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Total Synthesis of Halipeptins: Isolation of Halipeptin D and Synthesis of Oxazoline Halipeptin Analogues

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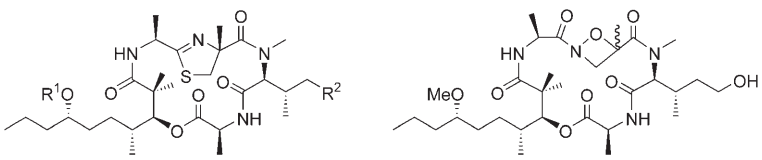
Abstract: The isolation from the marine sponge *Leiosella* cf. *arenifibrosa* and structural elucidation of halipeptin D (**5**), a relative of the previously isolated halipeptins A–C (**1**–**3**), is described along with the total synthesis of a number of oxazoline analogues (**7a**–**d** and *epi*-**7c**–**d**). The developed synthetic strategy provides a flexible entry into the various isomers of the polyketide domain of the halipeptins and improvises for a late stage construction of the oxazoline ring after a macrolactamization process which secures the required macrocycle.

Keywords: halipeptins · natural products · oxazolines · peptides · total synthesis

Introduction

The halipeptins (A–C, **1**–**3**, Figure 1) are a group of marine derived natural products whose structural identity and biological properties were shrouded with mystique until very recently. Their story began in 2001 when the Gomez-Paloma group reported the isolation of halipeptins A and B from the sponge *Haliclona* sp., the assignment of a striking, 1,2-oxazetidine-containing structure (i.e., **4**, Figure 1) to one of them (A), and the impressive antiinflammatory properties of halipeptin A (60% reduction of carrageenan-induced paw edema in mice at the *intraperitoneal* dose of 0.3 mg kg^{-1} body weight).[1] Soon thereafter in 2002, the isolation and more accurate structural assignment of halipeptin C[2] as a thiazoline-containing structure **3** forced the Gomez-Paloma group to revise their structures for halipeptins A and B from the oxazetidine structures[1,3] to the thiazoline structures **1** and **2**, respectively. Yet another halipeptin (halipeptin D, **5**, Figure 2) was later isolated (by Manam and Faulkner, see below) from a different marine species. It is important to note that neither we nor the Gomez-Paloma group[1] could assign absolute stereochemistries at C-3 and C-4 of the decanoic acid residue (e.g. **10a**, Figure 3), although the former group determined the stereochemical identity at C-7 as being (*S*) in halipeptin B (**2**).[1] Based on biosynthetic considerations, the assumption that all four halipeptins possess 7*S* configuration is reasonable but not conclusive. In addition, both we and the Gomez-Paloma group did recognize the *syn* relationship of the substituents at this



1: R^1 = Me, R^2 = CH_2OH: halipeptin A
2: R^1 = H, R^2 = CH_2OH: halipeptin B
3: R^1 = H, R^2 = H : halipeptin C

4

Figure 1. Structures of halipeptins A-C (**1**–**3**)[2] and the original structural assignment for halipeptin A (**4**).[1]

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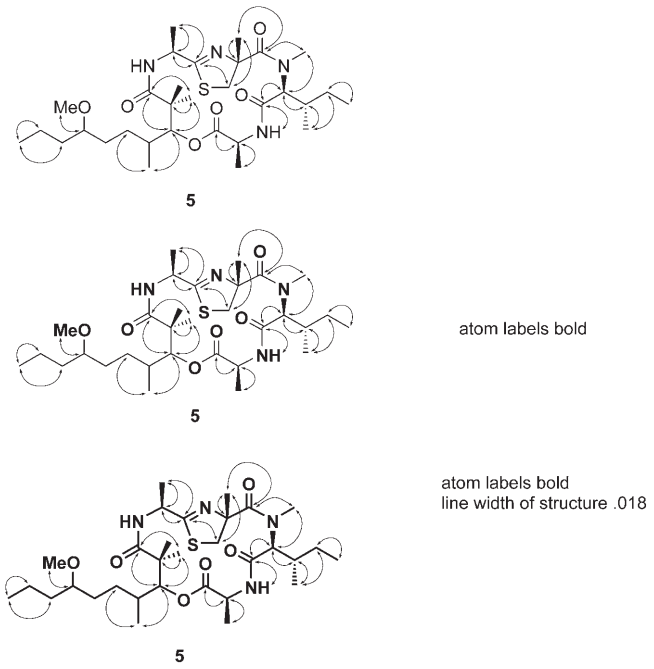


Figure 2. Proposed structure and HMBC correlations (curved arrows) of halipeptin D (**5**).

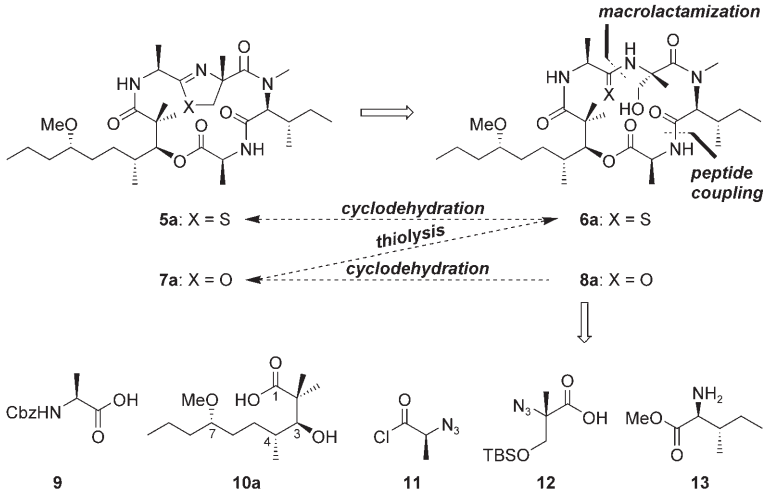


Figure 3. Retrosynthetic analysis of halipeptins (e.g. of one likely structure, **5a**, of halipeptin D) and their oxazoline counterparts (e.g. **7a**).

site (C-3/C-4), leaving open the precise structure as being either 3*S*,4*R*,7*S* or 3*R*,4*S*,7*S*. It was not until recently that the absolute configuration of halipeptin A[4,5] and halipeptin D[4] could be revealed by total synthesis and that further details about their biological activity were obtained.[4] In this article, we describe the isolation and structural elucidation of halipeptin D (**5**) and the total synthesis of a number of its oxazoline analogues.

Results and Discussion

Isolation and structural elucidation of halipeptin D: The isolation of halipeptin D (**5**, Figure 2) began with the collection of the sponge *Leiosella* cf. *arenifibrosa* from the northwestern waters off Boracay Island (Philippines) and was aided by chromatographic techniques and biological assays. Thus, the ethyl acetate soluble material from a methanol extract of the sponge was purified by chromatography on sephadex LH-20 by using methanol as eluent. The active fractions were combined and re-chromatographed, first on silica gel and then by normal-phase HPLC applying a hexane/ethyl acetate gradient. Halipeptin D was isolated along with several other highly active compounds; their structures and biological activities will be reported elsewhere in due course. The new halipeptin was obtained as a colorless viscous oil ($[\alpha]_D^{25} = -26.0$, $c = 0.2$, $CHCl_3$) and exhibited an $[M+H]^+$ ion at m/z 611.3932 and an $[M+Na]^+$ ion at m/z 633.3745 in its HRMS (MALDI FTMS), from which a molecular formula of $C_{31}H_{54}O_6N_4S$ was deduced. Preliminary ^1H and ^{13}C NMR studies suggested a peptide-type structure, a conclusion that was supported by IR bands at $\nu_{max} = 3412, 3366, 1731, 1672$ and 1637 cm^{-1}. The combined analysis of the ^{13}C and DEPT-135° NMR spectra indicated eleven methyl, six methylene, seven methine and two quaternary carbon atoms, one double bond (C=N), and four carbonyl groups from which three were associated with amides ($\delta =$ 169.2, 172.3 and 173.4 ppm) and one with an ester ($\delta =$ 169.5 ppm), based on the observed connectivities (see Figure 2). On the basis of 2D NMR analysis (Table 1), spin systems for two alanines [$\delta_H =$ 7.01 (d, NH), 4.79 (quintet, Hα), 1.42 (d, CH_3) and 7.22 (d, NH), 4.84 (quintet, Hα), 1.52 (d, CH_3)] were easily identified. The isoleucine spin system [$\delta_H =$ 5.01 (d, Hα), 2.22 (m, Hβ), 1.34 (m, Hγ), 0.98 (t, $CH_3\gamma$), 0.96 (d, $CH_3\beta$)] was also characterized through well defined 2D NMR connectivities. The N-Me group was assigned to isoleucine, based on the strong HMBC correlation between its signal and that of Cα[δ_H=2.81 (*N*Me)/ δ_C=65.4 (Cα)]. The COSY, TOCSY and HMBC data connected the other long chain fragment as 3-hydroxy-7-methoxy-2,2,4-trimethyl decanoic acid (e.g. **10a**, Figure 3). Database searches (MarinLit, SciFinder) for the defined substructures and the molecular formulae found only three near matches, halipeptins A-C (**1**–**3**, Figure 1), among which halipeptin A (**1**)[1,2] was the closest. Most significantly, the NMR spectroscopic data, including coupling constants, for halipeptin D were almost identical to those of halipeptin A

Table 1. ^{1}H, ^{13}C and HMBC data of halipeptin D (**5**) as isolated from *L.* cf. *arenifibrosa* ($CDCl_3$).

Residue	δ_C (100 MHz)	δ_H, mult, *J* in Hz (300 MHz)	HMBC
Ala 1			
CO	169.5		
α	49.9	4.79, quintet, 7.0	Me-β, CO
β	18.6	1.42, d, 7.0	Cα
NH		7.01, d, 7.0	CO-NMeIle
NMeIle			
CO	169.2		
α	65.4	5.01, d, 11.0	CO, Cβ, Me-β, NMe, CO-α-MeCys
β	34.1	2.22, m	
Me-β	18.3	0.96, d, 6.5	Cα, Cβ, Cγ
γ	25.6	1.34, m	
δ	13.1	0.98, t, 7.0	Cγ
NMe	31.2	2.81, s	Cα, CO-α-MeCys
α-MeCys			
CO	172.3		
α	84.2		
Me-α	23.7	1.47, s	Cα, Cβ, CO
β1	44.8	3.31, d, 12.0	Cα, SC=N-Ala2, Me-α
β2		4.16, d, 12.0	Cα, CO, Me-α
N			
Ala 2			
SC=N	177.0		
α	49.0	4.84, quintet, 7.0	SC=N, Cβ
β	22.6	1.52, d, 7.0	SC=N, Cα
NH		7.22, d, 7.0	CO-HTMMD
HTMMD			
1	173.4		
2	46.2		
Me-2	26.7	1.15, s	C1, C2, C3, Me′-2
Me′-2	22.9	1.22, s	C1, C2, C3, Me-2
3	82.8	4.71, d. 2.0	C1
4	34.7	1.92, m	
Me-4	15.0	0.82, d, 7.0	C3, C4, C5
5	32.4	1.37, m	
6	31.8	1.46, m	
7	80.8	3.10, m	
7-OMe	56.8	3.31, s	C-7
8	36.2	1.34, m	
9	19.1	1.30, m	
10	14.9	0.92, t, 6.5	C-8, C-9

(**1**). Hence, based on comparison with literature data,[2] the remaining residue was identified as α-methyl cysteine and structure **5** (Figure 2) was assigned to halipeptin D. The difference between halipeptins A (**1**) and D (**5**) is only an extra oxygen atom residing at the terminus of the hydroxyisoleucine side chain within the structure of the former natural product **1**.

In sharp contrast to the biological properties described for halipeptin A,[1] halipeptin D (**5**) obtained as described above exhibited a strong in vitro inhibitory activity against a human colon cancer (HCT-116) cell line ($IC_{50} = 7$ nM)[6] and an average $IC_{50} = 420$ nM against a BMS ODCA (oncology diverse cell panel) of tumor cell lines.[7] In light of its structural similarity to halipeptins A–C (**1**–**3**) for which no such activity was reported, the cytotoxicity of halipeptin D (**5**) was rather puzzling and compounded the intrigue surrounding these natural products. Because of the scarcity of the naturally occurring substances, and in order to demystify these ambiguities, we undertook their total synthesis.[4]

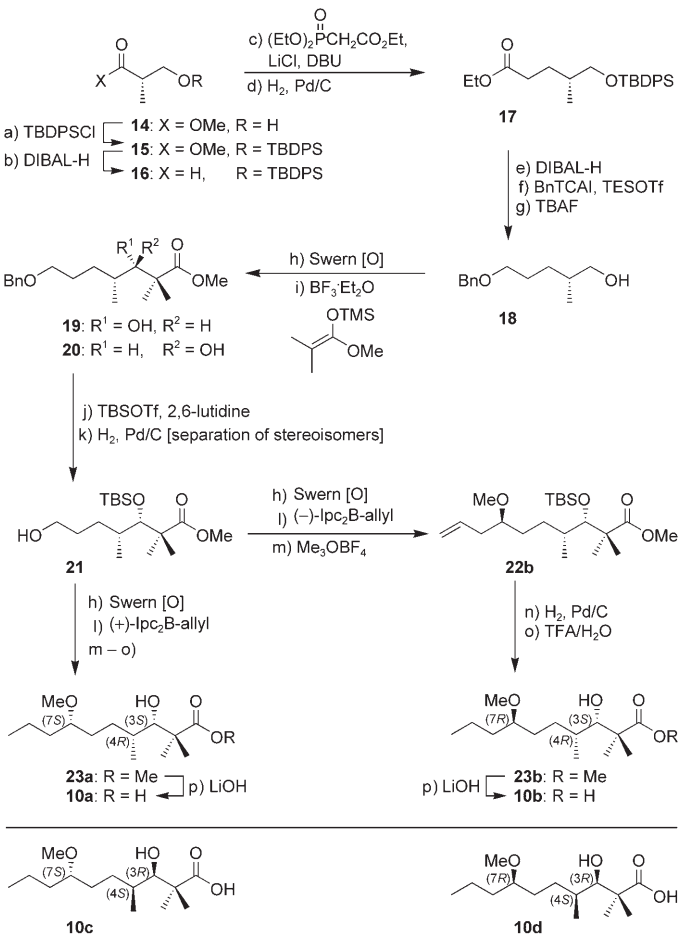
Total synthesis of oxazoline halipeptin analogues: In contemplating a synthetic pathway to the halipeptins (e.g. **5**, Figure 2), flexibility for the construction of all plausible isomers as well as their oxazoline counterparts (e.g. **7a**, Figure 3) was deemed important. In fact, the oxazoline analogues (e.g. **7a**) were defined as the first targets to be synthesized, for it was anticipated that they could serve as precursors to the naturally occurring thiazolines via a two-step thiolytic ring opening–cyclization sequence[8] (see Figure 3). The late-stage casting of the five-membered heterocycle within the halipeptin structure was preferred since the stereocenter adjacent to that structural motif was expected to readily isomerize;[8b,9] furthermore, the larger macrocycle involved in this approach was expected to form with greater ease than its oxazoline-containing counterpart due to less strain. The most suitable site for the macrocyclization was, however, not obvious at the outset, and it was only after considerable experimentation that successful entries into the macrocycle were found, the original of which will be reported here. Rupturing of all five strategic bonds as shown in Figure 3 revealed fragments **9**–**13** as the required building blocks for the projected constructions. Significantly, the routes chosen to synthesize some of these key intermediates could deliver any of the desired stereoisomers, thus satisfying our flexibility criteria.

The construction of the most likely required decanoic acid[10] fragments proceeded as exemplified for the two 3*S*,4*R* isomers **10a** and **10b** in Scheme 1. Thus, the readily available hydroxy methyl ester **14** was converted by a modification of a known sequence[11] and in high yield into alcohol **18** which, after Swern oxidation to the corresponding aldehyde,[12] was subjected to a Mukaiyama-type aldol reaction with methyl trimethylsilyl dimethylketene acetal in the presence of $BF_3{\cdot}Et_2O$ to afford a 7:3 mixture of the inseparable diastereomeric alcohols **19** and **20** in a combined 79% yield from alcohol **18**. Elaboration of the latter mixture by TBS protection (for abbreviations of reagents and protecting groups, see legends in schemes) and debenzylation afforded major isomer **21** in 88% (49% from alcohol **18**)

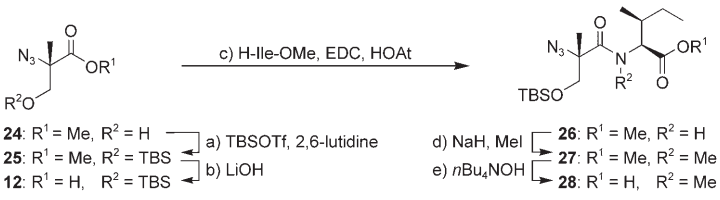
yield after chromatographic removal of its diastereomeric counterpart. Swern oxidation to the aldehyde, and Brown allylation employing (−)-$(Ipc)_2$ allylborane (>90% *dr*) followed by methylation of the resulting alcohol furnished compound **22b** in excellent overall yield (75%). Subsequent hydrogenation of the olefin, desilylation and saponification led to the targeted hydroxy acid **10b** in 92% overall yield from **22b**. The application of (+)-$(Ipc)_2$ allylborane in the allylation step led to hydroxy decanoic acid **10a**, and the remaining stereoisomers possessing 3,4-*syn* configuration (**10c** and **10d**) were obtained starting from *ent*-**14** by application of each of the enantiomeric allylboranes.

The synthesis of the highly congested fragment **28** featuring a carboxylic acid group and an azide moiety was carried out following the sequence shown in Scheme 2. Thus, the α-methyl serine methyl ester derivative **24**[13] was silylated and thence hydrolyzed under basic conditions to afford carboxylic acid **12** (96% yield). A stepwise coupling of **12** with isoleucine methyl ester followed by methylation of the nitrogen atom within the resulting amide **26** proved much superior to coupling of **12** with N-methyl isoleucine derivatives, and yielded compound **27** in 87% yield from acid **12**. Since azide reduction of **27** led to instantaneous cyclization to the corresponding diketopiperazine, chain elongation from the N-terminus of **27** was abandoned in favor of coupling the C-terminus to building block **31** (see Scheme 3). The required methyl ester hydrolysis within **27** proved troublesome and was best accomplished with aqueous nBu_4NOH[14] at 0°C in THF, furnishing the desired carboxylic acid **28** in a 70% crude yield.

The assembly of the synthesized fragments **10a–d** (Scheme 1), **28** (Scheme 2), and **11**[15] into the macrocyclization precursor **34** are shown in Scheme 3. Thus, coupling of, for example, decanoic acid segment **10a** with alanine methyl ester, followed by ester formation at the free hydroxyl group of the resulting product (**29a**) with a 19-fold excess of alanine-derived acid chloride **11**[15] in the presence of 4-DMAP at 50°C in DMF afforded the amide ester **30a** in 88% overall yield. Gratifyingly, no epimerization was observed under these rather harsh conditions. The configuration of the presumably stereochemically labile acid chloride **14** was shown to be intact by comparing the spectroscopic data of **30a** with those of a sample derived from **29a** and *ent*-**11**. Subsequent reduction of the azide group within **30a** was accomplished by catalytic hydrogenation (10% Pd/C), furnishing the desired amine **31a**. Coupling of the crude amine **31a** with a slight excess carboxylic acid fragment **28** in the presence of PyAOP, HOAt and iPr_2NEt afforded azide methyl ester **32a** in 71% overall yield from azide **30a**. Selective hydrolysis of the methyl ester within compound **32a**, under the mild conditions of Me_3SnOH,[16] gave carboxylic acid **33a** in 95% yield; the azide moiety was hydrogenolyzed, generating the required amino acid **34a**. Direct macrocyclization of **34a** could be carried out with a number of coupling agents (e.g. EDC/HOAt/iPr_2NEt/CH_2Cl_2: 33%, pentafluorophenyl diphenylphosphinate (FDPP)/iPr_2NEt/CH_2Cl_2: 25%), but was best achieved with HATU/HOAt/iPr_2NEt in CH_2Cl_2 at a 1 mM concentration yielding macrocycle **35a** in 68–74% overall yield in several experiments. Removal of the TBS group from compound **35a** led to its hydroxy counterpart **8a**, paving the way for the final step.



Scheme 1. Synthesis of hydroxy decanoic acids **10a–d**. a) TBDPSCl (1.0 equiv), imidazole (3.0 equiv), CH_2Cl_2, 25°C, 76 h, 99%; b) DIBAL-H (1.1 equiv), toluene, −78°C, 1.5 h; c) $(EtO)_2P(O)CH_2CO_2Et$ (1.2 equiv), LiCl (1.2 equiv), DBU (1.2 equiv), CH_3CN, 25°C, 19 h; d) H_2 (1 atm), 5% Pd/C (33% by weight), EtOAc, 25°C, 20 h, 82% (three steps); e) DIBAL-H (2.5 equiv), toluene, −78 → 25°C, 2 h, 93%; f) BnTCAI (1.5 equiv), TESOTf (2%), CH_2Cl_2, 25°C, 8 h; g) TBAF (3.0 equiv), THF, 25°C, 3 h, 69% (two steps); h) DMSO (2.8 equiv), $(COCl)_2$ (1.9 equiv), CH_2Cl_2, −78°C; then Et_3N (5.0 equiv), −78 → 25°C, 3 h, product not isolated; i) $BF_3{\cdot}Et_2O$ (1.1 equiv), $Me_2C{=}C(OMe)OTMS$ (1.2 equiv), CH_2Cl_2, −78°C, 1.5 h, 79% (two steps, **19**/**20** 7:3); j) TBSOTf (1.3 equiv), 2,6-lut. (1.5 equiv), CH_2Cl_2, 0°C, 1 h, 99%; k) H_2 (1 atm), 10% Pd/C (20% by weight), EtOH, 25°C, 24 h, separation of diastereoisomers, 88% (two steps, major isomer **21**); l) $(+)$-$(Ipc)_2$B-allyl (2.0 equiv), Et_2O, −100 → −46°C; then H_2O_2, aq NaOH; m) Me_3OBF_4 (10.0 equiv based on **21**), proton sponge (16 equiv), CH_2Cl_2, 25°C, 75% (three steps); n) H_2 (1 atm), 10% Pd/C (50% by weight), EtOH, 25°C, 2 h; o) TFA:H_2O (9:1), −10°C, 5 min, 93% (two steps); p) LiOH·H_2O (6.0 equiv), MeOH:H_2O (4:1), 25°C, 24 h, 99%. 2,6-lut. = 2,6-lutidine; BnTCAI = benzyl 2,2,2-trichloroacetimidate; DBU = 1,8-diazabicyclo-[5.4.0]-undec-7-ene; DIBAL-H = diisobutylalmuninumhydride; Ipc = isopinocampheyl; TBAF = tetra-*n*-butylammonium fluoride; TBDPSCl = *tert*-butyldiphenylsilyl chloride; TBS = *tert*-butylsilyl; TESOTf = triethylsilyl trifluoromethanesulfonate; TFA = trifluoroacetic acid; TMS = trimethylsilyl.

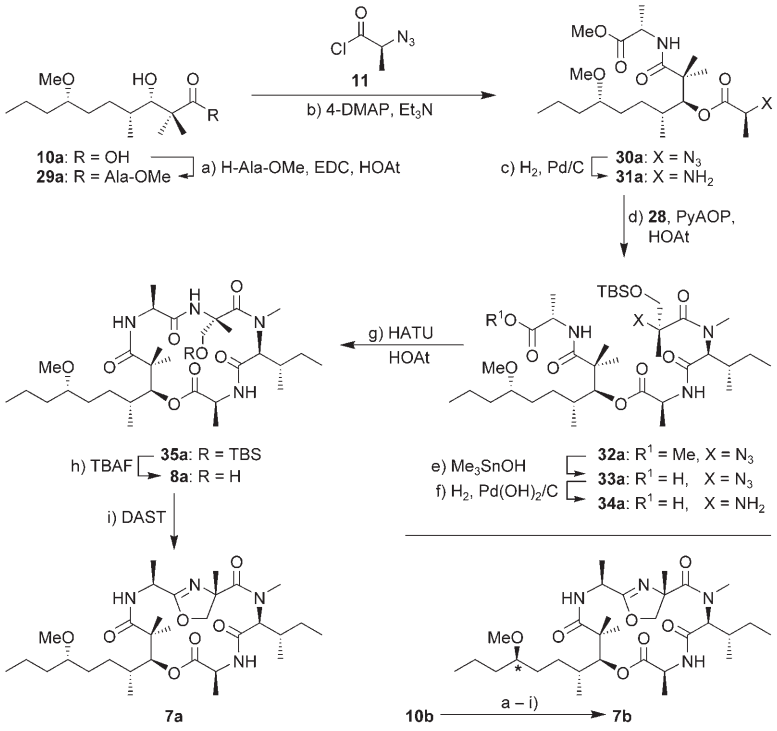


Scheme 2. Synthesis of Ser(αMe)-MeIle-OH dipeptide **28**. a) TBSOTf (2.0 equiv), 2,6-lut. (4.0 equiv), CH_2Cl_2, 0 °C, 2 h, 98 %; b) $LiOH \cdot H_2O$ (3.0 equiv), $MeOH/H_2O$ (4:1), 25 °C, 3 h, 96 %, c) H-Ile-OMe (1.3 equiv), EDC (1.1 equiv), HOAt (1.1 equiv), $i Pr_2NEt$ (3.0 equiv), CH_2Cl_2, 25 °C, 24 h, 91 %; d) NaH (3.0 equiv), MeI (4.0 equiv), DMF, 0 °C, 1 h, 96 %; e) nBu_4NOH (2.0 equiv), 0 °C, 6 h, approx. 70 %. EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HOAt = 1-hydroxy-7-azabenzotriazole.

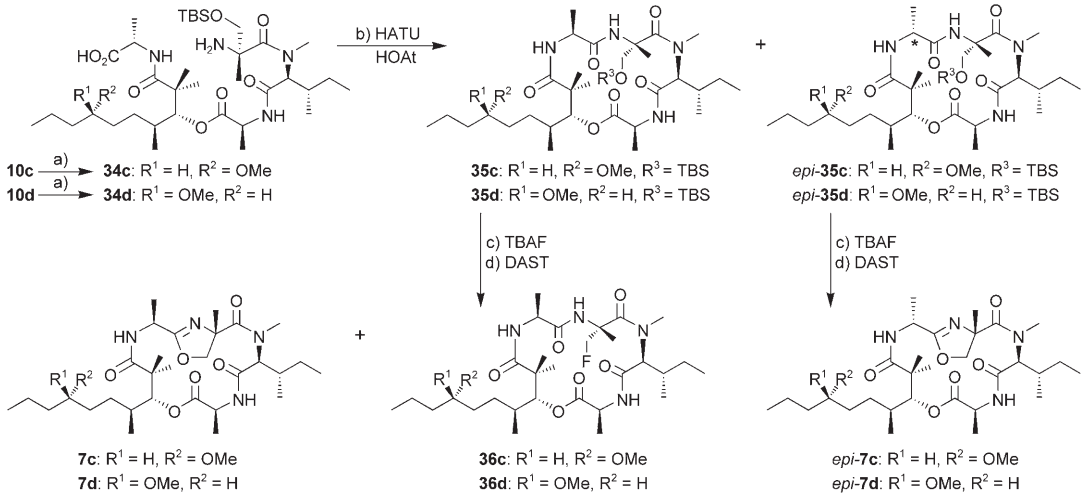
Indeed, exposure of crude **8a** to DAST[8c] at −78 °C generated oxazoline halipeptin D **7a** in 74 % yield. Starting from the other 3*S*,4*R*-decanoic acid (**10b**), differing in stereochemistry from **10a** only at the remote position C-7; the epimeric oxazoline **7b** was also obtained in almost identical overall yield (Scheme 3).

The synthetic sequence to **7a/b** was also employed to construct the oxazoline analogues **7c** and **7d** (Scheme 4). Starting from the 3*R*,4*S* decanoic acids **10c** and **10d** (Scheme 1), the macrocyclization substrates **34c** and **34d** were constructed as described for **34a/b** in Scheme 3. The further transformation of these compounds into oxazolines **7c** and **7d** was accompanied by a number of interesting observations. Thus, out of all coupling conditions applied to achieve macrocyclization of **34c** and **34d** (EDC/HOAt/$i Pr_2NEt/CH_2Cl_2$, FDPP/$i Pr_2NEt/CH_2Cl_2$, DPPA/$NaHCO_3$/DMF), only those employed previously (HATU/HOAt/$i Pr_2NEt/CH_2Cl_2$) furnished the desired cyclic depsipeptides, although the reaction was much slower and the yields of the macrocyclic products were considerably lower (36/44 %) than in the case of macrocyclization of the 3*S*,4*R*-isomers **34a** and **34b**. Additionally, the generated macrocycles **35c** and **35d** were accompanied by their alanine epimers, *epi*-**35c** and *epi*-**35d** (ca. 1:1 ratio, easily separable by silica gel flash column chromatography). After TBAF-induced desilylation, the resulting hydroxy amides **8c,d** and *epi*-**8c,d** (compare Figure 3) were subjected to DAST[8c] in order to generate the corresponding oxazolines. Presumably due to an unfavorable build-up of further ring strain, the yields in this step were again low. Starting from *epi*-**35c/d**, the oxazolines *epi*-**7c/d** were formed in 31/36 % yields. The reaction between the alcohols derived from **35c/d** by TBAF deprotection and DAST also furnished the corresponding cyclodehydration products, oxazolines **7c/d** (in 43/40 % yields), however, they were accompanied by major by-products, presumed to be the fluorinated compounds **36c/d** (45/51 %).[17]

Attempts towards thiolysis (H_2S under various conditions) of oxazoline halipeptin D (i.e.,**7a**) to the corresponding hydroxy thioamide (i.e., **6a**, Figure 3) as a prelude to the synthesis of halipeptin D (**5**), however, failed. Prolonged reaction times at elevated temperatures ($MeOH/Et_3N$ 2:1, saturation with H_2S, 60 °C, one week) only led to methanolic cleavage of the alanine ester bond without any incorporation of H_2S as suggested by MS fragmentation experiments. Apparently, the constraints imposed upon **7a** by its own molecular architecture did not allow it to undergo the intended rupture, demanding,



Scheme 3. Assembly of key building blocks **31a** and **8a** and synthesis of halipeptin D analogues **7a** and **7b** starting from 3(*S*),4(*R*) decanoic acids **10a** and **10b**. a) EDC (5.0 equiv), HOAt (4.0 equiv), H-Ala-OMe·HCl (4.0 equiv), $i Pr_2NEt$ (10.0 equiv), DMF, 25 °C, 3 h, 94 %; b) **11** (19 equiv), 4-DMAP (0.5 equiv), Et_3N (25 equiv), DMF, 50 °C, 24 h, 94 %; c) H_2 (1 atm), 10 % Pd/C (60 % by weight), 25 °C, 2 h; d) **28** (1.4 equiv), PyAOP (4.1 equiv), HOAt (3.7 equiv), $i Pr_2NEt$ (4.8 equiv), DMF, 25 °C, 15 h, 71 % (two steps); e) Me_3SnOH (20 equiv), 1,2-dichloroethane, 50 °C, 18 h, 95 %; f) H_2 (1 atm), 20 % $Pd(OH)_2/C$ (300 % by weight), EtOH, 0 °C, 0.5 h; g) HATU (1.5 equiv), HOAt (3.0 equiv), $i Pr_2NEt$ (3.0 equiv), CH_2Cl_2, 25 °C, 21 h, 74 % (two steps); h) TBAF (1.1 equiv), THF, −10 °C, 1.5 h; i) DAST (2.3 equiv), CH_2Cl_2, −78 → −12 °C, 1 h, 74 %. DAST = (diethylamino)sulfurtrifluoride; HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; PyAOP = (7-azabenzotriazole-1-yloxy) tripyrrolidinophosphonium hexaflurophosphate.



Scheme 4. Macrocyclization and oxazoline synthesis starting from linear depsipeptides **34c** and **34d** incorporating 3(*R*),4(*S*) decanoic acids **10c** and **10d**. a) as described for **34a** in Scheme 3; b) HATU (1.5 equiv), HOAt (3.0 equiv), *i*Pr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 24 h, **35c**: 14%, *epi*-**35c**: 22%, **35d**: 25%, *epi*-**35d**: 19%; c) TBAF (1.1 equiv), THF, 0 °C, 1 h (not isolated); d) DAST (3.0 equiv), CH_2Cl_2, −78 → −12 °C, 1 h, **7c**: 43%, **36c**: 45%, **7d**: 40%, **36d**: 51%, *epi*-**7c**: 31%, *epi*-**7d**: 36% (yields over two steps).

instead, a new strategy[4] for the total synthesis of halipeptin D and its siblings.

Biological evaluation of synthesized oxazoline halipeptin analogues: The synthesized halipeptin analogues **7a–d** and *epi*-**7c–d** were tested against HCT-116 human colon carcinoma cells and were found to be only weakly active (IC_{50} values: **7a**: 74.7 μM, **7b**: inactive, **7c**: 58.0 μM, **7d**: inactive, *epi*-**7c**: 8.2 μM, *epi*-**7d**: 4.6 μM).[18] These results were somewhat surprising in light of the previously attributed activity of halipeptin D (**5**) against a human colon cancer (HCT-116) cell line[6] and a BMS ODCA (oncology diverse cell panel) of tumor cell lines,[7] thereby inviting further investigations with the chemical synthesis of halipeptin D (**5**) became the most urgent. The accomplishment of this goal and a speculation regarding the above curiosity are reported elsewhere.[4]

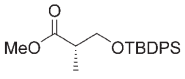
Conclusion

The isolation of halipeptin D (**5**) adds a new member to the growing class of halipeptins isolated from marine sponges. The potent cytotoxicity originally attributed to this new substance coupled with its scarcity and structural similarity to the previously isolated halipeptins A–C prompted us to undertake its total synthesis. The developed synthesis, however, failed to deliver the thiazoline-containing natural product, leading instead to a series of oxazoline analogues. The insignificant cytotoxicity of the synthesized analogues created a suspicion with regard to the initially obtained biological results from the naturally derived material, making the total synthesis of halipeptin D itself an even more urgent task. The completion of this task together with associated findings and the assignment of the absolute configuration of halipeptin D by total synthesis are described in a separate communication.[4]

Experimental Section

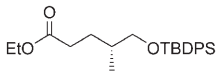
General procedures: All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions. Dry tetrahydrofuran (THF), toluene, diethyl ether (Et_2O) and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Reagents and dry *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO) and 1,2-dichloroethane were purchased at the highest commercial quality and used without further purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) by using UV light as visualizing agent and an aqueous (aq) solution of cerium ammonium nitrate, ammonium molybdate and sulfuric acid, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker DRX-600, DRX-500 and AMX-400 or Varian Inova-400 and Mercury-300 instruments and calibrated by using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrometer. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an API 100 Perkin–Elmer SCIEX single quadrupole mass spectrometer at 4000 V emitter voltage. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix-assisted laser-desorption ionization) or an Agilent ESI TOF (time of flight) mass spectrometer at 4000 V emitter voltage.

Compound 15: Hydroxy ester **14** (20.0 mL, 0.181 mol) and imidazole (37.03 g, 0.544 mol) were dissolved in CH_2Cl_2 (200 mL) and cooled to 0 °C. After the addition of TBDPSCl (47.0 mL, 0.18 mol) the solution was stirred for 76 h at ambient temperature and then washed with 1 M aq HCl (500 mL). The organic layer was washed with brine (500 mL), the aq layers were re-extracted with CH_2Cl_2

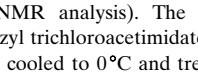


(2×150 mL), and the combined organic extracts were dried (Na_2SO_4), filtered through a plug of silica gel and evaporated to dryness yielding **15** (64.34 g, 0.180 mmol, 99%) as a colorless liquid. R_f=0.48 (silica gel, 10% EtOAc in hexanes); $[\alpha]_D^{25}$=+16.4 (c=1.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.65 (d, J=6.9 Hz, 4H), 7.45–7.35 (m, 6H), 3.77 (ddd, J=15.4, 9.8, 6.3 Hz, 2H), 3.68 (s, 3H), 2.72 (m, 1H), 1.16 (d, J=7.0 Hz, 3H), 1.03 ppm (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=175.4, 135.5, 134.8, 129.6, 127.6, 65.9, 51.5, 42.4, 26.7, 19.2, 13.4 ppm; IR (film): ν_{max}=3048, 2932, 2857, 1741, 1589, 1472, 1428, 1389, 1361, 1257, 1199, 1176, 1112, 1026, 823, 739, 702, 614, 505 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{21}H_{28}O_3SiNa$: 379.1705, found: 379.1700 $[M+Na]^+$.

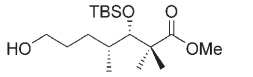
Compound 17: A 1.5 M DIBAL-H solution in toluene (6.0 mL, 9.0 mmol) was added at −78°C to a solution of ester **15** (2.92 g, 8.19 mmol) in toluene (80 mL). After 1.5 h, MeOH (5 mL) was added, the mixture was allowed to warm to 25°C and was then partitioned between water (500 mL) and Et_2O (200 mL). The organic layer was washed with brine (200 mL), the aq layers were re-extracted with Et_2O (2×100 mL) and the combined organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica gel, 2.5% EtOAc in hexanes) yielding TBDPS-protected (*S*)-3-hydroxy-2-methyl-propanal (2.58 g, 7.90 mmol, 96%) as a colorless liquid which was dissolved in acetonitrile (80 mL) and treated with triethyl phosphonoacetate (1.90 mL, 9.48 mmol) and DBU (1.45 mL, 9.48 mmol) in the presence of LiCl (400 mg, 9.48 mmol) at ambient temperature. After 19 h, the solution was partitioned between Et_2O (100 mL) and sat aq NH_4Cl (200 mL). The organic layer was washed with brine (200 mL), and the aq layers were re-extracted with Et_2O (100 mL). The combined organic layer was dried ($MgSO_4$), filtered through a plug of silica gel and evaporated to dryness yielding TBDPS-protected (*R*)-5-hydroxy-4-methyl-2-pentenoic acid ethyl ester (2.71 g, 7.20 mmol, 91%) as a colorless liquid. The product was dissolved in EtOAc (5 mL) and added to a suspension of Pd (5% on activated charcoal, 0.90 g) in EtOAc (50 mL). The mixture was then stirred under an H_2-atmosphere at ambient pressure for 20 h. Subsequent saturation with Ar, filtration of the catalyst and evaporation to dryness gave pentanoic ester **17** (2.71 g, 6.80 mmol, 82% from **15**) as a colorless liquid. R_f=0.47 (silica gel, 10% EtOAc in hexanes); $[\alpha]_D^{25}$=+2.5 (c=4.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.66 (dd, J=7.9, 1.5 Hz, 4H), 7.45–7.35 (m, 6H), 4.11 (q, J=7.0 Hz, 2H), 3.48 (m, 2H), 2.29 (m, 2H), 1.81 (m, 1H), 1.68 (m, 1H), 1.48 (m, 1H), 1.25 (t, J=7.0 Hz, 3H), 1.05 (s, 9H), 0.92 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.9, 135.6, 133.8, 129.6, 127.6, 68.4, 60.2, 35.2, 32.0, 28.4, 26.9, 19.3, 16.5, 14.2 ppm; IR (film): ν_{max}=3070, 2958, 2931, 2857, 1737, 1589, 1472, 1428, 1178, 1112, 824, 740, 702, 614, 505 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{24}H_{34}O_3SiNa$: 421.2169, found: 421.2167 $[M+Na]^+$.



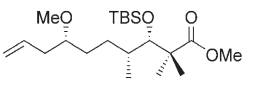
Compound 18: A 1 M solution of DIBAL-H in hexane (109 mL, 109 mmol) was added at −78°C to a solution of ester **17** (17.42 g, 43.7 mmol) in toluene (300 mL). The solution was allowed to warm to 25°C and stirred for 2 h before MeOH (20 mL) was added. The mixture was extracted with a sat aq K/Na tartrate (800 mL), the organic layer was washed with brine (300 mL), the aq layers were re-extracted with Et_2O (2×200 mL) and the combined organic layer was dried ($MgSO_4$). Filtration through a plug of silica gel, concentration and evaporation in vacuo afforded (*R*)-5-(*tert*-butyldiphenylsilyloxy)-4-methyl-pentanol (14.50 g, 40.1 mmol, 93%, pure based on ^{1}H NMR analysis). The product was dissolved in CH_2Cl_2 (200 mL), benzyl trichloroacetimidate (11.3 mL, 60.2 mmol) was added, the solution was cooled to 0°C and treated with TESOTf (180 μL, 0.80 mmol). After stirring for 8 h at ambient temperature, the solution was washed with brine (400 mL). The aq layer was re-extracted with CH_2Cl_2 (200 mL), and the combined organic layer was dried ($MgSO_4$), filtered through a plug of silica gel and evaporated, yielding a crude product (19.63 g) contaminated with major amounts of Bn_2O and BnOH. To a solution of this crude material (6.31 g) in THF (100 mL) was added TBAF (1 M in THF, 5% water, 39 mL, 39 mmol). The mixture was stirred at ambient temperature and after 3 h was washed with sat aq NH_4Cl (400 mL) and with brine (400 mL). The aq layers were re-extracted with Et_2O (2×150 mL) and the combined organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography (silica gel, 10 → 30% ethyl acetate in hexanes) to afford alcohol **18** (1.89 g, 9.06 mmol, 69% over two steps) as a colorless liquid. R_f=0.25 (silica gel, 30% EtOAc in hexanes); $[\alpha]_D^{25}$=+8.2 (c=6.8, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.30–7.15 (m, 5H), 4.23 (s, 2H), 3.39 (t, J=6.6 Hz, 2H), 3.42–3.29 (m, 2H), 2.1 (s, 1H), 1.62 (m, 1H), 1.53 (m, 1H), 1.40 (m, 1H), 1.11 (m, 1H), 0.84 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=138.4, 128.3, 127.6, 127.4, 72.8, 70.6, 67.8, 35.4, 29.5, 27.0, 16.5 ppm; IR (film): ν_{max}=3392, 3063, 2934, 2868, 1496, 1454, 1204, 1098, 1028, 736, 698, 619 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{13}H_{20}O_2Na$: 231.1355, found: 231.1350 $[M+Na]^+$.



Compound 21: A solution of DMSO (1.90 mL, 26.8 mmol) in CH_2Cl_2 (10 mL) was slowly added at −78°C to a solution of oxalyl chloride (1.57 mL, 17.6 mmol) in CH_2Cl_2 (100 mL). After 10 min, a solution of alcohol **18** (1.89 g, 9.06 mmol) in CH_2Cl_2 (10 mL) was added and the mixture was stirred for 0.5 h before the addition of Et_3N (6.25 mL, 47 mmol). After 3 h, the solution was allowed to warm to −20°C and was then poured into 1 M aq HCl (100 mL, pre-cooled to 0°C). The organic layer was washed with sat aq $NaHCO_3$ (100 mL) and with brine (100 mL), the aq layers were re-extracted with CH_2Cl_2 (100 mL), and the combined organic layer was dried (Na_2SO_4), filtered through a plug of silica gel and evaporated. The crude product was dissolved in CH_2Cl_2 (90 mL) and cooled to −78°C before $BF_3{\cdot}Et_2O$ (48%, 1.28 mL, 10 mmol) and methyl trimethylsilyl dimethylketene acetal (2.20 mL, 10.9 mmol) were added. The solution was stirred for 1.5 h at −78°C and then partitioned between ice cold Et_2O (300 mL) and 1 M aq HCl (100 mL). The organic layer was washed with brine (200 mL), the aq layers were re-extracted with Et_2O (200 mL), and the combined organic layer was dried (Na_2SO_4), filtered, concentrated and purified by flash column chromatography (silica gel, 25% EtOAc in hexanes) to yield an inseparable mixture of hydroxy esters **19** and **20** (2.205 g, 7.16 mmol, 79%, 7:3 according to ^{1}H NMR) as a colorless oil. This mixture was reacted with TBSOTf (2.2 mL, 9.3 mmol) and 2,6-lutidine (1.25 mL, 10.7 mmol) in CH_2Cl_2 (50 mL) at 0°C. After 1 h, the solution was washed with 1 M aq HCl (100 mL) and subsequently with brine (100 mL), the aq layers were re-extracted with CH_2Cl_2 (100 mL) and the combined organic layer was dried ($MgSO_4$), filtered through a plug of silica gel and evaporated to dryness. The residue was dissolved in EtOH (10 mL) and added to a suspension of Pd (10% on activated charcoal, 600 mg) in EtOH (40 mL) under an Ar atmosphere. The mixture was stirred under H_2 at ambient pressure and temperature for 18 h and then degassed, filtered and evaporated. The residue was purified by flash column chromatography (silica gel, 33 → 50% Et_2O in hexanes) to afford **21** (1.225 g, 3.68 mmol, 41% from **18**), its C-3 epimer (472 mg, 1.42 mmol, 16% from **18**) and a mixture of both (399 mg, 1.20 mmol, 13%, **21**/*epi*-**21** 1.2:1) as colorless oils. Compound **21**: R_f=0.26 (silica gel, 20% EtOAc in hexanes); $[\alpha]_D^{25}$=+9.0 (c=2.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.85 (d, J=1.5 Hz, 1H), 3.85 (s, 3H), 3.61 (t, J=6.6 Hz, 2H), 1.62–1.22 (m, 6H), 1.16 (s, 3H), 1.12 (s, 3H), 0.90 (s, 9H), 0.87 (d, J=6.8 Hz, 3H), 0.08 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=177.8, 79.2, 63.0, 51.6, 49.4, 35.5, 33.4, 30.9, 26.2, 23.5, 20.1, 18.6, 15.3, −3.0, −4.5 ppm; IR (film): ν_{max}=3356, 2953, 2885, 2857, 1728, 1472, 1257, 1142, 1110, 1065, 1004, 837, 774 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{17}H_{36}O_4SiNa$: 355.2275, found: 355.2278 $[M+Na]^+$.

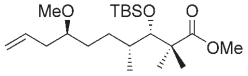


Compound 22a: Primary alcohol **21** (2.156 g, 6.48 mmol) was oxidized with DMSO (1.33 mL, 19.4 mmol), oxalyl chloride (11.5 mL, 12.9 mmol) and Et_3N (3.40 mL, 25.6 mmol) in CH_2Cl_2 (60 mL) as described above for the oxidation of primary alcohol **18**. After aq work-up and filtration through a pad of silica gel, the crude product was dissolved in Et_2O (30 mL) and the solution was cooled to

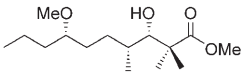


−100 °C. A solution of (+)-$(Ipc)_2BCH_2CHCH_2$ (approximately 0.2 M in Et_2O, 65 mL, 13 mmol) was added. After 4 h, the temperature was allowed to reach −46 °C and stirring at this temperature was continued for 0.5 h. The reaction mixture was treated with a solution of H_2O_2 (35% in H_2O, 16 mL) and NaOH (980 mg) in water (36 mL). After 5 min, the mixture was buffered by the addition of aq NaH_2PO_4 (4.43 g in 100 mL water) and allowed to warm to 25 °C. The organic layer was washed with brine (100 mL) and the aq layers were re-extracted with Et_2O (2× 100 mL). The combined organic layer was dried (Na_2SO_4), filtered through a plug of silica gel and concentrated, yielding a crude product that was contaminated with IpcOH. This mixture was dissolved in CH_2Cl_2 (100 mL) and proton sponge (1,8-bis[dimethylamino]-naphthalene, 25.72 g, 120 mmol) and Me_3OBF_4 (11.83 g, 80 mmol) were added. After 20 h, the solvent was removed and the residue was partitioned between Et_2O (300 mL) and sat aq citric acid (300 mL). The organic layer was washed with brine (500 mL), the aq layers were re-extracted with Et_2O (2×200 mL) and the combined organic layer was dried (Na_2SO_4), filtered through a plug of silica gel and evaporated. The residue was purified by flash column chromatography (silica gel, 30 → 55% CH_2Cl_2 in hexanes) to yield homoallylic ether **22a** (1.896 g, 4.89 mmol, 75% from alcohol **21**) as a colorless oil. R_f = 0.28 (silica gel, 5% EtOAc in hexanes); $[\alpha]_D^{25}$ = +14.4 (c = 2.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.78 (m, 1H), 5.09–5.01 (m, 2H), 3.82 (d, J = 1.5 Hz, 1H), 3.63 (s, 3H), 3.32 (s, 3H), 3.16 (d, J = 5.8 Hz, 1H), 2.24 (m, 2H), 1.50–1.25 (m, 5H), 1.15 (s, 3H), 1.10 (s, 3H), 0.89 (s, 9H), 0.83 (d, J = 6.7 Hz, 3H), 0.07 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.7, 134.8, 116.8, 80.3, 79.4, 56.5, 51.5, 49.3, 37.7, 35.8, 32.7, 31.4, 26.1, 23.2, 20.2, 18.5, 15.1, −3.0, −4.6 ppm; IR (film): ν_{max} = 3072, 2931, 2849, 1740, 1461, 1255, 1190, 1108, 832, 773 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{21}H_{42}O_4SiNa$: 409.2744, found: 409.2738 $[M+Na]^+$.

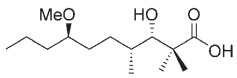
Compound 22b (prepared from **21** in 71% yield using (−)-$(Ipc)_2BCH_2CHCH_2$): R_f = 0.53 (silica gel, 30% Et_2O in hexanes); $[\alpha]_D^{25}$ = +6.5 (c = 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.81 (m, 1H), 5.11–5.03 (m, 2H), 3.83 (d, J = 1.3 Hz, 1H), 3.64 (s, 3H), 3.32 (s, 3H), 3.17 (m, 1H), 2.25 (dd, J = 7.0, 5.8 Hz, 2H), 1.51–1.18 (m, 5H), 1.16 (s, 3H), 1.11 (s, 3H), 0.90 (s, 9H), 0.85 (d, J = 6.6 Hz, 3H), 0.09 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.7, 134.8, 116.9, 80.6, 70.3, 56.6, 51.6, 49.3, 37.7, 35.8, 33.0, 31.5, 26.2, 23.2, 20.3, 18.6, 15.2, −2.9, −4.5 ppm; IR (film): ν_{max} = 2931, 2857, 2822, 1738, 1641, 1472, 1463, 1256, 1111, 835, 774 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{21}H_{42}O_4SiNa$: 409.2744, found: 409.2718 $[M+Na]^+$.



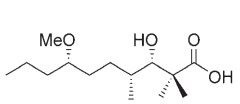
Compound 23a: Compound **22a** (1.896 g, 4.89 mmol) was dissolved in EtOH (10 mL) and added to a suspension of Pd (10% on activated charcoal, 1.05 g) in EtOH (30 mL). The mixture was stirred under an atmosphere of H_2 at ambient temperature for 2 h. After saturation with Ar, filtration of the catalyst and evaporation of the solvent, the crude saturated intermediate (1.833 g) was obtained. A portion of this intermediate (893 mg) was cooled to −10 °C and treated with a TFA/H_2O mixture (9:1, 20 mL). After 5 min, to the mixture was carefully added sat aq $NaHCO_3$ enough to neutralize all TFA, and the mixture was extracted with EtOAc (100 mL). The organic was washed with brine (100 mL), the aq layers were re-extracted with EtOAc (2×100 mL), and the combined organic layer was dried (Na_2SO_4), filtered through a plug of silica gel and evaporated to dryness to afford hydroxy ester **23a** (590 mg, 2.16 mmol, 93%) as a colorless viscous oil. R_f = 0.44 (silica gel, 20% EtOAc in hexanes); $[\alpha]_D^{25}$ = −9.8 (c = 2.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.64 (s, 3H), 3.42 (brs, 1H), 3.26 (s, 3H), 3.06 (m, 1H), 2.92 (brs, 1H), 1.59 (m, 1H), 1.56–1.22 (m, 8H), 1.24 (s, 3H), 1.12 (s, 3H), 0.86 (t, J = 7.1 Hz, 3H), 0.71 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.6, 80.8, 79.9, 56.4, 51.9, 45.7, 35.6, 34.6, 31.4, 31.2, 24.6, 21.9, 18.4, 14.2, 13.2 ppm; IR (film): ν_{max} = 3476, 2933, 2877, 1730, 1458, 1266, 1192, 1141, 1096, 988 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{15}H_{30}O_4Na$: 297.2036, found: 297.2036 $[M+Na]^+$.



Compound 23b (prepared from **22b** in 91% yield): R_f = 0.44 (silica gel, 20% EtOAc in hexanes); $[\alpha]_D^{25}$ = +1.35 (c = 1.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.69 (s, 3H), 3.46 (d, J = 2.0 Hz, 1H), 3.31 (s, 3H), 3.11 (m, 1H), 1.65 (m, 1H), 1.52–1.24 (m, 8H), 1.30 (s, 3H), 1.16 (s, 3H), 0.91 (t, J = 7.2 Hz, 3H), 0.75 ppm (d, J = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.7, 81.0, 80.3, 56.5, 53.4, 52.0, 35.7, 34.7, 31.5, 31.2, 25.0, 21.9, 18.4, 14.3, 13.0 ppm; IR (film): ν_{max} = 3482, 2934, 2874, 1729, 1459, 1380, 1262, 1192, 1140, 1096, 991 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{15}H_{30}O_4Na$: m/z: 297.2036, found: 297.2036 $[M+Na]^+$.

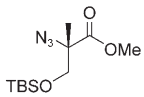


Compound 10a: LiOH·H_2O (184 mg, 4.38 mmol) was added at ambient temperature to a solution of methyl ester **23a** (200 mg, 0.730 mmol) in MeOH/H_2O 4:1 (7 mL). The reaction mixture was stirred for 24 h and then partitioned between EtOAc (50 mL) and 1 M aq HCl (50 mL). The organic layer was washed with brine (50 mL), the aq layers were re-extracted with EtOAc (2×50 mL) and the combined organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography (silica gel, 25% EtOAc in hexanes with 5% AcOH) to afford decanoic acid **10a** (187.3 mg, 0.720 mmol, 99%) as a colorless viscous oil. R_f = 0.23 (silica gel, 20% EtOAc in hexanes with 10% AcOH); $[\alpha]_D^{25}$ = −28.9 (c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.50 (d, J = 2.3 Hz, 1H), 3.29 (s, 3H), 3.13 (m, 1H), 1.67 (m, 1H), 1.49–1.22 (m, 8H), 1.33 (s, 3H), 1.13 (s, 3H), 0.87 (t, J = 7.2 Hz, 3H), 0.80 ppm (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.9, 81.1, 79.8, 56.3, 45.1, 35.4, 34.6, 30.9, 30.8, 25.5, 21.6, 18.4, 14.2, 12.9 ppm; IR (film): ν_{max} = 3426, 2927, 2871, 1698, 1460, 1255, 1150, 1088, 977 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{14}H_{28}O_4Na$: 283.1880, found: 283.1880 $[M+Na]^+$.

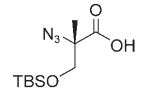


Compound 10b (prepared from ester **23b** in 81% yield): R_f = 0.15 (silica gel, 20% EtOAc in hexanes with 5% AcOH); $[\alpha]_D^{25}$ = −36.7 (c = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.54 (d, J = 1.9 Hz, 1H), 3.32 (s, 3H), 3.14 (m, 1H), 1.68 (m, 1H), 1.54–1.24 (m, 8H), 1.32 (s, 3H), 1.15 (s, 3H), 0.90 (t, J = 7.2 Hz, 3H), 0.83 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.7, 81.4, 79.4, 56.4, 45.2, 35.5, 34.6, 31.1, 31.0, 25.6, 21.6, 18.4, 14.2, 13.1 ppm; IR (film): ν_{max} = 3380, 2935, 2873, 1698, 1462, 1152, 1094, 980 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{14}H_{28}O_4Na$: 283.1880, found: 283.1874 $[M+Na]^+$.

Compound 25: A solution of compound **24** (327 mg, 2.06 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and 2,6-lutidine (0.96 mL, 8.24 mmol) and TBSOTf (0.94 mL, 4.09 mmol) were added. The solution was stirred for 2 h at 25 °C and then treated with MeOH (5 mL). Stirring was continued for 15 min, the solution was evaporated and the residue was purified by column chromatography (silica gel, 5% EtOAc in hexanes) to furnish azido ester **25** (550.1 mg, 2.02 mmol, 98%) as a colorless oil. **25**: R_f = 0.72 (silica gel, 10% EtOAc in hexanes); $[\alpha]_D^{25}$ = +28.5 (c = 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.95 (d, J = 9.8 Hz, 1H), 3.79 (s, 3H), 3.75 (d, J = 9.8 Hz, 1H), 1.31 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.8, 69.5, 67.6, 52.6, 25.6, 19.7, 18.1, −5.7, −5.8 ppm; IR (film): ν_{max} = 2955, 2931, 2142, 2104, 1745, 1462, 1389, 1362, 1258, 1106, 840, 779 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{11}H_{23}N_3O_3NaSi$: 296.1401, found: 296.1387 $[M+Na]^+$.

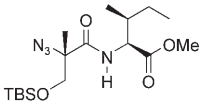


Compound 12: LiOH·H_2O (200 mg, 4.77 mmol) was added at ambient temperature to a solution of TBS-protected alcohol **25** (417 mg, 1.52 mmol) in MeOH/H_2O 4:1 (30 mL) and the reaction mixture was stirred for 3 h. The

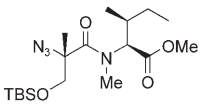


solution was partitioned between 1 M aq HCl (50 mL) and Et_2O (50 mL) and the organic layer was washed with brine (50 mL). The aq layers were re-extracted with Et_2O (3×50 mL) and the combined organic layer was dried (Na_2SO_4). Filtration followed by evaporation and flash column chromatography (silica gel, 5% MeOH in EtOAc) yielded carboxylic acid **12** (379 mg, 96%) as a colorless oil. R_f=0.61 (silica gel, 10% MeOH in EtOAc); $[\alpha]_D^{25}$=+12.4 (c=0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.97 (d, J=10.5 Hz, 1H), 3.80 (d, J=10.5 Hz, 1H), 1.39 (s, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.8, 69.1, 67.1, 25.6, 19.6, 18.1, −5.6, −5.8 ppm; IR (film): ν_{max}=3420, 2925, 2855, 2104, 1719, 1460, 1258, 1108, 834, 778 cm^{-1}; HRMS (negative ESI-TOF): m/z: calcd for $C_{10}H_{20}N_3O_3Si$: 258.1279, found: 258.1269 $[M-H]^-$.

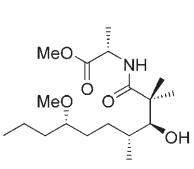
Compound 26: H-Ile-OMe (385 mg, 2.12 mmol), EDC·HCl (343 mg, 1.79 mmol), HOAt (244 mg, 1.79 mmol) and iPr$_2$NEt (0.85 mL, 4.88 mmol) were added to a solution of carboxylic acid **12** (422 mg, 1.63 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at ambient temperature for 24 h and then concentrated. The residue was purified by flash column chromatography (silica gel, 10 → 20% EtOAc in hexanes) affording compound **26** as a colorless oil (573 mg, 1.48 mmol, 91%). R_f=0.43 (silica gel, 20% EtOAc in hexanes); $[\alpha]_D^{25}$=+38.6 (c=0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.10 (d, J=8.5 Hz, 1H), 4.51 (dd, J=8.5, 5.0 Hz, 1H), 3.87 (d, J=10.3 Hz, 1H), 3.82 (d, J=10.3 Hz, 1H), 3.74 (s, 3H), 1.91–1.87 (m, 1H), 1.50 (s, 3H), 1.46–1.41 (m, 1H), 1.21–1.15 (m, 1H), 0.93–0.86 (m, 15H), 0.09 (s, 3H), 0.08 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9, 170.4, 68.4, 67.8, 56.5, 52.1, 37.8, 25.7, 25.1, 19.1, 18.2, 15.5, 11.5, −5.6, −5.7 ppm; IR (film): ν_{max}=3416, 2959, 2932, 2858, 2119, 1746, 1688, 1682, 1514, 1463, 1384, 1362, 1258, 1208, 1108, 1006, 840, 779 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{17}H_{35}N_4O_4Si$: 387.2422, found: 387.2423 $[M+H]^+$.



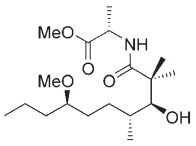
Compound 27: A solution of TBS-protected dipeptide **26** (572.8 mg, 1.48 mmol) in DMF (50 mL) was cooled to 0°C. NaH (60% in mineral oil, 179 mg, 4.48 mmol) was added followed by iodomethane (0.370 mL, 5.93 mmol) after 20 min. The reaction mixture was stirred at 0°C for 45 min before it was partitioned between Et_2O (50 mL) and sat aq NH_4Cl (50 mL). The organic layer was washed with brine (50 mL), the aq layers were re-extracted with Et_2O (2×50 mL), and the combined organic layer was dried ($MgSO_4$). Filtration, followed by evaporation and flash column chromatography (silica gel, 9% EtOAc in hexanes) gave pure compound **27** (572.5 mg, 96%) as a colorless oil. R_f=0.59 (silica gel, 20% EtOAc in hexanes); $[\alpha]_D^{25}$=−67.1 (c=0.8, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.82 (d, J=10.8 Hz, 1H), 4.10 (br d, J=9.6 Hz, 1H), 3.83 (d, J=10.2 Hz, 1H), 3.72 (br s, 3H), 3.26 (br s, 3H), 2.05 (m, 1H), 1.46 (br m, 4H), 1.10–1.07 (m, 1H), 0.97 (d, J=6.6 Hz, 3H), 0.91–0.88 (m, 13H), 0.10 (s, 3H), 0.09 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.0, 171.2, 69.5, 67.3, 61.9, 51.8, 32.7, 31.9, 30.3, 25.7, 25.1, 19.2, 18.2, 15.9, 10.6, −5.6, −5.7 ppm; IR (film): ν_{max}=2958, 2932, 2858, 2112, 1742, 1650, 1462, 1393, 1257, 1200, 1106, 1068, 1006, 838, 778 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{18}H_{37}N_4O_4Si$: 401.2578, found: 401.2581 $[M+H]^+$.



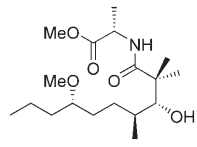
Compound 29a: Decanoic acid **10a** (514 mg, 1.98 mmol), H-Ala-OMe·HCl (1.122 g, 8.00 mmol), HOAt (1.081 g, 8.00 mmol) and EDC·HCl (1.926 g, 10.0 mmol) were dissolved in DMF (20 mL) and iPr$_2$NEt (2.7 mL, 20 mmol) was added. The solution was stirred at ambient temperature for 16 h and then partitioned between Et_2O (50 mL) and 1 M aq HCl (100 mL). The organic layer was washed with brine (100 mL), the aq layers were re-extracted with Et_2O (2×50 mL), and the combined organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography (silica gel, 45% EtOAc in hexanes) yielding amide **29a** (640 mg, 1.85 mmol, 94%) as a slightly yellowish viscous oil. R_f=0.43 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{25}$=−11.9 (c=1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.81 (d, J=7.0 Hz, 1H), 4.52 (dt, J=7.2 Hz, 1H), 3.80 (d, J=6.8 Hz, 1H), 3.72 (s, 3H), 3.42 (dd, J=6.8, 2.0 Hz, 1H), 3.29 (s, 3H), 3.10 (m, 1H), 1.64 (m, 1H), 1.48–1.27 (m, 8H), 1.37 (d, J=7.2 Hz, 3H), 1.31 (s, 3H), 1.13 (s, 3H), 0.88 (t, J=7.1 Hz, 3H), 0.76 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=178.0, 173.6, 80.9, 80.8, 56.5, 52.4, 47.9, 44.4, 35.6, 34.7, 31.2, 31.1, 26.9, 21.5, 18.5, 17.9, 14.3, 13.0 ppm; IR (film): ν_{max}=3324, 2938, 2864, 1742, 1636, 1531, 1452, 1374, 1213, 1177, 1149, 1094, 983 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{18}H_{36}NO_5$: 346.2593, found: 346.2583 $[M+H]^+$.



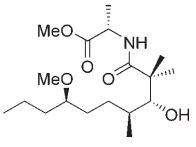
Compound 29b (prepared from **10b** in 84% yield): R_f=0.39 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{25}$=−9.2 (c=1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.83 (d, J=7.0 Hz, 1H), 4.52 (dt, J=7.0 Hz, 1H), 3.80 (d, J=6.6 Hz, 1H), 3.73 (s, 3H), 3.43 (dd, J=6.6, 2.0 Hz, 1H), 3.30 (s, 3H), 3.08 (m, 1H), 1.64 (m, 1H), 1.62–1.25 (m, 9H), 1.38 (d, J=7.1 Hz, 3H), 1.31 (s, 3H), 1.13 (s, 1H), 0.89 (t, J=7.0 Hz, 3H), 0.76 ppm (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=178.0, 173.6, 81.1, 80.7, 56.5, 52.4, 47.8, 44.3, 35.6, 34.7, 31.4, 31.1, 27.0, 21.5, 18.4, 17.9, 14.2, 13.0 ppm; IR (film): ν_{max}=3316, 2960, 2936, 2865, 1739, 1638, 1530, 1447, 1376, 1210, 1175, 1145, 1091, 985 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{18}H_{36}NO_5$: 346.2593, found: 346.2582 $[M+H]^+$.



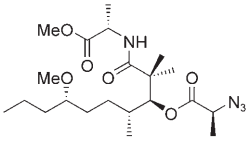
Compound 29c (prepared from decanoic acid **10c** in 88% yield): R_f=0.20 (silica gel, 33% EtOAc in hexanes); $[\alpha]_D^{25}$=+6.5 (c=0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.85 (d, J=7.0 Hz, 1H), 4.53 (d, J=7.0 Hz, 1H), 3.97 (d, J=7.4 Hz, 1H), 3.73 (s, 3H), 3.40 (dd, J=7.0, 1.8 Hz, 1H), 3.29 (s, 3H), 3.10–3.06 (m, 1H), 1.65–1.62 (m, 1H), 1.38 (d, J=7.4 Hz, 3H), 1.31 (s, 3H), 1.49–1.24 (m, 8H), 1.12 (s, 3H), 0.88 (d, J=7.2 Hz, 3H), 0.75 ppm (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.1, 173.6, 81.2, 81.1, 56.5, 52.5, 47.8, 44.0, 35.6, 34.9, 31.3, 31.3, 27.3, 21.8, 18.4, 18.2, 14.3, 12.8 ppm; IR (film): ν_{max}=3323, 2960, 2924, 2875, 1747, 1644, 1529, 1457, 1208, 1178, 1093, 984 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{18}H_{36}NO_5$: 346.2588, found: 346.2582 $[M+H]^+$.



Compound 29d (prepared from decanoic acid **10d** in 84% yield): R_f=0.20 (silica gel, 33% EtOAc in hexanes); $[\alpha]_D^{25}$=+13.3 (c=1.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.83 (d, J=7.0 Hz, 1H), 4.52–4.49 (m, 1H), 3.99 (d, J=7.0 Hz, 1H), 3.72 (s, 3H), 3.39 (d, J=5.3 Hz, 1H), 3.27 (s, 3H), 3.10–3.06 (m, 1H), 1.65–1.61 (m, 1H), 1.37 (d, J=7.0 Hz, 3H), 1.30 (s, 3H), 1.46–1.25 (m, 8H), 1.11 (s, 3H), 0.97 (t, J=7.0 Hz, 3H), 0.74 ppm (d, J=6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.1, 173.5, 81.2, 80.9, 56.5, 52.4, 47.8, 44.0, 35.6, 34.8, 31.2, 31.2, 27.2, 21.7, 18.4, 18.1, 14.3, 12.8 ppm; IR (film): ν_{max}=3320, 2957, 2933, 2872, 1746, 1643, 1522, 1455, 1376, 1310, 1213, 1176, 1092, 983 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{18}H_{36}NO_5$: 346.2588, found: 346.2584 $[M+H]^+$.

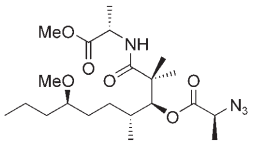


Compound 30a: A solution of (*S*)-2-azido propionic acid[15] (4.28 g, 37.2 mmol) in DMF (19 mL) was cooled (NaCl ice bath) and oxalyl chloride (2.85 mL, 32.8 mmol) was added cautiously. The solution was allowed to reach ambient temperature and was stirred for 0.5 h. The resulting mixture was then slowly added to a cooled (NaCl ice bath) solution of hydroxy

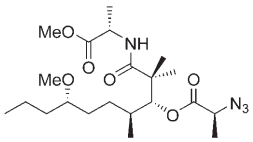


amide **29a** (592 mg, 1.71 mmol), 4-DMAP (115 mg, 0.943 mmol) and Et_3N (6.50 mL, 46.7 mmol) in DMF (10 mL). The reaction mixture was stirred at 50 °C for 24 h. After cooling to 25 °C, the mixture was partitioned between EtOAc (100 mL) and sat aq $NaHCO_3$ (200 mL). The organic layer was washed with 1 M aq HCl (200 mL) and with brine (200 mL), the aq layers were re-extracted with EtOAc (2×100 mL), and the combined organic layer was dried (Na_2SO_4). After filtration and evaporation, the residue was purified by flash column chromatography (silica gel, 25% EtOAc in hexanes) to yield ester **30a** (712 mg, 1.609 mmol, 94%) as a reddish oil. R_f=0.63 (silica gel, Et_2O); $[\alpha]_D^{25}$=+1.0 (c=0.95, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ=6.59 (d, J=6.9 Hz, 1H), 5.07 (d, J=1.9 Hz, 1H), 4.51 (m, 1H), 4.08 (m, 1H), 3.71 (s, 3H), 3.25 (s, 3H), 3.05 (m, 1H), 1.82 (m, 1H), 1.51 (d, J=7.1 Hz, 3H), 1.52–1.38 (m, 3H), 1.36 (d, J=7.2 Hz, 3H), 1.35–1.23 (m, 5H), 1.19 (s, 3H), 1.18 (s, 3H), 0.88–0.83 ppm (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=174.5, 173.5, 170.1, 82.1, 80.5, 57.9, 56.3, 52.3, 48.1, 45.9, 35.6, 34.1, 31.4, 31.0, 23.7, 22.5, 18.4, 17.9, 16.9, 14.6, 14.1 ppm; IR (film): ν_{max}=3397, 2948, 2869, 2820, 2102, 1742, 1657, 1518, 1448, 1379, 1339, 1304, 1259, 1194, 1095, 935 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{21}H_{39}N_4O_6$: 443.2864, found: 443.2859 $[M+H]^+$.

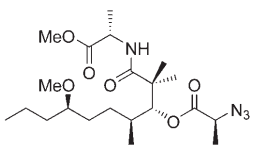
Compound 30b (prepared from **29b** in 65% yield): R_f=0.35 (silica gel, 33% EtOAc in hexanes); $[\alpha]_D^{25}$=+2.7 (c=0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.59 (d, J=6.9 Hz, 1H), 5.07 (d, J=2.8 Hz, 1H), 4.53 (dt, J=7.1 Hz, 1H), 4.09 (q, J=7.1 Hz, 1H), 3.72 (s, 3H), 3.27 (s, 3H), 1.84 (m, 1H), 1.53 (d, J=7.0 Hz, 3H), 1.47–1.40 (m, 3H), 1.39 (d, J=7.1 Hz, 3H), 1.30–1.20 (m, 5H), 1.19 (s, 3H), 1.19 (s, 3H), 1.19–1.13 (m, 1H), 0.89–0.86 ppm (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=174.6, 173.6, 170.1, 82.2, 80.6, 58.0, 56.3, 52.4, 48.2, 45.9, 35.5, 34.2, 31.3, 30.8, 23.9, 22.6, 18.5, 18.0, 17.0, 14.7, 14.2 ppm; IR (film): ν_{max}=3402, 2929, 2864, 2100, 1743, 1636, 1517, 1452, 1253, 1195, 1092 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{21}H_{39}N_4O_6$: 443.2864, found: 443.2862 $[M+H]^+$.



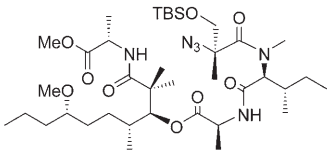
Compound 30c (prepared from **29c** in 95% yield): R_f=0.39 (silica gel, 33% EtOAc in hexanes); $[\alpha]_D^{25}$=+23.7 (c=0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.67 (d, J=6.5 Hz, 1H), 5.06 (d, J=2.6 Hz, 1H), 4.51 (dq, J=7.0, 6.5 Hz, 1H), 4.12 (q, J=7.0 Hz, 1H), 3.73 (s, 3H), 3.26 (s, 3H), 3.08–3.03 (m, 1H), 1.86–1.80 (m, 1H), 1.53 (d, J=7.0 Hz, 3H), 1.37 (d, J=7.4 Hz, 3H), 1.61–1.22 (m, 8H), 1.18 (s, 6H), 0.87 (t, J=7.0 Hz, 3H), 0.83 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.7, 173.5, 170.3, 82.3, 80.6, 57.6, 56.3, 52.4, 48.2, 46.0, 35.5, 34.1, 31.4, 30.7, 23.8, 22.7, 18.5, 18.4, 16.8, 14.4, 14.2 ppm; IR (film): ν_{max}=3396, 2960, 2935, 2875, 2100, 1747, 1669, 1517, 1457, 1378, 1196, 1093, 936 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{21}H_{39}N_4O_6$: 443.2864, found: 443.2864 $[M+H]^+$.



Compound 30d (prepared from **29d** in 98% yield): R_f=0.39 (silica gel, 33% EtOAc in hexanes); $[\alpha]_D^{25}$=+26.6 (c=0.9, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.65 (d, J=6.1 Hz, 1H), 5.06 (d, J=2.6 Hz, 1H), 4.53–4.48 (m, 1H), 4.11 (q, J=7.0 Hz, 1H), 3.72 (s, 3H), 3.26 (s, 3H), 3.07–3.03 (m, 1H), 1.84–1.80 (m, 1H), 1.54 (d, J=8.8 Hz, 3H), 1.37 (d, J=7.0 Hz, 3H), 1.45–1.26 (m, 8H), 1.18 (s, 6H), 0.87 (t, J=7.0 Hz, 3H), 0.83 ppm (d, J=6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.7, 173.5, 170.3, 82.3, 80.6, 57.6, 56.3, 52.4, 48.2, 46.0, 35.5, 34.1, 31.4, 30.8, 23.8, 22.7, 18.5, 18.4, 16.8, 14.,4, 14.2 ppm; IR (film): ν_{max}=3393, 2956, 2932, 2885, 2097, 1746, 1649, 1515, 1455, 1376, 1303, 1195, 1092, 934 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{21}H_{39}N_4O_6$: 443.2864, found: 443.2868 $[M+H]^+$.



Compound 32a: An aq nBu_4NOH solution (40%, 2.0 mL, 3.1 mmol) at 0 °C was added to a solution of methyl ester **27** (620 mg, 1.55 mmol) in THF (30 mL). The solution was stirred for 6 h at this temperature and then partitioned between a pre-cooled (0 °C) mixture of Et_2O (100 mL) and 1 M aq HCl (100 mL). The organic layer was washed with brine (100 mL) and the aq layers were re-extracted with Et_2O (2×50 mL). The combined organic layer was dried (Na_2SO_4), filtered and evaporated (during the work-up the temperature was kept at approximately 0 °C), yielding crude acid **28** (430 mg, ca. 1.1 mmol, 70%) which was subsequently coupled to amine **31a** without further purification.

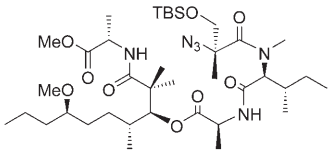


32a

Under an Ar atmosphere, Pd (10% on activated charcoal, 190 mg) was suspended in EtOH (20 mL). Azide **30a** (340 mg, 0.768 mmol) was added as a solution in EtOH (total volume 4 mL) and the mixture was saturated with H_2 at ambient temperature. After 2 h, the H_2 was exchanged with Ar, the catalyst was filtered off and the filtrate was concentrated to afford the crude amine **31a**. The residue was dried by azeotropic distillation with toluene (3×10 mL).

Amine **31a** and acid **28** obtained above were dissolved in DMF (10 mL) and at 0 °C, HOAt (384 mg, 2.82 mmol), PyOAP (1.669 mg, 3.19 mmol) and iPr$_2$NEt (0.64 mL, 3.70 mmol) were added. The resulting solution was stirred for 20 h at ambient temperature and then partitioned between Et_2O (50 mL) and sat aq NH_4Cl (100 mL). The organic layer was washed with brine (100 mL) and the aq layers were re-extracted with Et_2O (2×50 mL). The combined organic layer was dried (Na_2SO_4), filtered, evaporated and purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) yielding depsipeptide **32a** (430 mg, 0.548 mmol, 71% from azide **30a**) as a yellowish oil. R_f=0.31 (silica gel, 25% EtOAc in hexanes); $[\alpha]_D^{25}$=−69.7 (c=1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.77 (d, J=7.4 Hz, 1H), 6.60 (d, J=6.7 Hz, 1H), 5.07 (d, J=2.8 Hz, 1H), 4.58–4.52 (m, 3H), 4.15 (d, J=9.9 Hz, 1H), 3.81 (d, J=9.9 Hz, 1H), 3.45 (s, 3H), 3.29 (s, 3H), 3.20 (s, 3H), 3.07 (m, 1H), 2.16 (m, 1H), 1.79 (m, 1H), 1.61–1.43 (m, 2H), 1.42 (d, J=7.1 Hz, 3H), 1.41 (d, J=7.1 Hz, 3H), 1.41–1.36 Hz (m, 2H), 1.36 (s, 3H), 1.36–1.20 (m, 6H), 1.20 (s, 3H), 1.19 (s, 3H), 1.03 (m, 1H), 0.93–0.84 (m, 20H), 0.10 (s, 3H), 0.09 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.6, 173.5, 172.0, 171.7, 169.3, 81.5, 80.5, 69.8, 67.3, 61.9, 56.3, 52.3, 48.1, 48.0, 45.9, 35.6, 34.3, 31.3, 31.1, 31.1, 30.6, 30.2, 25.6, 24.3, 23.4, 22.8, 19.1, 18.4, 18.1, 18.0, 17.9, 15.5, 14.8, 14.2, 10.1, −5.6, −5.8 ppm; IR (film): ν_{max}=3342, 2955, 2941, 2865, 2097, 1743, 1666, 1619, 1519, 1455, 1378, 1255, 1190, 1091, 838, 779 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{38}H_{73}N_6O_9Si$: 785.5203, found: 785.5189 $[M+H]^+$.

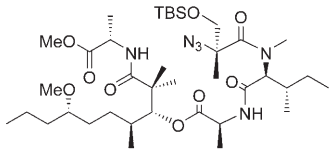
Compound 32b (prepared from **30b** in 64% yield): R_f=0.29 (silica gel, 25% EtOAc in hexanes): $[\alpha]_D^{25}$=−66.2 (c=0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ= 6.74 (d, J=7.4 Hz, 1H), 6.57 (d, J=6.9 Hz, 1H), 5.04 (d, J=2.7 Hz, 1H), 4.54–4.49 (m, 3H), 4.11 (d, J=9.9 Hz, 1H), 3.78 (d, J=9.9 Hz, 1H), 3.71 (s, 3H), 3.25 (s, 3H), 3.16 (s, 3H), 3.04 (m, 1H), 2.10 (m, 1H), 1.78 (m, 1H), 1.57–1.13 (m, 25H), 1.01 (m, 1H), 0.96–0.82 (m, 20H), 0.07 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=174.5, 173.6, 172.1, 171.8, 169.3, 81.7, 80.7, 69.8, 67.4, 62.0, 56.3, 52.4,



32b

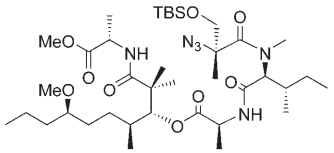
48.2, 48.1, 46.0, 35.5, 34.4, 31.3, 30.9, 30.6, 25.7, 24.4, 23.5, 22.9, 19.2, 18.4, 18.2, 18.1, 17.9, 15.6, 15.4, 14.7, 14.2, 10.2, −5.6, −5.7 ppm; IR (film): ν_{max} = 3342, 2931, 2860, 2108, 1743, 1666, 1631, 1519, 1455, 1373, 1255, 1096, 832, 779 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{38}H_{73}N_6O_9Si$: 785.5203, found: 785.5198 $[M+H]^+$.

Compound 32c (prepared from **30c** in 40% yield): R_f = 0.32 (silica gel, 33% EtOAc in hexanes): $[\alpha]_D^{25}$ = −51.9 (*c* = 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 6.96 (d, *J* = 6.8 Hz, 1H), 6.71 (d, *J* = 6.5 Hz, 1H), 4.97 (d, *J* = 2.0 Hz, 1H), 4.58–4.51 (m, 3H), 4.12 (d, *J* = 10.0 Hz, 1H), 3.79 (d, *J* = 10.0 Hz, 1H), 3.72 (s, 3H), 3.26 (s, 3H), 3.18 (s, 3H), 3.10–3.00 (m, 1H), 2.15–2.01 (m, 1H), 1.85–1.81 (m, 1H), 1.46–1.26 (m, 16H), 1.18 (s, 3H), 1.17 (s, 3H), 1.13–0.99 (m, 2H), 0.88 (s, 9H), 0.88–0.72 (m, 12H), 0.08 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.9, 173.7, 172.4, 172.1, 169.7, 81.7, 80.6, 69.8, 67.5, 61.9, 56.3, 52.3, 48.5, 48.1, 45.7, 35.6, 34.1, 31.3, 31.1, 30.8, 30.7, 25.7, 24.6, 24.4, 23.0, 19.3, 18.5, 18.3, 18.2, 17.8, 15.5, 14.3, 14.0, 10.2, −5.6, −5.7 ppm; IR (film): ν_{max} = 3372, 3311, 2960, 2924, 2875, 2112, 1747, 1668, 1620, 1505, 1462, 1359, 1251, 1196, 1160, 1099, 1069, 845 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{38}H_{73}N_6O_9Si$: 785.5203, found: 785.5202 $[M+H]^+$.



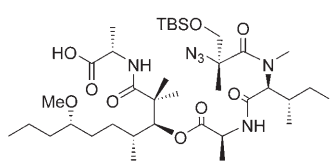
32c

Compound 32d (prepared from **30d** in 46% yield): R_f = 0.32 (33% EtOAc in hexanes); $[\alpha]_D^{25}$ = −53.0 (*c* = 0.6, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ = 6.95 (d, *J* = 6.6 Hz, 1H), 6.70 (d, *J* = 6.5 Hz, 1H), 4.97 (d, *J* = 1.7 Hz, 1H), 4.57–4.53 (m, 3H), 4.12 (d, *J* = 9.9 Hz, 1H), 3.80 (d, *J* = 9.9 Hz, 1H), 3.72 (s, 3H), 3.26 (s, 3H), 3.18 (s, 3H), 3.06–3.02 (m, 1H), 2.12–2.08 (m, 1H), 1.84–1.81 (m, 1H), 1.59 (s, 3H), 1.46–1.20 (m, 15H), 1.18 (s, 3H), 1.17 (s, 3H), 1.06–0.99 (m, 1H), 0.92–0.87 (m, 15H), 0.84 (t, *J* = 7.4 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.08 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.9, 173.6, 172.4, 172.1, 169.7, 81.7, 80.6, 69.8, 67.4, 61.9, 56.4, 52.3, 48.5, 48.1, 45.7, 35.7, 34.1, 31.3, 31.2, 31.1, 30.8, 25.7, 24.6, 24.4, 23.0, 19.3, 18.4, 18.3, 18.2, 17.8, 15.5, 14.3, 14.0, 10.2, −5.6, −5.7 ppm; IR (film): ν_{max} = 3381, 3320, 2957, 2932, 2860, 2108, 1746, 1655, 1618, 1522, 1461, 1382, 1255, 1195, 1158, 1098, 1067, 837 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{38}H_{73}N_6O_9Si$: 785.5203, found: 785.5200 $[M+H]^+$.



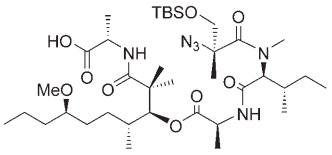
32d

Compound 33a: Methyl ester **32a** (61.8 mg, 0.079 mmol) was dissolved in 1,2-dichloroethane (5 mL). The solution was degassed with Ar and Me_3SnOH (290 mg, 1.60 mmol) was added. The reaction vessel was sealed and heated to 50 °C for 18 h. After cooling to 25 °C, the suspension was diluted with CH_2Cl_2 (20 mL) and evaporated. The residue was dissolved in Et_2O (20 mL) and washed with 1 M aq HCl (50 mL) and subsequently with brine (50 mL). The aq layers were re-extracted with Et_2O (3 × 20 mL) and the combined organic layers dried (Na_2SO_4), filtered and evaporated. The crude product was purified by flash column chromatography (silica gel, 40% EtOAc in hexanes with 2% AcOH) to give acid **33a** (57.8 mg, 0.075 mmol, 95%) as a colorless viscous oil. R_f = 0.20 (silica gel, 40% EtOAc in hexanes with 2% AcOH); $[\alpha]_D^{25}$ = −36.8 (*c* = 0.6, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ = 6.93 (d, *J* = 7.9 Hz, 1H), 6.63 (d, *J* = 7.0 Hz, 1H), 5.06 (d, *J* = 2.6 Hz, 1H), 4.58–4.50 (m, 3H), 4.09 (d, *J* = 10.1 Hz, 1H), 3.79 (d, *J* = 10.1 Hz, 1H), 3.26 (s, 3H), 3.20 (s, 3H), 3.06 (m, 1H), 2.09 (m, 1H), 1.78 (m, 1H), 1.45–1.21 (m, 13H), 1.41 (d, *J* = 7.2 Hz, 3H), 1.38 (d, *J* = 7.1 Hz, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 1.00 (m, 1H), 0.91–0.81 (m, 12H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.4, 175.4, 172.2, 171.5, 169.3, 81.3, 80.7, 69.7, 67.4, 62.1, 56.2, 48.2, 48.1, 46.1, 35.5, 34.2, 31.3, 31.3, 31.0, 30.7, 30.2, 29.6, 25.6, 24.3, 23.5, 22.0, 18.4, 18.4, 18.1, 17.9, 17.5, 15.5, 14.9, 14.2, 10.1, −5.6, −5.8 ppm; IR (film): ν_{max} = 3331, 2931, 2861, 2108, 1737, 1684, 1625, 1461, 1373, 1255, 1196, 1108, 1061, 844 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{37}H_{71}N_6O_9Si$: 771.5029, found: 771.5029 $[M+H]^+$.



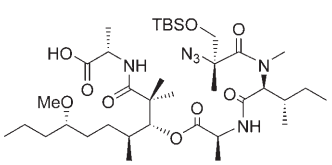
33a

Compound 33b (prepared from methyl ester **32b** in 92% yield): R_f = 0.20 (silica gel, 40% EtOAc in hexanes with 2% AcOH); $[\alpha]_D^{25}$ = −31.2 (*c* = 0.7, EtOH); ^1H NMR (500 MHz, $CDCl_3$): δ = 6.91 (d, *J* = 7.6 Hz, 1H), 6.54 (d, *J* = 6.9 Hz, 1H), 5.05 (d, *J* = 2.2 Hz, 1H), 4.56 (m, 2H), 4.52 (m, 1H), 4.08 (d, *J* = 10.0 Hz, 1H), 3.77 (d, *J* = 10.0 Hz, 1H), 3.26 (s, 3H), 3.19 (s, 3H), 3.06 (m, 1H), 2.10 (m, 1H), 1.79 (m, 1H), 1.45–1.18 (m, 19H), 1.18 (s, 3H), 1.16 (s, 3H), 0.98 (m, 1H), 0.91–0.81 (m, 12H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5, 175.5, 172.2, 171.4, 169.2, 81.4, 80.8, 69.7, 67.4, 62.1, 56.3, 48.2, 48.1, 46.2, 35.5, 34.2, 31.4, 31.3, 30.9, 30.8, 29.7, 25.7, 24.3, 23.5, 21.8, 19.1, 18.4, 18.2, 17.8, 17.5, 15.6, 14.8, 14.2, 10.2, −5.6, −5.8 ppm; IR (film): ν_{max} = 3331, 2931, 2861, 2108, 1737, 1684, 1625, 1461, 1373, 1255, 1196, 1108, 844 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{37}H_{71}N_6O_9Si$: 771.5029, found: 771.5029 $[M+H]^+$.



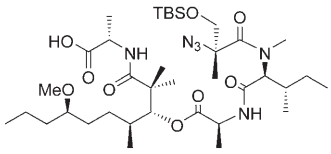
33b

Compound 33c (prepared from methyl ester **32c** in 90% yield): R_f = 0.21 (silica gel, EtOAc); $[\alpha]_D^{25}$ = −40.4 (*c* = 0.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 9.7 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 4.91 (d, *J* = 2.2 Hz, 1H), 4.69–4.63 (m, 1H), 4.53–4.47 (m, 2H), 4.02 (d, *J* = 12.3 Hz, 1H), 3.76 (d, *J* = 12.3 Hz, 1H), 3.26 (s, 3H), 3.20 (s, 3H), 3.05–3.02 (m, 1H), 2.11–2.05 (m, 1H), 1.89–1.83 (m, 1H), 1.44–1.40 (m, 10H), 1.38–1.22 (m, 8H), 1.18 (s, 3H), 1.17 (s, 3H), 1.10–0.93 (m, 2H), 0.89 (s, 9H), 0.88–0.81 (m, 10H), 0.72 (d, *J* = 8.4 Hz, 3H), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.9, 175.3, 172.2, 171.8, 168.9, 82.0, 80.6, 69.4, 67.8, 62.9, 56.4, 48.6, 48.6, 45.4, 35.5, 33.8, 31.5, 31.3, 31.3, 30.9, 30.3, 25.7, 24.9, 24.1, 22.5, 19.5, 18.4, 18.2, 18.1, 15.8, 14.2, 13.6, 10.6, −5.6, −5.7 ppm; IR (film): ν_{max} = 3329, 2957, 2920, 2858, 2117, 1743, 1620, 1527, 1459, 1385, 1255, 1194, 1150, 1101, 1070, 835, 780 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{37}H_{71}N_6O_9Si$: 771.5046, found: 771.5051 $[M+H]^+$.



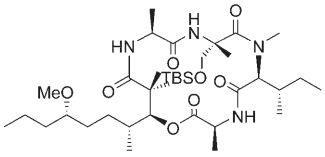
33c

Compound 33d (prepared from methyl ester **32d** in 88% yield): $R_f = 0.36$ (silica gel, 5% MeOH in EtOAc); $[\alpha]_D^{25} = -38.3$ ($c = 3.2$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (brs, 1H), 6.89 (d, $J = 6.2$ Hz, 1H), 4.95 (brs, 1H), 4.66–4.59 (m, 1H), 4.53 (d, $J = 11.1$ Hz, 1H), 4.47 (m, 1H), 4.06 (d, $J = 9.8$ Hz, 1H), 3.77 (d, $J = 9.8$ Hz, 1H), 3.26 (s, 3H), 3.19 (s, 3H), 3.07–3.01 (m, 1H), 2.14–2.05 (m, 1H), 1.86–1.81 (m, 1H), 1.56–1.19 (m, 19H), 1.17 (s, 6H), 1.08–0.95 (m, 1H), 0.88–0.81 (m, 18H), 0.73 (d, $J = 9.1$ Hz, 3H), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 172.1, 172.0, 169.1, 81.8, 80.7, 69.6, 67.7, 62.6, 56.4, 48.7, 48.5, 45.6, 35.7, 33.9, 31.6, 31.4, 31.1, 31.1, 25.7, 24.2, 22.8, 19.4, 18.5, 18.4, 18.2, 18.1, 15.8, 14.2, 14.0, 10.4, −5.6, −5.7 ppm; IR (film): $\nu_{max} = 3342$, 2955, 2919, 2861, 2108, 1743, 1619, 1537, 1455, 1384, 1255, 1190, 1155, 1096, 838, 779 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{37}H_{71}N_6O_9Si$: 771.5046, found: 771.5039 $[M+H]^+$.



33d

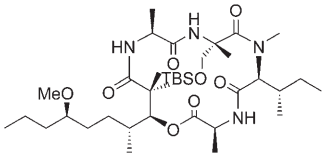
Compound 35a: $Pd(OH)_2$ (20% on activated charcoal, 200 mg) was suspended in EtOH (8 mL). The mixture was stirred for 0.5 h under an atmosphere of H_2 and subsequently degassed with Ar. Azide **33a** (61.8 mg, 0.080 mmol), dissolved in EtOH (2 mL), was added and the mixture was stirred for 0.5 h under an atmosphere of H_2. After saturation with Ar, the catalyst was filtered off, the filtrate was evaporated, and the residue was taken up in toluene (3×5 mL) and evaporated to dryness. The resulting



35a

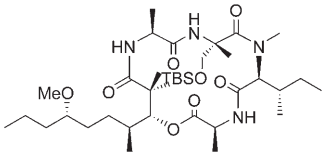
crude amino acid **34a** was dissolved in CH_2Cl_2 (40 mL) and the resulting solution was added to a solution of HATU (45.4 mg, 0.120 mmol), HOAt (32.7 mg, 0.241 mmol) and iPr$_2$NEt (40 μL, 0.24 mmol) in CH_2Cl_2 (40 mL) over a period of 4 h at ambient temperature. After 17 h of stirring, the solution was concentrated to approximately 20 mL and washed with sat aq $NaHCO_3$ (50 mL) and then with brine (50 mL). The aq layers were re-extracted with CH_2Cl_2 (2×20 mL) and the combined organic layer was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by flash column chromatography (silica gel, 55% EtOAc in hexanes) yielding macrocycle **35a** (43.3 mg, 0.060 mmol, 74%) as a white wax. **35a**: $R_f = 0.28$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{25} = -38.0$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, spectrum contains at least three sets of poorly resolved signals due to hindered rotation): δ = 7.85 (brs, 1H), 7.76 (brs, 1H), 7.54 (d, $J = 6.9$ Hz, 1H), 7.37 (d, $J = 6.4$ Hz, 1H), 7.26 (brs, 1H), 7.00 (d, $J = 6.1$ Hz, 1H), 4.92 (d, $J = 2.5$ Hz, 1H), 4.90 (brs, 2H), 4.79–4.57 (m, 5H), 4.48 (m, 2H), 4.31 (brd, $J = 8$ Hz, 1H), 4.21 (d, $J = 10.1$ Hz, 2H), 4.12–3.99 (m, 1H), 3.91–3.67 (m, 2H), 3.84 (d, $J = 10.1$ Hz, 2H), 3.61 (brs, $J = 8$ Hz, 1H), 3.26 (s, 3H), 3.25 (s, 3H), 3.08–3.00 (brs, 3H), 3.02 (s, 3H), 2.75 (m, 1H), 2.69 (s, 3H), 2.04–1.93 (m, 1H), 1.93–1.77 (m, 3H), 1.59–0.73 (m), 0.07–0.00 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, at least two sets of poorly resolved signals): δ = 175.9, 175.5, 174.5, 172.3, 171.9, 170.0, 170.3, 169.4, 167.7, 164.4, 81.3, 80.6, 80.5, 80.3, 77.2, 69.2, 65.7, 64.3, 64.1, 61.1, 59.8, 56.5, 50.2, 49.9, 48.8, 48.2, 48.1, 46.4, 45.7, 39.9, 39.9, 37.6, 36.2, 35.6, 34.6, 33.6, 33.3, 31.7, 31.6, 31.4, 31.3, 30.9, 30.6, 29.7, 26.9, 26.6, 25.9, 25.8, 23.2, 21.7, 20.6, 20.5, 18.4, 18.2, 18.1, 17.9, 17.3, 16.5, 16.4, 15.0, 14.8, 14.2, 12.6, 12.4, 11.9, 10.8, −5.4, −5.5 ppm; IR (film): $\nu_{max} = 3370$, 3301, 2956, 2927, 2858, 1744, 1675, 1636, 1518, 1459, 1380, 1252, 1212, 1094, 1065, 966, 838, 774 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{37}H_{71}N_4O_8Si$: 727.5035 found: 727.5030 $[M+H]^+$.

Compound 35b (obtained from **33b** in 73% yield): $R_f = 0.24$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{25} = -75.1$ ($c = 0.4$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, spectrum contains at least three sets of poorly resolved signals due to hindered rotation): δ = 7.77 (brs, 1H), 7.63 (brs, 1H), 7.55 (d, $J = 6.8$ Hz, 1H), 7.38 (d, $J = 6.4$ Hz, 1H), 7.26 (brs, 1H), 6.99 (d, $J = 6.1$ Hz, 1H), 4.98–4.87 (m, 1.5H), 4.93 (d, $J = 2.5$ Hz, 1H), 4.78–4.66 (brs, 1.5H), 4.69 (d, $J = 8.0$ Hz, 1H), 4.63 (dt, $J = 6.7$ Hz, 1H), 4.43 (dt, $J = 7.1$ Hz, 1H), 4.31 (brd, $J = 9.1$ Hz, 1H), 4.21 (d, $J = 10.1$ Hz, 1H), 3.91 (d, $J = 3.1$ Hz, 0.5H), 3.88 (d, $J = 10.1$ Hz, 1H), 3.80 Hz (d, $J = 9.5$ Hz, 0.5H), 3.69 (d, $J = 9.4$ Hz, 0.5H), 3.60 (brd, $J = 9.2$ Hz, 1H), 3.26 (s, 3H), 3.24 (s, 3H), 3.12–2.98 (brs, 3H), 3.02 (s, 3H), 2.19 (s, 1.5H), 2.04–1.75 (m, 5H), 1.68 (m, 1H), 1.62–0.74 (m, >120H), 0.14–[−0.06 ppm] (m, 15H); IR (film): $\nu_{max} = 4338$, 3307, 2931, 2861, 1743, 1678, 1637, 1519, 1455, 1378, 1255, 1096, 1067, 834, 779 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{37}H_{71}N_4O_8Si$: 727.5035 found: 727.5038 $[M+H]^+$.



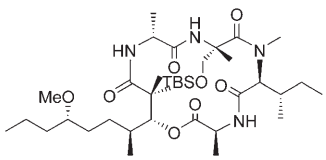
35b

Compound 35c/*epi*-35c (obtained from **33c**; **35c**: 14%, *epi*-**35c**: 22%). **35c**: $R_f = 0.36$ (silica gel, 5 0% EtOAc in hexanes); $[\alpha]_D^{32} = -55.3$ ($c = 0.7$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.50 (brd, $J = 5.2$ Hz, 1H), 7.33 (d, $J = 6.3$ Hz, 1H), 7.13 (brs, 1H), 6.96 (s, 1H), 6.83 (brs, 1H), 6.71 (d, $J = 5.9$ Hz, 1H), 4.90 (s, 1H), 4.81 (s, 1H), 4.62 (d, $J = 7.7$ Hz, 1H), 4.62–4.51 (m, 1H), 4.44–4.38 (m, 1H), 4.29–4.27 (m, 1H), 4.12 (d, $J = 10.3$ Hz, 1H), 3.84 (d, $J = 10.3$ Hz, 1H), 3.63 (brd, $J = 9.2$ Hz, 1H), 3.29 (s, 3H), 3.27 (s, 1H), 3.11 (s, 1H), 3.08–3.01 (m, 1H), 2.71 (s, 3H), 2.04–2.00 (m, 1H), 1.87–1.80 (m, 1H), 1.60 (s, 3H), 1.53 (s, 1H), 1.41 (s, 3H), 1.35 (d, $J = 6.6$ Hz, 3H), 1.16 (s, 3H), 1.13 (s, 1H), 1.06 (d, $J = 6.3$ Hz, 3H), 1.46–1.19 (m, 9H), 0.87 (s, 9H), 0.94–0.85 (m, 13H), 0.05 (s, 6H), 0.02 ppm (s, 6H); IR (film): $\nu_{max} = 3305$, 2962, 2928, 2873, 1744, 1683, 1638, 1516, 1455, 1256, 1095, 1067, 840, 773 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{37}H_{71}N_4O_8Si$: 727.5035, found: 727.5037 $[M+H]^+$.



35c

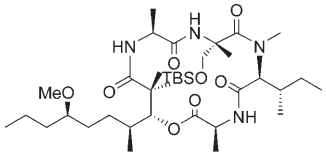
Compound *epi*-35c: $R_f = 0.28$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{25} = -7.3$ ($c = 0.2$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, spectrum contains at least two sets of poorly resolved signals due to hindered rotation): δ = 6.68 (brs, 1H), 6.64 (brd, $J = 7.0$ Hz, 1H), 6.38 (s, 1H), 5.01 (d, $J = 2.6$ Hz, 1H), 4.98–4.95 (m, 1H), 4.50–4.45 (m, 1H), 3.90–3.88 (m, 2H), 3.56 (d, $J = 10.3$ Hz, 1H), 3.27 (s, 3H), 3.07–3.02 (m, 1H), 2.92 (s, 3H), 2.04–1.97 (m, 1H), 1.88–1.84 (m, 1H), 1.70 (d, $J = 7.7$ Hz, 3H), 1.55 (s, 3H), 1.29 (d, $J = 7.0$ Hz, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 1.52–1.06 (m,



epi-**35c**

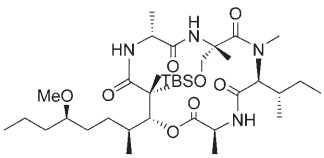
9H), 1.00 (d, $J=6.3$ Hz, 3H), 0.91 (s, 9H), 0.93–0.90 (m, 4H), 0.88 (t, $J=7.0$ Hz, 3H), 0.83 (t, $J=7.4$ Hz, 3H), 0.10 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, signals of most abundant rotomer): δ = 175.8, 172.0, 170.9, 170.7, 170.6, 80.6, 79.8, 66.0, 61.7, 56.4, 51.3, 48.5, 46.1, 35.5, 34.2, 31.3, 30.9, 30.3, 25.8, 24.4, 24.3, 22.3, 20.3, 19.4, 18.4, 18.2, 16.9, 16.8, 14.8, 14.3, 10.9, −5.4, −5.6 ppm; IR (film): $\nu_{max}=3370$, 3304, 2956, 2917, 2858, 1749, 1641, 1518, 1459, 1360, 1252, 1193, 1119, 1099, 961, 838, 779 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{37}H_{71}N_4O_8Si$: 727.5035, found: 727.5033 $[M+H]^+$.

Compound 35d/*epi*-35d (obtained from **33d**; **35d**: 25%, *epi*-**35d**: 19%). **35d**: $R_f=0.32$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{25}=-46.7$ ($c=0.7$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, spectrum contains at least two sets of poorly resolved signals due to hindered rotation): $\delta=7.52$ (d, $J=6.6$ Hz, 1H), 7.34 (d, $J=6.0$ Hz, 1H), 7.02 (brs, 1H), 6.72 (d, $J=6.0$ Hz, 1H), 4.91 (brs, 1H), 4.81 (brs, 1H), 4.63 (d, $J=8.4$ Hz, 1H), 4.59–4.54 (m, 1H), 4.42–4.39 (m, 1H), 4.29 (brd, $J=9.6$ Hz, 1H), 4.12 (d, $J=9.6$ Hz, 1H), 3.84 (d, $J=9.6$ Hz, 1H), 3.63 (brd, $J=9.6$ Hz, 1H), 3.30–3.27 (m, 3H), 3.10 (s, 3H), 3.05 (m, 1H), 2.70 (s, 1H), 2.02 (m, 1H), 1.84–1.79 (m, 1H), 1.62–1.60 (m, 3H), 1.53 (s, 3H), 1.35 (d, $J=6.6$ Hz, 3H), 1.23 (s, 3H), 1.15 (s, 3H), 1.72–1.07 (m, 10H), 0.92–0.87 (m, 18H), 0.64 (d, $J=5.4$ Hz, 1H), 0.57 (d, $J=6.6$ Hz, 3H), 0.04 (s, 6H), 0.02 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, major signals): δ = 175.3, 174.8, 174.7, 172.7, 172.5, 171.7, 171.5, 169.7, 169.3, 81.4, 81.3, 80.8, 80.7, 64.7, 64.7, 60.7, 60.3, 56.5, 50.3, 49.6, 49.4, 48.6, 45.1, 44.9, 36.4, 35.7, 33.9, 33.7, 33.5, 31.7, 31.6, 31.4, 31.2, 31.0, 29.7, 26.6, 25.9, 25.8, 25.6, 22.6, 22.2, 19.5, 19.4, 18.5, 18.3, 18.2, 18.1, 17.7, 14.3, 14.1, 13.3, 12.9, −5.3, −5.2 ppm; IR (film): $\nu_{max}=3303$, 2944, 2920, 2585, 1743, 1638, 1515, 1459, 1373, 1249, 1095, 1064, 959, 835, 774 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{37}H_{71}N_4O_8Si$: 727.5035, found: 727.5036 $[M+H]^+$.



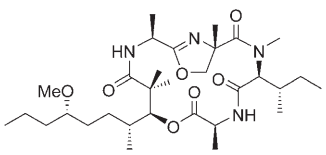
35d

Compound *epi*-35d: $R_f=0.24$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{25}=-8.8$ ($c=0.5$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, spectrum contains at least two sets of poorly resolved signals due to hindered rotation): δ = 6.74–6.65 (brs, 1H), 6.66 (d, $J=7.4$ Hz, 1H), 6.45 (brs, 1H), 6.03 (brs, 1H), 5.00 (d, $J=2.3$ Hz, 1H), 4.95 (m, 1H), 4.48 (dq, $J=7.2$ Hz, 1H), 4.12–4.03 (m, 1H), 3.92–3.84 (m, 1H), 4.92 (d, $J=3.1$ Hz, 1H), 3.87 (d, $J=10.2$ Hz, 1H), 3.81 (d, $J=9.5$ Hz, 1H), 3.73–3.66 (m, 1H), 3.69 (d, $J=9.5$ Hz, 1H), 3.57 (d, $J=10.2$ Hz, 1H), 3.26 (brs, 6H), 3.07–2.99 (m, 2H), 2.92 (s, 3H), 2.91 (brs, 3H), 2.05–1.96 (m, 1H), 1.96–1.88 (m, 2H), 1.88–1.79 (m, 1H), 1.72–1.06 (m, > 60H), 0.94–0.79 (m, > 40H), 0.10 (s, 6H), 0.05–0.02 (m, 4H), 0.04 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, major signals): δ = 175.8, 172.0, 170.6, 167.7, 164.4, 80.7, 79.7, 69.2, 66.0, 65.7, 61.7, 59.7, 56.6, 51.3, 48.5, 46.0, 37.6, 33.6, 31.6, 29.7, 26.6, 25.8, 24.4, 24.2, 22.3, 20.3, 19.4, 16.9, 16.8, 14.8, 14.3, 14.1, 12.4, 10.9, −5.5, −5.6 ppm; IR (film): $\nu_{max}=3367$, 3296, 2956, 2932, 2860, 1746, 1655, 1643, 1509, 1455, 1393, 1362, 1257, 1195, 1101, 835, 780 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{37}H_{71}N_4O_8Si$: 727.5035, found: 727.5030 $[M+H]^+$.



epi-**35d**

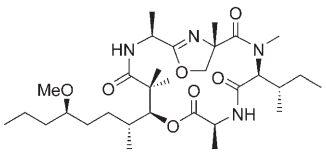
Compound 7a: Macrocycle **35a** (21.6 mg, 0.030 mmol) was dissolved in THF (5 mL) and treated with a 1 M TBAF solution in THF (water content ~5%, 34 μL, 0.034 mmol) at −10 °C. After 1.5 h at that temperature,



7a

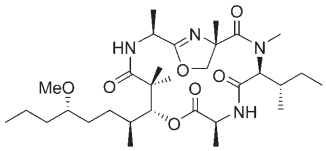
all starting material was consumed and the solution was partitioned between EtOAc (10 mL) and sat aq NH_4Cl (30 mL). The organic layer was washed with brine (30 mL), the aq layers were re-extracted with EtOAc (2×10 mL) and the combined organic layers dried over Na_2SO_4. After filtration through a plug of silica and evaporation of the solvents, the residue was taken up in toluene (3×10 mL) and evaporated to dryness. The crude hydroxy amide **8a** thus obtained was dissolved in CH_2Cl_2 (10 mL), cooled to −78 °C and reacted with DAST (9 μL, 0.07 mmol). After 0.5 h, the temperature was raised to −12 °C and after an additional 0.5 h, sat aq $NaHCO_3$ (10 mL) was added. After washing of the organic layer with brine (10 mL), the aq layers were re-extracted with CH_2Cl_2 (2×10 mL), and the combined organic layer was dried (Na_2SO_4), filtered and evaporated. The resulting residue was purified by flash column chromatography (silica gel, 40 → 50% EtOAc in hexanes) to afford oxazoline **7a** (12.9 mg, 0.022 mmol, 74%) as a colorless oil. $R_f=0.38$ (silica gel, 60% EtOAc in hexanes); $[\alpha]_D^{25}=-68.8$ ($c=0.4$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.78$ (d, $J=10.1$ Hz, 1H), 7.07 (d, $J=8.3$ Hz, 1H), 5.01 (dq, $J=10.1$, 7.0 Hz, 1H), 4.84 (d, $J=2.6$ Hz, 1H), 4.81 (d, $J=9.2$ Hz, 1H), 4.79–4.72 (m, 2H), 4.29 (d, $J=9.2$ Hz, 1H), 3.27 (s, 3H), 3.07–3.04 (m, 1H), 2.80 (s, 3H), 2.24–2.17 (m, 1H), 1.94–1.88 (m, 1H), 1.52–1.39 (m, 3H), 1.42–1.41 (m, 6H), 1.36 (d, $J=7.0$ Hz, 3H), 1.36–1.23 (m, 6H), 1.20 (s, 3H), 1.18 (s, 3H), 0.98–0.94 (m, 4H), 0.90–0.86 (m, 6H), 0.83 ppm (d, $J=7.0$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.9, 171.8, 171.0, 169.0, 168.6, 82.5, 80.5, 79.2, 74.3, 64.1, 56.5, 48.8, 45.6, 43.7, 35.6, 34.5, 33.2, 31.5, 31.2, 29.7, 27.3, 26.5, 24.8, 22.3, 19.3, 19.1, 18.4, 16.8, 14.3, 14.3, 12.4 ppm; IR (film): $\nu_{max}=3323$, 2982, 1727, 1663, 1527, 1451, 1286, 1251, 1216, 1140, 1063, 981, 746, 699 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{31}H_{55}N_4O_7$: 595.4065, found: 595.4067 $[M+H]^+$.

Compound 7b (obtained from **35b** in 63% yield): $R_f=0.38$ (silica gel, 60% EtOAc in hexanes); $[\alpha]_D^{25}=-50.8$ ($c=0.6$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.78 (d, $J=10.1$ Hz, 1H), 7.06 (d, $J=7.9$ Hz, 1H), 5.01 (dq, $J=10.1$, 7.1 Hz, 1H), 4.84 (d, $J=2.6$ Hz, 1H), 4.81 (d, $J=9.2$ Hz, 1H), 4.77–4.74 (m, 1H), 4.73 (d, $J=11.0$ Hz, 1H), 4.29 (d, $J=9.2$ Hz, 1H), 3.27 (s, 3H), 3.07 (m, 1H), 2.80 (s, 3H), 2.24–2.17 (m, 1H), 1.94–1.88 (m, 1H), 1.48–1.42 (m, 3H), 1.42 (s, 3H), 1.42 (d, $J=6.2$ Hz, 3H), 1.36 (d, $J=7.0$ Hz, 3H), 1.36–1.23 (m, 6H), 1.20 (s, 3H), 1.17 (s, 3H), 0.98–0.92 (m, 4H), 0.91–0.84 (m, 6H), 0.83 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.9, 171.8, 171.1, 168.9, 168.6, 82.6, 80.5, 79.1, 74.3, 64.1, 56.4, 48.8, 45.6, 43.7, 35.5, 34.5, 33.2, 31.2, 30.8, 29.7, 27.3, 26.6, 24.8, 22.3, 19.3, 19.0, 18.4, 16.8, 14.3, 14.2, 12.4 ppm; IR (film): $\nu_{max}=3295$, 2926, 2868, 1749, 1673, 1634, 1513, 1450, 1380, 1242, 1086, 1029, 965 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{31}H_{55}N_4O_7$: 595.4065, found: 595.4056 $[M+H]^+$.

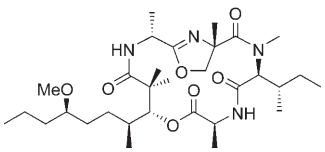


7b

Compound 7c (obtained from **35c** in 43% yield): $R_f=0.35$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{25}=-8.3$ ($c=0.1$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=8.16$ (d, $J=10.0$ Hz, 1H), 7.08 (d, $J=7.6$ Hz, 1H), 5.00 (d, $J=2.0$ Hz, 1H), 4.96–4.81 (m, 3H), 4.63 (d, $J=10.8$ Hz, 1H), 4.25 (d, $J=9.1$ Hz, 1H), 3.27 (s, 3H), 3.03–2.98 (m, 1H), 2.80 (s, 3H), 2.23–2.14 (m, 1H), 1.94–1.89 (m, 1H), 1.45 (s, 3H), 1.42 (d, $J=4.4$ Hz, 3H), 1.35 (d, $J=7.0$ Hz, 3H), 1.47–1.22 (m, 9H), 1.19 (s, 3H), 1.14 (s, 3H),



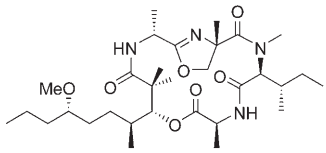
7c



epi-**7d**

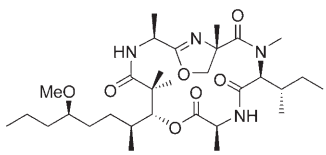
1.08–0.99 (m, 1H), 0.96–0.93 (m, 6H), 0.92–0.84 ppm (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.8, 171.6, 170.4, 170.2, 168.7, 81.8, 80.6, 78.9, 74.8, 64.6, 56.5, 48.1, 45.2, 43.6, 35.6, 34.3, 33.2, 31.1, 30.0, 29.7, 27.8, 27.3, 24.6, 22.1, 20.2, 19.4, 18.5, 17.4, 14.2, 13.7, 12.4 ppm; IR (film): ν_{max}= 2919, 1729, 1680, 1636, 1554, 1516, 1453, 1385, 1259, 1240, 1095, 1041, 972, 798, 609 cm^{-1}; HRMS (ESI-TOF): *m*/*z*: calcd for $C_{31}H_{55}N_4O_7$: 595.4065, found: 595.4057 $[M+H]^+$.

Compound *epi*-7c (obtained from *epi*-**35c** in 31% yield): R_f=0.21 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{25}$=−46.2 (*c*=0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.50 (d, *J*=10.0 Hz, 1H), 6.50 (d, *J*=7.4 Hz, 1H), 5.06 (d, *J*=11.2 Hz, 1H), 5.00 (d, *J*=2.3 Hz, 1H), 4.79 (d, *J*=9.7 Hz, 1H), 4.89–4.72 (m, 2H), 4.34 (d, *J*=9.7 Hz, 1H), 3.30 (s, 3H), 3.13–3.07 (m, 1H), 2.82 (s, 3H), 2.23–2.16 (m, 1H), 1.80–1.75 (m, 1H), 1.48 (s, 3H), 1.39 (d, *J*=7.0 Hz, 3H), 1.28 (s, 3H), 1.20–1.18 (m, 6H), 1.52–1.31 (m, 9H), 1.01–0.97 (m, 4H), 0.94 (d, *J*=6.5 Hz, 3H), 0.89 (t, *J*=7.2 Hz, 3H), 0.81 ppm (d, *J*=6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.8, 172.2, 170.7, 170.6, 168.4, 81.6, 80.7, 79.1, 75.1, 63.8, 56.5, 47.5, 46.8, 43.9, 35.6, 33.0, 32.7, 32.5, 31.2, 29.7, 28.2, 25.2, 23.8, 19.1, 19.1, 18.4, 18.4, 16.6, 15.4, 14.3, 12.2 ppm; IR (film): ν_{max}=3317, 2958, 2925, 2870, 1743, 1694, 1667, 1628, 1530, 1454, 1312, 1252, 1094, 1056, 974, 794 cm^{-1}; HRMS (ESI-TOF): *m*/*z*: calcd for $C_{31}H_{55}N_4O_7$: 595.4065, found: 595.4071 $[M+H]^+$.



epi-**7c**

Compound 7d (obtained from **35d** in 40% yield): R_f=0.42 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{25}$=−18.0 (*c*=0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.16 (d, *J*=10.0 Hz, 1H), 7.08 (d, *J*=7.5 Hz, 1H), 5.00 (d, *J*=1.5 Hz, 1H), 4.88 (d, *J*=9.0 Hz, 1H), 4.93–4.82 (m, 2H), 4.63 (d, *J*=10.5 Hz, 1H), 4.25 (d, *J*=9.0 Hz, 1H), 3.25 (s, 3H), 3.00–2.98 (m, 1H), 2.80 (s, 3H), 2.18 (m, 1H), 1.90 (m, 1H), 1.45 (s, 3H), 1.43 (d, *J*= 7.5 Hz, 3H), 1.36 (d, *J*=7.0 Hz, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 1.45–1.14 (m, 10H), 0.96–0.95 (m, 6H), 0.91–0.88 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 171.6, 170.4, 170.2, 168.7, 81.5, 80.7, 78.8, 74.8, 64.5, 56.6, 48.1, 45.2, 43.6, 35.6, 34.2, 33.2, 31.4, 30.9, 30.0, 27.8, 27.3, 24.6, 22.0, 20.2, 19.4, 18.3, 17.5, 14.3, 14.0, 12.4 ppm; IR (film): ν_{max}= 3421, 3296, 2958, 2935, 2868, 1746, 1633, 1509, 1458, 1374, 1233, 1092, 1041, 968 cm^{-1}; HRMS (ESI-TOF): *m*/*z*: calcd for $C_{31}H_{55}N_4O_7$: 595.4065, found: 595.4061 $[M+H]^+$.



7d

Compound *epi*-7d (obtained from *epi*-**35d** in 36% yield): R_f=0.23 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{25}$=−51.0 (*c*=0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.48 (d, *J*=10.0 Hz, 1H), 6.49 (d, *J*=7.0 Hz, 1H), 5.06 (d, *J*=11.0 Hz, 1H), 5.01 (d, *J*=2.5 Hz, 1H), 4.80 (d, *J*=9.5 Hz, 1H), 4.86–4.74 (m, 2H), 4.33 (d, *J*=9.5 Hz, 1H), 3.29 (s, 3H), 3.30–3.18 (m, 1H), 2.82 (s, 3H), 2.20–2.15 (m, 1H), 1.79–1.72 (m, 1H), 1.49 (s, 3H), 1.39 (d, *J*=7.5 Hz, 3H), 1.28 (s, 3H), 1.49–1.22 (m, 9H), 1.19 (d, *J*= 7.5 Hz, 3H), 1.18 (s, 3H), 0.99–0.96 (m, 4H), 0.94 (d, *J*=6.5 Hz, 3H), 0.89 (t, *J*=7.0 Hz, 3H), 0.82 ppm (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.8, 172.2, 170.6, 170.6, 168.3, 81.3, 80.7, 79.1, 75.1, 63.8, 56.5, 47.5, 46.7, 43.9, 35.7, 33.0, 32.7, 32.6, 31.6, 29.7, 28.2, 25.2, 23.8, 19.1, 19.1, 18.4, 18.4, 16.6, 15.7, 14.3, 12.2 ppm; IR (film): ν_{max}= 3319, 2958, 2919, 2850, 1741, 1635, 1556, 1537, 1454, 1312, 1253, 1126, 1097, 965 cm^{-1}; HRMS (ESI-TOF): *m*/*z*: calcd for $C_{31}H_{55}N_4O_7$: 595.4065, found: 595.4058 $[M+H]^+$.

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