeOH–^{i}PrEtN (7:2:1) for 30 min and washed with DMF (×3), MeOH (×3), and CH_2Cl_2 (×3). The Fmoc group was removed with piperidine–DMF (1:4, 4 mL, 2×30 min) and DBU–piperidine–DMF (2:2:96, 4 mL, 30 min), and the resin was washed as described above. Fmoc-D-Leu-OH (1.7 g, 4.8 mol, 3 equiv) in DMF (6 mL) was preincubated for 10 min with 2,6-lutidine (1.1 mL, 9.6 mmol, 6 equiv) and HATU (1.8 g, 4.7 mmol, 2.95 equiv) before addition to the resin and the reaction was allowed to proceed on a rocking table for 17 h. After applying the standard washing procedure outlined above the Fmoc group was removed with piperidine–DMF (1:4, 4 mL, 2×30 min) and DBU–piperidine–DMF (2:2:96, 4 mL, 30 min) and then the resin was again washed with DMF (×3), MeOH (×3), and CH_2Cl_2 (×3). Fmoc-L-Phe-OH (1.9 g, 4.8 mmol, 3 equiv), 2,6-lutidine (1.1 mL, 9.6 mmol, 6 equiv), and HATU (1.8 g, 4.7 mmol, 2.95 equiv) in DMF (6 mL) were preincubated for 10 min before addition to the resin and the coupling reaction was allowed to proceed for 24 h before washing with DMF (×3), MeOH (×3), and CH_2Cl_2 (×3). To check the identity of the resin-bound peptide, a small sample of the resin (100 mg, ~0.86 mmol/g) was cleaved with TFA–CH_2Cl_2 (1:1, 2 mL, 2×30 min) and purification of the residue by preparative reversed-phase HPLC afforded Fmoc-protected tripeptide (23 mg, 46%) as a fluffy white material; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (dd, J=14.9, 7.9 Hz, 2H), 7.88 (d, J=7.5 Hz, 2H), 7.67 (dd, J=16.3, 7.8 Hz, 3H), 7.41 (t, J=7.5 Hz, 2H), 7.35–7.15 (m, 7H), 4.40–4.26 (m, 2H), 4.24–4.08 (m, 4H), 2.94 (dd, J=13.4, 5.6 Hz, 1H), 2.80 (dd, J=13.4, 9.6 Hz, 1H), 1.46–1.33 (m, 3H), 1.29 (d, J=7.32, 1H), 0.80 (d, J=6.1, 3H), 0.76 (d, J=6.1, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4, 172.2, 171.6, 156.3, 144.3, 144.2, 141.1, 141.1, 138.2, 129.8, 128.5, 128.1, 127.5, 126.7, 125.8, 120.6, 66.2, 56.7, 50.8, 47.9, 47.0, 41.3, 38.1, 24.3, 23.7, 21.9, 17.4. The N-terminal Fmoc group was removed with piperidine–DMF (1:4, 4 mL, 2×30 min) and DBU–piperidine–DMF (2:2:96, 4 mL, 30 min) and the resin was washed with DMF (×3), MeOH (×3), and CH_2Cl_2 (×3) to give resin **3**.

4.3. ±-β-Hydroxyoctanoic acid (±-Hoa) (4)

To a solution of ethyl diazoacetate (3.3 mL, 31.6 mmol, 1 equiv) in dry CH_2Cl_2 (55 mL) was added $SnCl_2$ (600 mg, 3.2 mmol, 0.1 equiv) under nitrogen atmosphere. A solution of hexanal (4.7 mL, 37.9 mmol, 1.2 equiv) in dry CH_2Cl_2 (65 mL) was added dropwise to the suspension at room temperature. After evolution of nitrogen had stopped (≈2 h), the reaction was transferred to a separatory funnel and quenched with brine (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3×50 mL), the organic layers were collected, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography (heptane–EtOAc, 9:1) afforded the β-ketoester (5.88 g, 90%) as pale yellow oil; R_f 0.45 (heptane–EtOAc, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (q, 2H), 3.35 (s, 2H), 2.46 (t, J=7.4 Hz, 3H), 1.51 (t, 2H), 1.28–1.14 (m, 6H), 0.81 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 167.5, 61.5, 49.5, 43.2, 31.3, 23.3, 22.6, 14.3, 14.1; in agreement with previously reported data.[27] To a solution of the β-ketoester (1 g, 5.3 mmol, 1 equiv) in MeOH–AcOH (95·5, 35 mL) at 0 °C was slowly added Bu_4NBH_4 (2.75 g, 10.7 mmol, 2 equiv). The mixture was stirred at 0 °C for 2 h and then another equivalent of Bu_4NBH_4 was added, since TLC showed the reaction to be incomplete. The mixture was then stirred at room temperature

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overnight. Another 5 equiv of Bu_4NBH_4 were added (1 equiv every hour). The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL), washed with 1 M aqueous HCl (50 mL), which was back extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (heptane–EtOAc, 1:10→1:1) afforded the ethyl β-hydroxyoctanoate (817 mg, 80%) as a colorless oil; R_f 0.36 (heptane–EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (q, J=7.1 Hz, 2H), 4.06–3.88 (m, 1H), 2.48 (dd, J=16.4, 3.3 Hz, 1H), 2.37 (dd, J=16.4, 8.8 Hz, 1H), 1.64–1.21 (m, 8H), 0.87 (t, 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 68.2, 60.9, 41.5, 36.7, 31.9, 25.4, 22.8, 14.4, 14.2; in agreement with previous data.[30] To the ethyl β-hydroxyoctanoate (817 mg, 4.3 mmol, 1.0 equiv) in THF (22 mL) was added aqueous LiOH (6.5 mL, 1.0 M, 1.5 equiv) and the mixture was stirred at room temperature for 1 h. Then the THF was removed in vacuo and the remaining solution was acidified with concentrated HCl, extracted with EtOAc (3×30 mL), and the organic layers were dried with Na_2SO_4, filtered, and concentrated to afford the β-hydroxy acid **4** (486 mg, 70%) as a colorless oil, which was used without further purification; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09–3.96 (m, 1H), 2.55–2.38 (m, 2H), 1.62–1.15 (m, 8H), 0.89 (t, J=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 68.3, 41.3, 36.7, 31.9, 25.3, 22.8, 14.2; in agreement with previously reported data.[31]

4.4. 3-(((*S*)-2-((*tert*-Butoxycarbonyl)amino)-4-methylpentanoyl)oxy)octanoic acid (5)

To an ice-cooled solution of **4** (284 mg, 1.8 mmol, 1 equiv) in MeOH (2 mL) was added a solution of $CsCO_3$ (347 mg, 1.1 mmol, 0.6 equiv) in water (1 mL). After 30 min, the solvents were removed under reduced pressure and the $CsCO_3$ salt was dissolved in DMF (10 mL, 0.2 M). Benzyl bromide (232 μl, 2 mmol, 1.1 equiv) was added and the resulting suspension was stirred for 16 h. The mixture was then quenched with water (30 mL), the aqueous phase extracted with EtOAc (3×30 mL), and the combined organic phases were washed with water (5×20 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. Without further purification, benzylester (267 mg, 1.1 mmol, 1 equiv) and Boc-L-Leu-OH (319 mg, 1.3 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (15 mL, 0.2 M) at 0 °C and treated with DIC (344 μl, 2.1 mmol, 2 equiv) and DMAP (13 mg, 0.1 mmol, 0.1 equiv) allowing the mixture to reach room temperature while stirring was continued for 16 h. The precipitate was removed by filtration and washed with CH_2Cl_2 (10 mL). The combined organic layers were washed with 1 M HCl (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by flash chromatography (2–4% MeOH in CH_2Cl_2) to give fully protected dimer (200 mg, 40%) as a colorless oil; R_f 0.48 (CH_2Cl_2–MeOH 96:4); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.53–7.27 (m, 5H), 7.19 (d, J=7.7 Hz, 1H), 5.74 (s, 2H), 5.21–4.93 (m, 1H), 3.88 (ddd, J=12.7, 11.2, 7.2 Hz, 2H), 2.76–2.52 (m, 2H), 1.66–1.40 (m, 7H), 1.35 (s, 9H), 1.28–1.09 (m, 2H), 0.80 (ddd, J=13.6, 7.9, 4.7 Hz, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 170.2, 155.4, 135.8, 128.7, 128.5, 128.5, 71.6, 66.7, 52.4, 41.8, 39.3, 33.9, 31.5, 28.4, 24.8, 23.0, 22.5, 22.0, 14.1; MS calcd for $C_{26}H_{41}NO_6Na^+$ [M+Na]$^+$ 486.3, found 486.2. This dimer (200 mg, 0.43 mmol, 1 equiv) was dissolved in EtOH (10 mL, 0.2 M) and degassed with N_2. Palladium on activated carbon (39 mg, 0.1 equiv, 0.1% w/w) was added and the mixture was degassed with N_2 again, before stirring under H_2 atmosphere for 16 h. The catalyst was removed by filtration through by a pad of Celite, which was washed with CH_2Cl_2 (50 mL). The solvents were removed under reduced pressure affording title compound **5** (121 mg, 76%) as a colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.13–4.99 (m, 1H), 3.87 (m, 1H), 2.58–2.29 (m, 2H), 1.46 (m, J=23.1 Hz, 11H), 1.34 (m, J=4.8 Hz, 9H), 1.22 (m, 2H), 0.82 (ddd, J=9.8, 6.5, 2.8 Hz, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6, 171.4, 155.4, 78.0, 70.6, 52.4, 44.0, 41.0, 33.4, 30.9, 28.1, 24.2, 23.9, 22.7, 13.8; MS calcd for $C_{19}H_{35}NO_6Na^+$ [M+Na]$^+$ 396.2, found 396.2.

4.5. Diastereomeric mixture of solonamide B (2) and β^3-*epi*-solonamide B (β^3-*epi*-2)

Polystyrene 2-chlorotrityl-bound L-Phe-D-Leu-D-Ala (**3**) (0.13 mmol, 1 equiv) was added to a fritted syringe and swelled with CH_2Cl_2. Dimer **5** (60 mg, 0.16 mmol, 1.2 equiv) was pre-incubated for 10 min with ^{i}PrEtN (85 μl, 0.53 mmol, 4 equiv) and HATU (100 mg, 0.27 mmol, 2 equiv) before addition to the resin, and the reaction was allowed to proceed for 7 h on a rocking table. The resin was then washed with DMF (×3), MeOH (×3), and CH_2Cl_2 (×3) and treated with TFA–CH_2Cl_2 (1:1, 2 mL, 2×30 min) followed by washing with CH_2Cl_2 (3×2 mL). All the fractions were pooled in a round-bottomed flask, concentrated under reduced pressure, and co-evaporated with toluene (×2), toluene–CH_2Cl_2 (1:1, ×2), and hexane–CH_2Cl_2 (1:1, ×2) to furnish a crude linear precursor (40 mg, 51%), which was cyclized without purification. To a stirred solution of crude linear peptide (40 mg) in DMF (140 mL) was added ^{i}PrEtN (46 μl, 0.26 mmol, 4 equiv) and HATU (50 mg, 0.13 mmol, 2 equiv) and the reaction was stirred at room temperature for 16 h. The DMF was evaporated and the residue was purified by preparative reversed-phase HPLC to give the two diastereoisomers (5 mg and 4 mg, respectively, total yield of 23%) as white fluffy solids. For full characterization, see Sections 4.34 and 4.36, respectively.

4.6. (*S*)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)ethanone (7)

(*S*)-4-Benzylthiazolidine-2-thione **6** (18.4 g, 88 mmol, 1 equiv), DMAP (1.1 g, 8.8 mmol, 0.1 equiv) and NEt_3 (18.4 mL, 132 mmol, 1.5 equiv) were dissolved in dry CH_2Cl_2 (240 mL) and cooled to 0 °C. AcCl (9.4 mL, 132 mmol, 1.5 equiv) was added dropwise and the reaction was allowed to reach room temperature and stirred overnight. The mixture was then quenched with satd NH_4Cl (200 mL), diluted with Et_2O (300 mL), and the organic phase was washed with satd $CuSO_4$ (3×100 mL), water (100 mL), and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Recrystallization of the crude material from EtOH afforded acetylated auxiliary **7** (18 g, 81%) as yellow needles; $[\alpha]_D^{20}$ +335° (*c* 13, CH_2Cl_2) previously reported $[\alpha]_D^{20}$ +211° (*c* 10, $CHCl_3$);[32] Mp 111–115 °C previously reported 88–90 °C;[33] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.12 (m, 5H), 5.31 (m, 2H), 3.31 (dd, J=11.5, 7.2 Hz, 1H), 3.15 (dd, J=13.2, 3.8 Hz, 1H), 2.97 (dd, J=13.2, 10.6 Hz, 1H), 2.82 (d, J=11.5 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 170.8, 136.5, 129.5, 128.9, 127.2, 68.3, 58.3, 36.7, 27.1.

4.7. General procedure for the aldol reactions

Acetylated auxiliary (1.7 equiv) was dissolved in CH_2Cl_2 (0.2 M). $TiCl_4$ (1.8 equiv) and *i*PrEtN (1.8 equiv) were added dropwise and the resulting suspension was cooled to −78 °C and stirred for 2 h. The appropriate aldehyde (1 equiv) in CH_2Cl_2 (0.2 M) was then added dropwise and the mixture was stirred at −78 °C for 4–24 h. The reaction was then quenched with satd NH_4Cl (50 mL) and water (50 mL) before Et_2O (200 mL) was added. The organic phase was washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to give a yellow crude material (general selectivities obtained: (*S*,*S*)-(*S*,*R*) 6:1→3:1), which was purified by column chromatography.

4.8. (*S*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxyhexan-1-one (8)

Compound **7** was reacted with butanal according to General procedure 4.7 and subsequent flash chromatography

(heptane–EtOAc, 9:1→5:1) afforded the title compound **8** (2.2 g, 58%) as a yellow oil; R_f 0.08 (heptane–EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.07 (m, 5H), 5.33 (m, 1H), 4.19–4.02 (m, 1H), 3.67–2.77 (m, 6H), 1.56–1.25 (m, 4H), 0.88 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 174.0, 136.5, 129.6, 129.1, 127.4, 68.4, 68.3, 45.6, 38.9, 36.9, 32.2, 18.8, 14.1; in agreement with previously reported data.[32]

4.9. (*S*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxyoctan-1-one (9)

Compound **7** was reacted with hexanal according to General procedure 4.7 and subsequent flash chromatography (heptane–EtOAc, 9:1→5:1) afforded the title compound **9** (2.2 g, 54%) as a yellow oil; $[\alpha]_D^{20}$ −11° (*c* 14, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.42–7.05 (m, 5H), 5.32 (m, 1H), 4.14–3.97 (m, 1H), 3.64–2.70 (m, 6H), 1.61–1.13 (m, 8H), 0.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 173.4, 135.9, 129.2, 129.0, 127.5, 67.6, 65.1, 45.9, 40.2, 38.3, 36.9, 32.1, 18.8, 14.0; UPLC-MS gradient A t_R 2.18 min (>95%); MS calcd for $C_{18}H_{26}NO_2S_2$ $[M+H]^+$ 352.1, found 352.1.

4.10. General procedure for the hydrolysis of aldol adducts

Aldol adduct (1 equiv) was dissolved in THF (0.2 M), aqueous LiOH (1 M, 4 equiv) was added, and the mixture was stirred at room temperature for 3 h. The THF was removed and the aqueous phase was washed with EtOAc (3×100 mL), then acidified with 2 M HCl and extracted with EtOAc (3×100 mL), dried ($MgSO_4$), filtered, and concentrated to afford the corresponding acid.

4.11. (*S*)-3-Hydroxyhexanoic acid (S-10)

Procedure 4.10 afforded the desired product (1.12 g, 79%) as a colorless oil; $[\alpha]_D^{20}$ +21° (*c* 5, CH_2Cl_2), previously reported $[\alpha]_D^{20}$ +29° (*c* 5, $CHCl_3$);[34] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (m, 1H), 2.45 (ddd, J=25.4, 16.5, 6.1 Hz, 2H), 1.53–1.25 (m, 4H), 0.87 (t, J=8.7, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 67.8, 41.1, 38.5, 18.7, 13.9; in agreement with previously reported data.[35]

4.12. (*S*)-3-Hydroxyoctanoic acid (S-11)

Procedure 4.10 afforded the desired product (951 mg, 95%) colorless oil; $[\alpha]_D^{20}$ +24.6° (*c* 5, CH_2Cl_2), previously reported $[\alpha]_D^{20}$ +14.2° (*c* 5, $CHCl_3$);[35] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (m, 1H), 2.57–2.37 (m, 2H), 1.60–1.18 (m, 8H), 0.86 (t, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 68.3, 41.2, 36.4, 31.6, 25.1, 22.5, 14.0.

4.13. D-Phenylalaninol (12)

$NaBH_4$ (6.7 g, 209 mmol, 2.3 equiv) and D-phenylalanine (15 g, 91 mmol, 1 equiv) were dissolved in dry THF (250 mL) and cooled to 0 °C on an ice-water bath. Iodine (22 g, 91 mmol, 1 equiv) in dry THF (75 mL) was added dropwise and after gas evolution stopped, the mixture was heated to reflux overnight. Then the mixture was cooled to room temperature and MeOH was slowly added until a clear solution emerged (≈200 mL). Solvents were removed, the resulting white paste was dissolved in aqueous NaOH (2 M, 300 mL), and the mixture was stirred at room temperature for 8 h. The aqueous phase was extracted with CH_2Cl_2 (3×200 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to afford D-phenylalaninol **12** (13.2 g, 99%) as a white viscous oil, which was used without further purification; $[\alpha]_D^{20}$ +20° (*c* 13, CH_2Cl_2), previously reported $[\alpha]_D^{20}$ +23° (*c* 10, H_2O);[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (m, 5H), 3.56 (dd, J=10.7, 3.8 Hz, 1H), 3.32 (dd, J=10.7, 7.2 Hz, 1H), 3.10–2.96 (m, 1H), 2.72 (dd, J=13.5, 5.2 Hz, 1H), 2.45 (dd, J=13.5, 8.7 Hz, 1H), 2.11 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 129.2, 128.6, 126.5, 66.2, 54.2, 40.8; in agreement with previously reported data.[37]

4.14. (*R*)-1-(4-Benzyl-2-thioxothiazolidin-3-yl)ethanone (13)

D-Phenylalaninol **12** (13.2 g, 91 mmol, 1 equiv) was dissolved in aqueous KOH (3 M, 200 mL). CS_2 (26 mL, 436 mmol, 5 equiv) was added and the solution was heated at reflux overnight. The solution was extracted with CH_2Cl_2 (3×200 mL), dried (Na_2SO_4), filtered, and concentrated to afford (*R*)-4-benzylthiazolidine-2-thione (15.6 g, 86%), which was used without further purification. $[\alpha]_D^{20}$ −97° (*c* 13, CH_2Cl_2); Mp 86–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.46–7.16 (m, 5H), 4.54–4.43 (m, 1H), 3.57 (dd, J=11.2, 7.7 Hz, 1H), 3.31 (dd, J=11.2, 6.7 Hz, 1H), 3.03 (ddd, J=34.4, 13.6, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 135.9, 129.2, 129.1, 127.5, 65.2, 40.0, 38.1; in agreement with previously reported data.[38] The auxiliary (15.6 g, 75 mmol, 1 equiv), DMAP (912 mg, 7.5 mmol, 0.1 equiv), and NEt_3 (16 mL, 112 mmol, 1.5 equiv) were dissolved in dry CH_2Cl_2 (200 mL) and cooled to 0 °C. AcCl (8 mL, 112 mmol, 1.5 equiv) was added dropwise and the reaction was allowed to reach room temperature and stirred overnight. Then, the reaction was quenched with satd NH_4Cl (200 mL), diluted with Et_2O (200 mL), and the organic phase was washed with satd $CuSO_4$ (3×100 mL), water (100 mL), and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude compound as a yellow solid. Recrystallization from EtOH afforded the title compound **13** (11.7 g, 62%) as yellow needles; $[\alpha]_D^{20}$ −48° (*c* 25, CH_2Cl_2), previously reported $[\alpha]_D^{20}$ −210° (*c* 10, $CHCl_3$);[38] Mp 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.12 (m, 5H), 5.42–5.19 (m, 1H), 3.31 (dd, J=11.5, 7.2, 0.9 Hz, 1H), 3.15 (dd, J=13.2, 3.8 Hz, 1H), 2.97 (dd, J=13.2, 10.6 Hz, 1H), 2.82 (d, J=11.5 Hz, 1H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 170.8, 136.5, 129.5, 128.9, 127.3, 68.2, 36.7, 31.8, 23.1.

4.15. (*R*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxyhexan-1-one (14)

Compound **13** was reacted with butanal according to General procedure 4.7 and subsequent flash chromatography (heptane–EtOAc, 9:1→5:1) furnished title compound **14** (2 g, 53%) as a yellow oil; R_f 0.16 (heptane–EtOAc, 4:1); $[\alpha]_D^{20}$ −117° (*c* 6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.19 (m, 5H), 5.42 (m, 1H), 4.26–4.12 (m, 1H), 3.73–2.84 (m, 6H), 1.68–1.36 (m, 4H), 0.97 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 173.9, 136.4, 129.5, 129.0, 127.3, 68.3, 68.2, 45.5, 38.8, 36.8, 32.0, 18.7, 14.0; UPLC-MS gradient A t_R 2.39 min (>95%); MS calcd for $C_{16}H_{21}NO_2S_2Na^+$ $[M+Na]^+$ 346.1, found 346.2.

4.16. (*R*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxyoctan-1-one (15)

Compound **13** was reacted with hexanal according to General procedure 4.7 and subsequent flash chromatography (heptane–EtOAc, 15:1→8:1) afforded title compound **15** (3.6 g, 44%) as a yellow oil; R_f 0.11 (heptane–EtOAc 4:1); $[\alpha]_D^{20}$ −87° (*c* 9, CH_2Cl_2), previously reported $[\alpha]_D^{20}$ −72.6° (*c* 9, $CHCl_3$);[39] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.03 (m, 5H), 5.33 (m, 1H), 4.12–4.03 (m, 1H), 3.65–2.75 (m, 6H), 1.64–1.15 (m, 8H), 0.83 (t, J=8.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 173.4, 136.4, 129.5, 129.0, 127.3, 68.4, 67.9, 45.9, 36.9, 36.4, 32.1, 31.8, 25.3, 22.6, 14.1.

4.17. (*R*)-3-Hydroxyhexanoic acid (R-10)

Hydrolysis of **14** following General procedure 4.10 furnished the desired hydroxy acid (445 mg, 54%) as a colorless oil; $[\alpha]_D^{20}$ −18° (*c* 87, CH_2Cl_2), previously reported $[\alpha]_D^{20}$ −20° (*c* 2, $CHCl_3$);[28] ^{1}H NMR

(400 MHz, $CDCl_3$) δ 4.12–3.97 (m, 1H), 2.61–2.40 (m, 2H), 2.10 (s, 1H), 1.61–1.31 (m, 4H), 0.94 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 67.9, 41.1, 38.5, 18.6, 13.9.

4.18. (*R*)-3-Hydroxyoctanoic acid (R-11)

Hydrolysis of **15** following General procedure 4.10 furnished the desired hydroxy acid (1.7 g, 69%) as a colorless oil; $[\alpha]_D^{20}$ −12° (*c* 5, CH_2Cl_2), previously reported $[\alpha]_D^{20}$ −23° (*c* 2, $CHCl_3$);[40] ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (m, 1H), 2.57–2.37 (m, 2H), 1.60–1.18 (m, 8H), 0.86 (t, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 68.3, 41.2, 36.4, 31.6, 25.1, 22.5, 14.0.

4.19. General procedure for benzylester protection

To an ice-cooled solution of hydroxy acid (1 equiv) in MeOH (2 mL) was added a solution of $CsCO_3$ (0.6 equiv) in water (1 mL). After 30 min, the solvents were removed under reduced pressure and the $CsCO_3$ salt was dissolved in DMF (0.2 M). Benzyl bromide (1.1 equiv) was added and the suspension was stirred overnight. The mixture was then quenched with water (30 mL) and the aqueous phase was extracted with EtOAc (3×30 mL). The combined organic layers were washed with water (5×20 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to give crude benzylester, which was used without further purification.

4.20. General procedure for dimer coupling

A mixture of Boc-L-Leu-OH (1.2 equiv) and benzylester (1 equiv) was dissolved in CH_2Cl_2 (0.2 M) and treated with DIC (2 equiv) and DMAP (0.1 equiv) at 0 °C. The resulting mixture was allowed to reach room temperature and stirred overnight. The forming precipitate was removed by filtration and washed with CH_2Cl_2 (10 mL). The combined organic phase was washed with 1 M HCl (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered, and concentrated. The crude oil was purified by flash chromatography (2–4% MeOH in CH_2Cl_2) to afford the desired dimers.

4.21. Benzyl (3*R*)-3-(((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpentanoyl)oxy)hexanoate (16)

Subjecting (***R***)-**10** to General procedures 4.19 and 4.20 followed by purification by flash chromatography (heptane–EtOAc, 4:1→3:1) gave the title compound (609 mg, 61%) as an oil; R_f 0.8 (heptane–EtOAc, 1:1); $[\alpha]_D^{20}$ −50° (*c* 10, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 5.22 (m, 1H), 5.09–4.94 (m, 2H), 4.17 (m, 1H), 2.69–2.42 (m, 2H), 1.68–1.43 (m, 4H), 1.36 (s, 9H), 1.32–1.13 (m, 3H), 0.93–0.67 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 170.0, 155.3, 135.7, 128.6, 128.4, 128.4, 79.6, 71.2, 52.3, 39.2, 36.1, 28.3, 24.8, 22.9, 21.9, 18.3, 13.8; HRMS calcd for $C_{24}H_{37}NO_6Na^+$ $[M+Na]^+$ 458.2513, found 458.2516.

4.22. Benzyl (3*R*)-3-(((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpentanoyl)oxy)octanoate (17)

Subjecting (***R***)-**11** to General procedures 4.19 and 4.20 followed by purification by flash chromatography afforded the title compound (200 mg, 40%) as a colorless oil; R_f 0.84 (CH_2Cl_2–MeOH, 9:1); $[\alpha]_D^{20}$ −46° (*c* 5, DMSO); ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.27 (m, 5H), 7.19 (d, J=7.7 Hz, 1H), 5.74 (s, 1H), 5.21–4.93 (m, 1H), 3.88 (ddd, J=12.7, 11.2, 7.2 Hz, 2H), 2.76–2.52 (m, 2H), 1.66–1.40 (m, 7H), 1.35 (s, 9H), 1.28–1.09 (m, 2H), 0.80 (ddd, J=13.6, 7.9, 4.7 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 170.0, 155.3, 135.7, 128.6, 128.4, 128.3, 71.5, 66.5, 52.3, 41.7, 39.1, 33.8, 31.4, 28.3, 24.6, 22.9, 22.4, 21.9, 13.9; HRMS calcd for $C_{26}H_{41}NO_6Na^+$ $[M+Na]^+$ 486.2826, found 486.2833.

4.23. Benzyl (3*S*)-3-(((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpentanoyl)oxy)hexanoate (20)

Subjecting (***S***)-**10** to General procedures 4.19 and 4.20 followed by purification by flash chromatography afforded the title compound (469 mg, 62%) as a colorless oil; R_f 0.59 (10% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$ +72° (*c* 6, DMSO); ^1H NMR (400 MHz, DMSO-d_6) δ 7.33–7.19 (m, 5H), 5.27–5.14 (s, 1H), 5.02 (s, 2H), 4.83 (d, J=8.5 Hz, 1H), 4.16 (m, 1H), 2.67–2.41 (m, 2H), 1.66–1.17 (m, 16H), 0.87–0.73 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 170.3, 156.2, 136.3, 128.8, 128.5, 128.5, 78.6, 70.8, 65.9, 55.3, 40.0, 39.0, 36.0, 28.6, 21.1, 18.1, 14.1; HRMS calcd for $C_{24}H_{37}NO_6Na^+$ $[M+Na]^+$ 458.2513, found 458.2528.

4.24. Benzyl (3*S*)-3-(((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpentanoyl)oxy)octanoate (21)

Subjecting (***S***)-**11** to General procedures 4.19 and 4.20 followed by purification by flash chromatography afforded the title compound (394 mg, 76%) as a colorless oil; R_f 0.8 (CH_2Cl_2–MeOH, 9:1); $[\alpha]_D^{20}$ +48° (*c* 10, DMSO); ^1H NMR (400 MHz, DMSO-d_6) δ 7.45–7.30 (m, 5H), 7.21 (d, J=7.8 Hz, 1H), 5.26–5.01 (m, 3H), 3.90 (m, 1H), 2.77–2.54 (m, 2H), 1.75–1.16 (m, 20H), 0.84 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.7, 170.3, 156.0, 136.6, 128.9, 128.4, 128.3, 78.5, 70.9, 40.0, 39.0, 33.9, 31.4, 28.5, 24.6, 24.4, 21.6, 21.1, 14.2; HRMS calcd for $C_{26}H_{41}NO_6Na^+$ $[M+Na]^+$ 486.2829, found 486.2845.

4.25. General procedure for Bn deprotection

The dimer (1 equiv) was dissolved in EtOH (0.2 M) and degassed with N_2. Palladium on activated carbon (0.1% wt, 0.1 equiv) was added and the mixture was degassed with N_2. The mixture was stirred with H_2 atm overnight. The catalyst was filtered by a pad of Celite and washed with CH_2Cl_2 (50 mL). The solvents were removed under reduced pressure affording the compounds.

4.26. (3*R*)-3-(((*S*)-2-((*tert*-Butoxycarbonyl)amino)-4-methylpentanoyl)oxy)hexanoic acid (18)

Deprotection of **16** by General procedure 4.25 afforded building block **18** (220 mg, 42%) as a colorless oil; R_f 0.11 (heptane–EtOAc, 1:1); $[\alpha]_D^{20}$ −1.3° (*c* 3, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 5.24–5.13 (m, 1H), 4.17 (m, 1H), 2.64–2.46 (m, 2H), 1.68–1.42 (m, 4H), 1.37 (s, 9H), 1.32–1.15 (m, 3H), 0.91–0.82 (m, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 177.4, 174.6, 157.6, 79.1, 71.1, 57.7, 42.0, 36.1, 28.1, 22.9, 22.7, 21.4, 18.1, 13.5; HRMS calcd for $C_{17}H_{31}NO_6Na^+$ $[M+Na]^+$ 368.2043, found 368.2057.

4.27. 3(*R*)-3-(((*S*)-2-((*tert*-Butoxycarbonyl)amino)-4-methylpentanoyl)oxy)octanoic acid (19)

Deprotection of **17** by General procedure 4.25 afforded building block **19** (275 mg, 87%) as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.76 (m, 1H), 4.18 (m, 1H), 2.67–2.40 (m, 2H), 1.67–1.39 (m, 8H), 1.41–1.30 (m, 9H), 1.31–1.08 (m, 3H), 0.96–0.74 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 170.0, 155.3, 79.7, 71.5, 52.3, 41.8, 41.7, 39.1, 33.8, 31.4, 28.3, 24.64, 22.9, 22.4, 22.4, 13.9; UPLC-MS gradient A t_R 2.51 min (>95%); MS calcd for $C_{19}H_{36}NO_6Na^+$ $[M+Na]^+$ 396.2, found 396.2.

4.28. (3*S*)-3-(((*S*)-2-((*tert*-Butoxycarbonyl)amino)-4-methylpentanoyl)oxy)hexanoic acid (22)

Deprotection of **20** by General procedure 4.25 afforded building block **22** (269 mg, 72%) as a colorless oil; $[\alpha]_D^{20}$ +5° (*c* 3, DMSO); ^1H

NMR (400 MHz, DMSO-d_6) δ 5.10 (m, 1H), 3.89 (m, 1H), 2.58–2.42 (m, 2H), 1.73–1.20 (m, 16H), 0.92–0.76 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.1, 172.0, 156.0, 78.6, 70.9, 52.5, 40.0, 39.0, 36.1, 28.6, 24.7, 23.2, 21.9, 18.1, 14.2; HRMS calcd for $C_{17}H_{31}NO_6Na^+$ $[M+Na]^+$ 368.2043, found 368.2060.

4.29. (3*S*)-3-(((*S*)-2-((*tert*-Butoxycarbonyl)amino)-4-methylpentanoyl)oxy)octanoic acid (23)

Deprotection of **21** by General procedure 4.25 afforded building block **23** (244 mg, 79%) as a colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.18–4.98 (m, 1H), 3.93–3.80 (m, 1H), 2.66 (ddd, J=24.1, 15.7, 6.3 Hz, 2H), 1.61–1.09 (m, 20H), 0.96–0.68 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.1, 170.3, 156.0, 78.5, 70.9, 66.1, 52.5, 39.0, 33.9, 31.4, 28.6, 24.6, 24.4, 23.1, 14.2; UPLC-MS gradient A t_R 2.44 min (>95%); MS calcd for $C_{19}H_{36}NO_6$ $[M+H]^+$ 374.3, found 374.2.

4.30. (4*R*)-4-Methoxybenzyl 3-(((*R*)-2-(((benzyloxy)carbonyl)-amino)-4-methylpentanoyl)oxy)octanoate (24)

(***R***)-**11** (1 g, 6.2 mmol, 1.1 equiv) was dissolved in HPLC grade acetone (40 mL). PMB-Cl (98 μl, 5.7 mmol, 1 equiv), TBAI (105 mg, 0.28 mmol, 0.05 equiv), and K_2CO_3 (1.2 g, 8.5 mmol, 1.5 equiv) were added and the mixture was stirred at reflux for 16 h. Then, EtOAc (50 mL) and water (50 mL) were added and the aqueous phase was back extracted with EtOAc (2×50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give a crude oil, which was purified by flash chromatography (heptane–EtOAc, 4:1) to afford (*R*)-4-methoxybenzyl 3-hydroxyoctanoate (882 mg, 55%) as a colorless oil; R_f 0.6 (heptane–EtOAc, 1:1); $[\alpha]_D^{20}$ −5° (*c* 6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J=8.7 Hz, 2H), 6.90 (d, J=8.7 Hz, 2H), 5.10 (s, 2H), 4.02 (m, 1H), 3.82 (s, 3H), 2.99 (br s, 1H), 2.59–2.35 (m, 2H), 1.58–1.24 (m, 8H), 0.90 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 159.7, 130.2, 127.8, 114.0, 68.1, 66.3, 55.3, 41.5, 36.5, 31.7, 25.2, 22.6, 14.0; HRMS calcd for $C_{30}H_{41}NO_7K^+$ $[M+K]^+$ 319.1306, found 319.1364. The PMB-ester (200 mg, 0.71 mmol, 1 equiv), DIC (223 μl, 1.43 mmol, 2 equiv), and DMAP (9 mg, 0.07 mmol, 0.1 equiv) were dissolved in dry CH_2Cl_2 and stirred for 10 min at 0 °C. Then Cbz-L-Leu-OH (208 mg, 0.79 mmol, 1.2 equiv) was added and the mixture was slowly heated to room temperature and allowed to proceed under stirring for 16 h. The formed urea biproduct was removed by filtration and washed with CH_2Cl_2 (20 mL). The combined organic phase was washed with 1 M HCl (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography (2–4% MeOH in CH_2Cl_2) to afford the desired dimer (335 mg, 90%) as a colorless oil; R_f 0.76 (heptane–EtOAc, 1:1); $[\alpha]_D^{20}$ −15° (*c* 27, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.10 (m, 8H), 6.81 (d, J=6.7 Hz, 2H), 5.27–5.12 (m, 1H), 5.10–4.90 (m, 4H), 4.32–4.16 (m, 1H), 3.72 (s, 3H), 2.65–2.38 (m, 2H), 1.70–1.30 (m, 5H), 1.19 (m, 6H), 0.81 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 170.1, 159.7, 155.9, 136.3, 130.3, 128.7, 128.2, 128.1, 128.1, 127.8, 114.0, 71.7, 66.9, 66.4, 55.3, 52.7, 41.8, 39.1, 33.7, 31.4, 24.8, 24.6, 22.9, 22.4, 21.9, 13.9; HRMS calcd for $C_{30}H_{41}NO_7Na^+$ $[M+Na]^+$ 550.2775, found 550.2789.

4.31. (3*R*)-3-(((*R*)-2-(((Benzyloxy)carbonyl)amino)-4-methylpentanoyl)oxy)octanoic acid (25)

Compound **24** (700 mg, 1.33 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C. Et_3SiH (2.2 mL, 13.8 mmol, 10 equiv) was added in one portion and TFA (10 mL) was added slowly. The mixture was stirred at 0 °C for 3 h whereafter the solvents were removed and the residue was purified by flash chromatography (heptane–EtOAc, 3:1→2:1) to afforded the title compound **25** (483 mg, 89%) a colorless oil; R_f 0.2 (heptane–EtOAc, 1:1); $[\alpha]_D^{20}$ −8° (*c* 30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.26 (m, 5H), 5.38–5.04 (m, 3H), 4.44–4.20 (m, 1H), 2.73–2.47 (m, 2H), 1.79–1.20 (m, 11H), 0.92 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 172.6, 156.3, 136.1, 128.5, 128.2, 128.1, 71.6, 67.3, 52.7, 41.5, 41.2, 38.8, 33.8, 31.4, 31.4, 24.8, 24.7, 24.6, 22.9, 22.4, 21.7, 14.0; HRMS calcd for $C_{22}H_{33}NO_6Na^+$ $[M+Na]^+$ 430.2200, found 430.2212.

4.32. H-L-Phe-D-Leu-D-Ala-OBn (26)

Boc-D-Ala-OBn (2.3 g, 8.2 mmol, 1 equiv) was stirred with TFA–CH_2Cl_2 (1:1, 10 mL) and stirred for 2 h. The solvents were removed and the mixture was co-evaporated with toluene (2×10 mL), toluene–CH_2Cl_2 (1:1, 2×10 mL), and hexane–CH_2Cl_2 (1:1, 2×10 mL) and the mixture was used without further purification. Boc-D-Leu-OH (3.1 g, 13.5 mmol, 1.1 equiv) was dissolved in CH_2Cl_2 (70 mL). HOBt (1.8 g, 13.5 mmol, 1.1 equiv) and DIC (2.1 mL, 13.5 mmol, 1.1 equiv) were added and the suspension was activated for 10 min. The crude oil in CH_2Cl_2 (60 mL) was added to the mixture and was stirred at room temperature 6 h and then quenched with brine (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were washed with 2 M HCl (3×50 mL) and satd aq $NaHCO_3$ (50 mL) and then dried with $MgSO_4$ and concentrated to a crude oil, which was purified by flash chromatography (2–6% MeOH in CH_2Cl_2) affording a colorless oil (2.44 g, 76%). Boc-D-Leu-D-Ala-OBn (2.4 g, 6.1 mmol, 1 equiv) was stirred with TFA–CH_2Cl_2 (1:1, 10 mL) and stirred for 3 h. The solvents were removed and the mixture was co-evaporated with toluene (2×10 mL), toluene–CH_2Cl_2 (1:1, 2×10 mL) and hexane–CH_2Cl_2 (1:1, 2×10 mL) and the mixture was used without further purification. Boc-L-Phe-OH (2.5 g, 9.4 mmol, 1.1 equiv) and HOBt (1.3 g, 9.4 mmol, 1.1 equiv) was dissolved in dry CH_2Cl_2 (50 mL). DIC (1.5 mL, 9.4 mmol, 1.1 equiv) was added and the suspension is stirred for 10 min. The crude oil in CH_2Cl_2 (40 mL) was added to the solution and the mixture was stirred at room temperature overnight and then quenched with brine (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were washed with 2 M HCl (3×50 mL), saturated aqueous $NaHCO_3$ (50 mL) and then dried with $MgSO_4$ and concentrated. The crude oil was purified by flash chromatography (2–4% MeOH in CH_2Cl_2) affording Boc-L-Phe-D-Leu-D-Ala-OBn (2.5 g, 55%) as an oil; R_f 0.6 (CH_2Cl_2–MeOH, 95:5); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (d, J=6.9 Hz, 1H), 8.07 (d, J=8.6 Hz, 1H), 7.47–7.13 (m, 10H), 6.98 (d, J=7.8 Hz, 1H), 5.17–4.97 (m, 2H), 4.31 (p, J=7.1 Hz, 2H), 4.16 (m, 1H), 2.81 (m, 2H), 1.42–1.14 (m, 15H), 0.90–0.64 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2, 172.0, 171.3, 155.3, 137.8, 136.0, 129.4, 129.2, 128.4, 128.0, 127.7, 126.2, 78.1, 65.9, 55.9, 50.2, 47.7, 40.9, 28.1, 23.8, 23.2, 21.4, 16.6. The fully protected tripeptide (900 mg, 1.7 mmol, 1 equiv) was then treated with TFA–CH_2Cl_2 (1:1, 10 mL) for 3 h. The solvents were removed and the residue was co-evaporated with toluene (2×10 mL), toluene–CH_2Cl_2 (1:1, 2×10 mL), and hexane–CH_2Cl_2 (1:1, 2×10 mL). The resulting crude compound was purified by preparative RP-HPLC affording **26** (580 mg, 79%) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (dd, J=13.3, 7.7 Hz, 2H), 8.13 (d, J=4.9 Hz, 1H), 7.45–7.11 (m, 10H), 5.21–5.00 (m, 4H), 4.41–4.25 (m, 2H), 4.15–3.98 (m, 1H), 2.99 (m, 2H), 1.36–1.08 (m, 6H), 0.74 (dd, J=10.9, 6.2 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.6, 171.9, 168.0, 136.4, 135.3, 129.9, 128.9, 128.8, 128.5, 128.3, 127.5, 66.4, 53.7, 51.0, 48.1, 41.6, 37.7, 24.1, 23.5, 21.9, 17.1; UPLC-MS gradient A t_R 1.46 min (>95%); MS calcd for $C_{25}H_{33}N_3O_4[M+H]^+$ 440.3, found 440.3; HRMS calcd for $C_{25}H_{33}N_3O_4[M+H]^+$ 440.2544, found 440.2552;

4.33. Solonamide A (1)

Polystyrene 2-chlorotrityl-bound Fmoc-L-Phe-D-Leu-D-Ala (600 mg, 0.51 mmol, 1 equiv) was added to a fritted syringe and swelled with CH_2Cl_2 before the Fmoc group was removed with

piperidine–DMF (1:4, 4 mL, 2×30 min) and DBU–piperidine–DMF (2:2:96, 4 mL, 30 min). Then the resin was washed with DMF (×3), MeOH (×3), and CH_2Cl_2 (×3) and dimer **18** (200 mg, 0.56 mmol, 1.1 equiv) was preincubated for 10 min with ^{i}PrEtN (350 μl, 2.02 mmol, 4 equiv) and HATU (385 mg, 1.01 mmol, 2 equiv) before addition to the resin and the reaction was allowed to proceed on a rocking table for 24 h and the resin was washed with DMF (×3), MeOH (×3) and CH_2Cl_2 (×3). The resin was treated TFA–CH_2Cl_2 (1:1, 2 mL, 2×30 min) followed by washing with CH_2Cl_2 (3×2 mL) and all the fractions were pooled in a round-bottomed flask and concentrated under reduced pressure. Co-evaporation with toluene (×2), toluene–CH_2Cl_2 (1:1, ×2), and hexane–CH_2Cl_2 (1:1, ×2) afforded the crude (201 mg, 64%) To a stirred solution the crude linear precursor (108 mg, 0.19 mmol, 1 equiv) in DMF (190 mL) was added ^{i}PrEtN (130 μl, 0.74 mmol, 4 equiv). HATU (142 mg, 0.37 mmol, 2 equiv) was added and the reaction was stirred at room temperature overnight, and then DMF is evaporated. The residue was purified by preparative reversed-phase HPLC to give cyclic depsipeptide (2.5 mg, 3%) as a white fluffy solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, *J*=5.6 Hz, 1H), 8.62 (d, *J*=3.1 Hz, 1H), 7.49 (d, *J*=8.9 Hz, 1H), 7.30–7.16 (m, 5H), 7.06 (d, *J*=9.8 Hz, 1H), 5.23–5.11 (m, 1H), 4.48 (m, 1H), 4.27 (m, 1H), 4.19 (m, 1H), 3.57 (m, 1H), 2.96 (dd, *J*=13.3, 6.1 Hz, 1H), 2.78–2.64 (m, 2H), 2.12 (dd, *J*=13.5, 10.3 Hz, 1H), 1.71–1.59 (m, 2H), 1.58–1.40 (m, 4H), 1.33 (d, *J*=7.4 Hz, 3H), 1.31–1.15 (m, 3H), 1.07–0.94 (m, 1H), 0.90–0.85 (m, 6H), 0.83 (d, *J*=6.4 Hz, 4H), 0.71 (d, *J*=6.6 Hz, 4H), 0.54 (d, *J*=6.4 Hz, 3H); UPLC-MS gradient A t_R 2.14 min (>95%). MS calcd for $C_{30}H_{46}N_4O_6$ $[M+H]^+$ 559.3, found 559.3.

4.34. Solonamide B (2)

Procedure 1. Polystyrene 2-chlorotrityl-bound H-L-Phe-D-Leu-D-Ala-OH **3** (0.32 mmol, 1 equiv) was added to a fritted syringe and swelled with CH_2Cl_2. Dimer **19** (130 mg, 0.35 mmol, 1.1 equiv) was preincubated for 10 min with HATU (241 mg, 0.63 mmol, 2 equiv) and ^{i}PrEtN (221 μl, 1.27 mmol, 4 equiv) before addition to the resin and the reaction was allowed to proceed on a rocking table for 24 h and the resin was washed with DMF (×3), MeOH (×3) and CH_2Cl_2 (×3). The resin was treated TFA–CH_2Cl_2 (1:1, 2 mL, 2×30 min) followed by washing with CH_2Cl_2 (3×2 mL) and all the fractions were pooled in a round-bottomed flask and concentrated under reduced pressure. Co-evaporation with toluene (×2), toluene–CH_2Cl_2 (1:1, ×2), and hexane–CH_2Cl_2 (1:1, ×2) afforded the crude linear precursor (127 mg, 66%). To a solution of the crude in DMF (210 mL) were added ^{i}PrEtN (146 μl, 0.84 mmol, 4 equiv) and HATU (160 mg, 0.42 mmol, 2 equiv), and the dilute reaction mixture was stirred at room temperature overnight. The solvent was then removed under reduced pressure and the residue was purified by preparative reversed-phase HPLC. Lyophilization of the pure fractions gave cyclic depsipeptide **2** (1 mg, 2%) as a white fluffy solid.

Procedure 2. Dimer **25** (270 mg, 0.66 mmol, 1 equiv), PyBOP (461 mg, 0.79 mmol, 1.2 equiv), and ^{i}PrEtN (139 μl, 0.79 mmol, 1.2 equiv) were dissolved in DMF (5 mL) and stirred 10 min. Trimer **26** (320 mg, 0.73 mmol, 1.1 equiv) in DMF (5 mL) was added and stirring was continued for 16 h at room temperature. Solvents were removed and the crude pentamer (530 mg, 0.64 mmol, 1 equiv) was dissolved in EtOH (10 mL) and degassed with argon. Then, Pd/C (106 mg, 0.1 equiv) was added and the mixture was again degassed with argon. The mixture was stirred under an H_2 atm overnight, the catalyst was removed by filtration through a pad of Celite, and the solvent was removed under reduced pressure to afford the linear crude product as an oil. This was divided into two equal portions and two cyclization procedures were performed. (A) HATU (294 mg, 0.77 mmol, 2 equiv) and ^{i}PrEtN (269 μl, 1.54 mmol, 4 equiv) were dissolved in CH_2Cl_2 (20 mL), and linear peptide (233 mg, 0.39 mmol, 1 equiv) in DMF–CH_2Cl_2, 10:1 (25 mL) was added by syringe pump over 4 h and stirred at room temperature for additional 2 h. Then the solvents were removed and the residue purified by preparative reversed-phase HPLC to afford solonamide B **2** (3 mg, 1%). (B) To a stirred solution of crude linear precursor (233 mg, 0.39 mmol, 1 equiv) in DMF (385 mL) was added *i*PrEtN (269 μl, 1.54 mmol, 4 equiv) and HATU (294 mg, 0.77 mmol, 2 equiv) and the reaction was stirred at room temperature overnight. Concentration, purification of the crude residue by preparative reversed-phase HPLC, and lyophilization gave cyclic depsipeptide solonamide B (2 mg, 1%) as a white fluffy solid.

$[\alpha]_D^{20}$ +4° (*c* 2, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, *J*=5.6 Hz, 1H), 8.61 (d, *J*=3.2 Hz, 1H), 7.49 (d, *J*=8.9 Hz, 1H), 7.30–7.16 (m, 5H), 7.06 (d, *J*=9.7 Hz, 1H), 5.19–5.07 (m, 1H), 4.47 (td, *J*=10.1, 4.3 Hz, 1H), 4.27 (m, 1H), 4.19 (m, 1H), 3.57 (m, 1H), 2.96 (dd, *J*=13.4, 6.1 Hz, 1H), 2.78–2.64 (m, 2H), 2.12 (dd, *J*=13.5, 10.2 Hz, 1H), 1.71–1.60 (m, 2H), 1.59–1.36 (m, 4H), 1.33 (d, *J*=7.4 Hz, 3H), 1.25 (t, *J*=9.3 Hz, 7H), 1.06–0.95 (m, 1H), 0.90–0.81 (m, 9H), 0.71 (d, *J*=6.6 Hz, 3H), 0.54 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.3, 171.6, 171.2, 170.2, 136.3, 129.2, 128.9, 126.4, 72.3, 55.8, 52.9, 48.8, 47.9, 39.2, 38.8, 36.1, 34.0, 30.9, 23.7, 22.9, 22.9, 21.8, 21.1, 20.4, 16.4, 13.5; UPLC-MS gradient A t_R 2.35 min (>95%); MS calcd for $C_{32}H_{50}N_4O_6$ $[M+H]^+$ 587.4, found 587.3; HRMS calcd for $C_{32}H_{50}N_4O_6$ $[M+H]^+$ 587.3803, found 587.3813.

4.35. β^3-*epi*-Solonamide A (β^3-*epi*-1)

Polystyrene 2-chlorotrityl-bound H-L-Phe-D-Leu-D-Ala **3** (0.38 mmol, 1 equiv) was added to a fritted syringe and swelled with CH_2Cl_2. Dimer **22** (150 mg, 0.42 mmol, 1.1 equiv) was preincubated for 10 min with ^{i}PrEtN (243 μl, 1.5 mmol, 4 equiv) and HATU (288 mg, 0.76 mmol, 2 equiv) before addition to the resin and the reaction was allowed to proceed on a rocking table for 24 h and the resin was washed with DMF (×3), MeOH (×3) and CH_2Cl_2 (×3). The resin was treated TFA–CH_2Cl_2 (1:1, 2 mL, 2×30 min) followed by washing with CH_2Cl_2 (3×2 mL) and all the fractions were pooled in a round-bottomed flask and concentrated under reduced pressure. Co-evaporation with toluene (×2), toluene–CH_2Cl_2 (1:1, ×2) and hexane–CH_2Cl_2 (1:1, ×2) afforded the crude (108 mg, 50%) To a stirred solution of crude (108 mg, 0.19 mmol, 1 equiv) in DMF (190 mL) was added ^{i}PrEtN (130 μl, 0.74 mmol, 4 equiv). HATU (142 mg, 0.37 mmol, 2 equiv) was added and the reaction was stirred at room temperature overnight, and the DMF was evaporated. The residue was purified by preparative reversed-phase HPLC to give cyclic depsipeptide (4 mg, 4%) as a white fluffy solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 (d, *J*=7.3 Hz, 1H), 8.31 (d, *J*=5.4 Hz, 1H), 7.42 (d, *J*=7.5 Hz, 1H), 7.32–7.18 (m, 6H), 4.85 (m, 1H), 4.37 (dd, *J*=13.4, 7.6 Hz, 1H), 4.30 (m, 1H), 4.13 (p, *J*=7.1 Hz, 1H), 3.87 (m, 1H), 2.91 (dd, *J*=13.4, 7.2 Hz, 1H), 2.83 (dd, *J*=13.4, 8.4 Hz, 1H), 2.54 (m, 2H), 2.39 (dd, *J*=14.8, 4.0 Hz, 1H), 1.74 (m, 1H), 1.57 (m, 1H), 1.50 (m, 3H), 1.34 (m, 2H), 1.27 (m, 2H), 1.20 (d, *J*=7.0 Hz, 3H), 1.00 (m, 1H), 0.87 (m, 6H), 0.83 (d, *J*=5.9 Hz, 3H), 0.73 (d, *J*=6.6 Hz, 3H), 0.64 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.0, 172.1, 171.0, 169.2, 169.2, 136.8, 128.1, 127.5, 126.0, 71.1, 55.0, 51.8, 51.5, 48.3, 39.3, 39.1, 38.2, 36.7, 34.5, 24.1, 23.3, 22.7, 22.0, 21.7, 20.6, 17.8, 1v7.5, 13.5. UPLC-MS gradient A t_R 2.19 min (>95%); MS calcd for $C_{30}H_{46}N_4O_6$ $[M+H]^+$ 559.3, found 559.3; HRMS calcd for $C_{30}H_{46}N_4O_6$ $[M+H]^+$ 559.3490, found 559.3506.

4.36. β^3-*epi*-Solonamide B (β^3-*epi*-2)

Polystyrene 2-chlorotrityl-bound Fmoc-L-Phe-D-Leu-D-Ala (190 mg, 0.08 mmol, 1 equiv) was added to a fritted syringe and swelled with CH_2Cl_2 before the Fmoc group was removed with piperidine–DMF (1:4, 4 mL, 2×30 min) and DBU–piperidine–DMF (2:2:96, 4 mL, 30 min) and then the resin was washed with DMF

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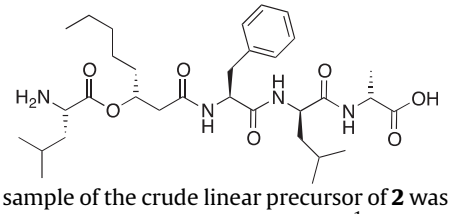
(×3), MeOH (×3), and CH_2Cl_2 (×3). Dimer **23** (33 mg, 0.09 mmol, 1.1 equiv) was preincubated for 10 min with ^{i}PrEtN (51 μl, 0.32 mmol, 4 equiv) and HATU (61 mg, 0.16 mmol, 2 equiv) before addition to the resin and the reaction was allowed to proceed on a rocking table for 24 h and the resin was washed with DMF (×3), MeOH (×3), and CH_2Cl_2 (×3). The resin was treated TFA–CH_2Cl_2 (1:1, 2 mL, 2×30 min) followed by washing with CH_2Cl_2 (3×2 mL) and all fractions were pooled in a round-bottomed flask and concentrated under reduced pressure. Co-evaporation with toluene (×2), toluene–CH_2Cl_2 (1:1, ×2), and hexane–CH_2Cl_2 (1:1, ×2) afforded the crude linear precursor (35 mg, 45%). To a stirred solution of crude (35 mg, 0.058 mmol, 1 equiv) in DMF (60 mL) was added ^{i}PrEtN (40 μl, 0.23 mmol, 4 equiv) and HATU (44 mg, 0.12 mmol, 2 equiv) and the reaction was stirred at room temperature overnight, after which DMF was evaporated. The residue was purified by preparative reversed-phase HPLC to give cyclic depsipeptide (2 mg, 7%) as a white fluffy solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 (d, J=7.3 Hz, 1H), 8.30 (d, J=5.4 Hz, 1H), 7.42 (d, J=7.5 Hz, 1H), 7.31–7.16 (m, 6H), 4.85 (t, J=12.0 Hz, 1H), 4.37 (dd, J=13.4, 7.7 Hz, 1H), 4.29 (m, 1H), 4.13 (m, 1H), 3.92–3.82 (m, 1H), 2.91 (dd, J=13.4, 7.3 Hz, 1H), 2.83 (dd, J=13.4, 8.4 Hz, 1H), 2.55 (dd, J=14.8, 8.0 Hz, 1H), 2.38 (dd, J=14.8, 3.9 Hz, 1H), 1.74 (d, J=7.4 Hz, 1H), 1.61 (d, J=8.2 Hz, 1H), 1.50 (t, J=8.0 Hz, 3H), 1.38–1.22 (m, 8H), 1.20 (d, J=7.0 Hz, 3H), 1.05–0.93 (m, 1H), 0.89–0.79 (m, 9H), 0.73 (d, J=6.6 Hz, 3H), 0.64 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.2, 171.2, 170.1, 169.1, 136.7, 129.3, 128.6, 126.4, 71.4, 55.2, 52.1, 51.7, 48.5, 39.4, 39.3, 38.0, 36.8, 32.2, 31.1, 24.1, 24.0, 23.1, 23.0, 22.1, 22.0, 21.6, 20.6, 17.5, 13.6. UPLC-MS gradient A t_R 2.29 min (>95%); MS calcd for $C_{32}H_{50}N_4O_6$ $[M+H]^+$ 587.4, found 587.3; HRMS calcd for $C_{32}H_{50}N_4O_6$ $[M+H]^+$ 587.3803, found 587.3822.

4.37. Linear solonamide B



A small sample of the crude linear precursor of **2** was purified by preparative RP-HPLC affording (4 mg, 2%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35–8.25 (m, 3H), 8.21 (d, J=7.1 Hz, 1H), 7.27–7.14 (m, 5H), 5.08 (m, 1H), 4.65–4.54 (m, 1H), 4.31 (m, 1H), 4.15 (m, 1H), 3.92 (m, 1H), 2.94 (dd, J=13.5, 5.8 Hz, 1H), 2.74 (dd, J=13.4, 9.1 Hz, 1H), 2.47–2.33 (m, 2H), 1.78–1.47 (m, 3H), 1.44–1.32 (m, 5H), 1.29 (d, J=7.8 Hz, 3H), 1.26–1.12 (m, 6H), 0.89–0.85 (m, 9H), 0.82 (d, J=6.2 Hz, 3H), 0.77 (d, J=6.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4, 172.2, 171.1, 169.8, 168.8, 137.9, 129.7, 128.4, 126.7, 73.6, 54.3, 51.1, 50.8, 48.0, 41.3, 38.7, 33.3, 31.4, 24.4, 24.3, 24.2, 23.7, 22.5, 22.4, 22.4, 21.8, 17.3, 14.3; UPLC-MS gradient A t_R 1.60 min (>95%); HPLC gradient C t_R 11.03 min (>95%); MS calcd for $C_{32}H_{52}N_4O_7$ $[M+H]^+$ 605.4, found 605.3; HRMS calcd for $C_{32}H_{52}N_4O_7$ $[M+H]^+$ 605.3909, found 605.3910.

4.38. Agar diffusion assay

The principle and method for the *S. aureus* screening assay used was as previously described by Nielsen et al.[41] The strains used for the screening assay were PC322, PC203, and the supernatant of strain 8325-4 (AIP-I). Briefly, bacteria were grown on tryptic soy broth agar (TSA) plates. Overnight cultures were prepared by inoculating a single colony into tryptic soy broth (TSB) (10 mL) and grown at 37 °C while shaking. Serial dilutions to 1000× were made after the optical density (OD) at 10× was adjusted to 0.35 (OD600). TSA was melted and 5-bromo-4-chloro-3-indolyl β-D-galactopyranoside (X-gal) (150 μg×mL^{-1}) and erythromycin (5 μg×mL^{-1}) were added. For each small plate 800 μL of bacterial dilution were mixed with 20 mL TEX (TSA, X-gal, and erythromycin), or 2 mL bacterial dilution mixed with 50 mL TEX for large plates. Plates were allowed to cool for 45 min. Once thoroughly dried, wells were drilled into the agar. Test sample or control (20 μL) were added per well and the plates were incubated at 37 °C. Incubation was allowed until the blue color appeared in the plates and this varied between approximately 9–48 h.

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Supplementary data

Copies of NMR spectra are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.05.107.

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