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Synthesis and Biological Evaluation of Dichlorinated Chondramide Derivatives

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Straightforward synthetic protocols for the synthesis of new ethyl-substituted dichlorinated chondramides with different methyl-substitution patterns in the polyketide fragment have been developed. The methyl groups at the ε-position can be removed completely without a significant influence on the biological activity. In contrast, after removal of the α-methyl group, a significant drop in activity is observed. This is also observed if the configuration of the α-methyl group is inverted.

Introduction

Chondramides A–D, isolated by Höfle and Reichenbach from terrestrial myxobacteria in 1995,[1] belong to a very interesting class of cyclodepsipeptides. They are structurally closely related to the highly cytotoxic jasplakinolide (jaspamide)[2] and geodeamolide[3] (Figure 1), which were isolated from sponges in the 1980s. Many of these cyclic peptides show interesting biological properties, and are therefore interesting candidates for the development of drugs.[4] They can stabilize the actin cytoskeleton,[5] thereby altering, for example, anaphase chromosome movements,[6] and inducing apoptosis in a wide range of cancer cell lines.[7] Recently, the miuraenamides, isolated from marine myxobacteria,[8] joined this class of compounds, all of which have a high affinity for actin.[9] Biosynthetically, these peptides are synthesized on multienzyme complexes consisting of polyketide synthase (PKS) modules and nonribosomal peptide synthetase (NRPS) modules.[10] While jasplakinolide and geodeamolide are obviously produced by the same (or at least very similar) PKS, variations are found in the central part of the tripeptide fragment. On the other hand, jasplakinolide and the chondramides have almost the same peptide fragment, but differ slightly in the polyketide unit.

Interestingly, in most derivatives, the central aromatic amino acid is halogenated, even in the "terrestrial" chondramides (Figure 1, R^1 = Cl, at least in some derivatives). Very recently, Müller et al. isolated a set of new chondramide A and C derivatives (Figure 1), containing a halogenated β-tyrosine at the *C*-terminus of the tripeptide (**A3**; R^2 = Cl), and with excellent biological activities.[11] Doubly chlorinated derivatives could also be found in the

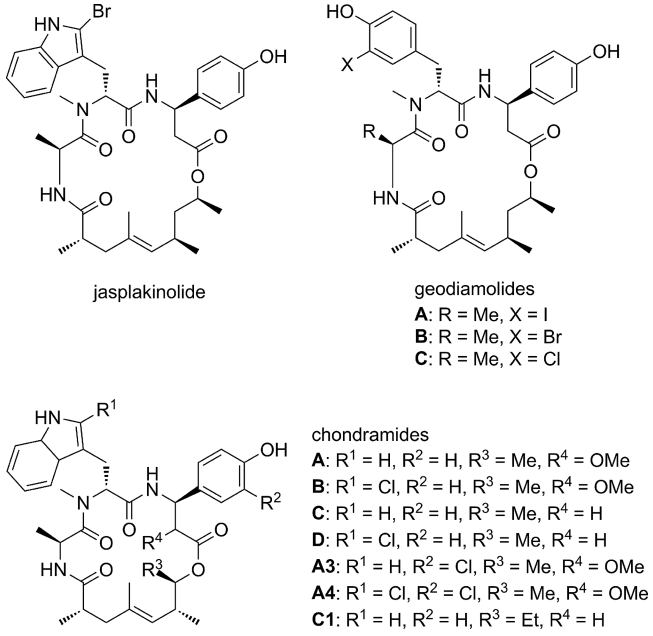

Figure 1. Actin-stabilizing cyclodepsipeptides.

chondramide A series (R^4 = OCH_3; **A4**), but so far not in the chondramide C series (R^4 = H). Interestingly, some derivatives contain an ethyl substituent (R^3) at the end of the hydroxycarboxylic acid (**C1**), which clearly indicates that the biosynthesis of these compounds starts with the incorporation of a propionyl-CoA and not as usual with acetyl-CoA.

Interestingly, chondramide C has a slightly higher cytotoxicity than chondramides A and B, which shows that the α-methoxy group on the tyrosine is not essential for a high biological activity. Therefore, the structurally simpler chondramide C should be a suitable candidate for the development of actin-binding anticancer drugs. Very recently, we showed that dichlorination significantly increases the cytotoxicity of chondramide derivatives. Even when the methyl

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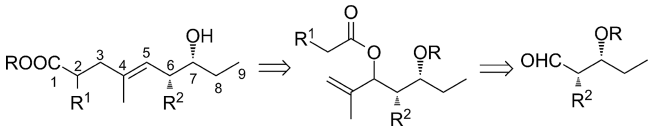
substituents in the polyketide fragment were removed completely, the biological activity could be retained by introduction of a second chlorine atom into the β-tyrosine ($R^1 = R^2 = Cl$).[12]

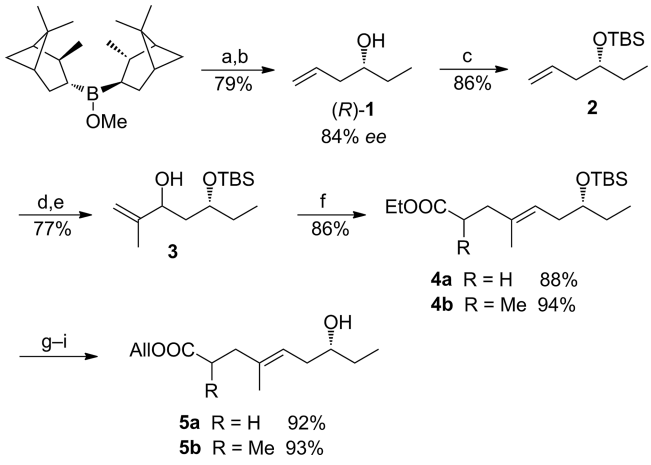
These results were quite surprising, since structure–activity relationship (SAR) studies by Kalesse et al.[13] and by Waldmann and Arndt et al.[14] using nonhalogenated chondramide C derivatives clearly indicate that the methyl groups in the polyketide fragment have an influence on the conformation, and as a result of that, also on the biological activity of the chondramides. Maier et al. investigated the influence of several chondramide A derivatives bearing different substituents in the *para* position of the β-tyrosine.[15] No significant influence was observed if the OH functionality was replaced by other small substituents (electron-donating or -withdrawing). Obviously, this position is suitable for modifications. To the best of our knowledge, (doubly) halogenated derivatives have not been investigated so far, except for our simplified chondramides described recently.[12] Because of our ongoing interest in the synthesis of peptidic natural products, especially those with anticancer activity,[16] we decided to also investigate the influence of the substitution pattern on the cytotoxicity of dichlorinated chondramides, focussing on the new ethyl-substituted derivatives. We were interested in seeing whether we could remove some of the methyl groups individually, or whether we could replace them by other functionalities to allow the subsequent introduction of labels (fluorescence, photoaffinity, etc.) for biological studies. The *trans* double bond of the polyketide fragment should be introduced by a Claisen rearrangement of a suitable acylated allyl alcohol according to Scheme 1.



Scheme 1. Retrosynthesis of the polyketide fragment.

Results and Discussion

We started our investigations with the simplest polyketide fragment containing only the ethyl substituent at C-7 (Scheme 2). To introduce this (*R*)-configured stereogenic centre, we decided to use an enantioselective allylation using Brown's *B*-allyldiisopinocampheylborane (Ipc_2B-all).[17] This reagent can easily be prepared from commercially available *B*-methoxydiisopinocampheylborane (Ipc_2B-OMe) and allylmagnesium bromide. Our best results were obtained when the Grignard reagent was used in a slight shortfall (0.9 equiv.). In this case, an enantiomeric ratio of 92:8 [(*R*)/(*S*)] could be obtained with an acceptable yield. Subsequent silylation of (*R*)-**1** gave access to chiral silyl ether (*R*)-**2** (84% *ee*), which could be purified by microdistillation. We did not try to increase the enantiomeric purity of the alcohol (or the silyl ester), because in the cyclodepsipeptide the undesired stereoisomer could easily be removed by flash chromatography. Therefore, (*R*)-**2** was subjected to ozonolysis, which, after a reductive work-up, gave rise to the corresponding aldehyde. This was directly (without further purification) transformed into allyl alcohol **3** by Grignard addition. The newly formed stereogenic centre was obtained as a 1:1 mixture in good overall yield. For the synthesis of the simplified hydroxy acid derivatives, this diastereomeric mixture was not separated, but directly subjected to the next step, a Johnson ortho ester rearrangement.[18] α-Unsubstituted ester **4a** was obtained from the orthoacetate, while α-methylated ester **4b** was formed in the reaction with the corresponding orthopropionate. Both esters were obtained in excellent yield.

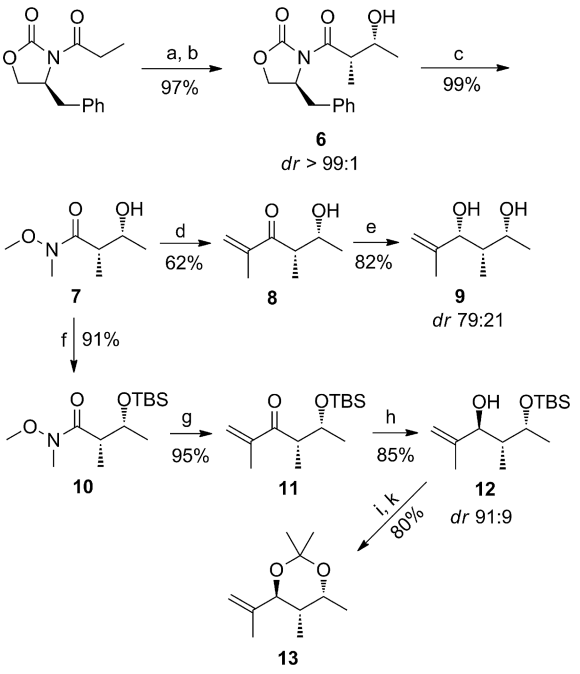


Scheme 2. Synthesis of simplified ω-hydroxy esters **5**. (a) Allylmagnesium bromide (0.9 equiv.), Et_2O, –78 °C to room temp., 16 h; (b) EtCHO, –78 °C, 3 h; (c) TBSCl (TBS = *tert*-butyldimethylsilyl), imidazole, DMF, 0 °C to r.t., 16 h; (d) 1. O_3, CH_2Cl_2, –78 °C; 2. PPh_3, –78 °C, 1 h; (e) 2-propenylmagnesium bromide, THF, 0 °C to r.t., 16 h; (f) $RCH_2C(OEt)_3$, EtCOOH, 136 °C, 16 h; (g) NaOH, EtOH; (h) allyl bromide, K_2CO_3, DMF, r.t., 16 h; (i) AcOH, THF/H_2O, 50 °C, 2 h.

Ester **4b** was used further as a diastereomeric mixture, and the diastereomers were easily separated later in the cyclic peptide. This allows the influence of the α-methyl group on the biological activity of the chondramide derivatives to be determined. In principle, after desilylation, esters **4** can be coupled to the corresponding peptide. But before the cyclization can take place, the ethyl ester has to be removed, and this caused problems in several cases, since we were unable to cleave the ethyl ester selectively in presence of the β-tyrosine ester. Therefore, we decided to change the ester functionality into an allyl ester, which can be removed by Pd catalysis. Subsequent desilylation gave hydroxy esters **5** in excellent overall yields.

The synthesis of the more complex polyketide with all the substituents in place started with an aldol reaction using Evans's method (Scheme 3). The boron enolate of chirally modified propionamide was treated with propionaldehyde to give *syn*-aldol product **6** in excellent yield and with excellent stereoselectivity.[19] Only one stereoisomer could be detected by HPLC, which can be explained by a strong preference for one of the stereoisomeric cyclic transition states. In

the presence of the Lewis acid Me_3Al, **6** could be directly converted into the corresponding enantiopure Weinreb amide (i.e., **7**) in excellent yield.[20] It is worth mentioning that an alternative route under basic conditions using imidazole and *N*,*O*-dimethylamine·HCl resulted in a partial epimerization of **6**. Grignard addition of 2-propenylmagnesium bromide to **7** gave the α,β-unsaturated ketone **8**, which had to be reduced to the *anti,syn*-configured diol. After selective protection of the secondary alcohol, this (*S*)-configured allylic alcohol should allow the stereoselective introduction of the α-methyl group through an Ireland–Claisen rearrangement. Because of the required *anti* orientation of the two OH functionalities, we decided to apply Evans's protocol for OH-directed ketone reduction using triacetoxyborohydride.[21] Coordination of the borohydride to the backward-oriented OH group of **8** should allow reduction of the ketone from the back side, resulting in an *anti* 1,3-diol. Surprisingly, the yield and diastereoselectivity of the reduction were poor, and the best results were obtained using a carefully optimized temperature program. But nevertheless, we were not able to get a diastereoselectivity better than 4:1. Since we failed to introduce a silyl protecting group regioselectively onto the secondary alcohol of **9** without affecting the allylic alcohol, we decided to change the order of the reaction steps.

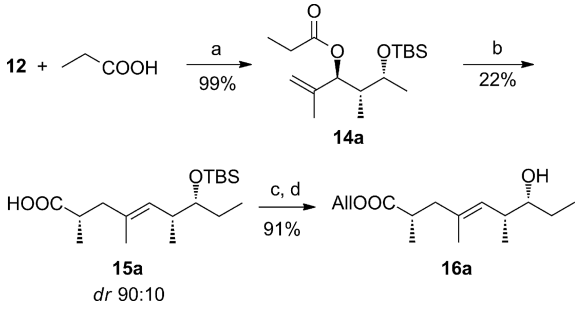


Scheme 3. Stereoselective synthesis of chiral building block **12**. (a) NEt_3, Bu_2BOTf, CH_2Cl_2, 0 °C; (b) 1. EtCHO, –78 °C, 30 min; 2. –78 °C to room temp., 60 min; (c) MeONHMe·HCl, $AlMe_3$, CH_2Cl_2, –20 °C to r.t.; (d) 2-propenylmagnesium bromide, THF, 0 °C to r.t., 16 h; (e) $Me_4N^+(AcO)_3BH^-$ (8 equiv.), MeCN/AcOH, 1. –40 °C, 1 h; 2. –35 °C, 15 h; 3. –15 °C, 24 h; (f) TBSCl, imidazole, DMF, r.t., 16 h; (g) 2-propenylmagnesium bromide, THF, 0 °C to r.t., 12 h; (h) $NaBH_4$ (1.5 equiv.), $CeCl_3$ (1.05 equiv.), MeOH, –78 °C to r.t., 16 h; (i) TBAF (tetrabutylammonium fluoride), THF, r.t., 16 h; (k) acetone, 2,2-dimethoxypropane, pyridinium *p*-toluenesulfonate, CH_2Cl_2, r.t., 16 h.

Weinreb amide **7** was directly converted into silyl-protected derivative **10**, which then was then subjected to the Grignard addition to give protected ketone **11**. Since the Evans protocol is not applicable to protected hydroxy ketones, we investigated the reduction of the ketone with a wide range of other reducing reagents. No reaction was observed using N-selectride or DIBAL-H (diisobutylaluminium hydride), but $NaBH_4$ gave rise to a 6:1 diastereomeric mixture in around 55% yield, almost independent of the reaction temperature and the amount of reducing agent used. By far the best results were obtained under Luche conditions using $NaBH_4/CeCl_3$ at –78 °C.[22] The required monoprotected diol (i.e., **12**) was obtained in good yield with a diastereomeric ratio of 10:1. Interestingly, the diastereomer formed had the opposite configuration to that formed in the $(AcO)_3BH^-$ reduction (i.e., **9**). Enantiomerically pure **12** could be obtained by flash chromatography (85% yield).

To establish the absolute configuration of the newly formed stereogenic centre, we converted **12** into the corresponding acetonide (i.e., **13**; Scheme 3), which could be subjected to detailed NMR spectroscopic analysis.[23] While the *syn*,*syn* acetonide should exist in a well-defined chair conformation, one might expect a twist-boat conformation for the *anti,syn* isomer. The methyl groups of the acetal in particular, as well as the quaternary *C*-atom (C_q), of these two isomers differ significantly in their ^{13}C NMR spectra. The shifts observed (i.e., CH_3: δ = 23.70 and 24.90 ppm, C_q: δ = 100.50 ppm) fit perfectly with the *anti* acetonide. This is also true of the coupling constants ($J_{4,5}$ = 8.8 and $J_{3,4}$ = 8.0 Hz), which indicate bond angles of around 20 or 170°.

To finish the synthesis of the required polyketide building block, enantiopure **12** was coupled with propionic acid to give allyl ester **14a**, which could be subjected to a Claisen rearrangement (Scheme 4). To get a clean chirality transfer from the alcohol to the α substituent, the subsequent Claisen rearrangement has to proceed via the corresponding (*Z*)-enolate (derivative). For the rearrangement of propionate **14a** we chose the Ireland–Claisen variant,[24] an approach Maier et al. also used in their synthesis of geodeam-

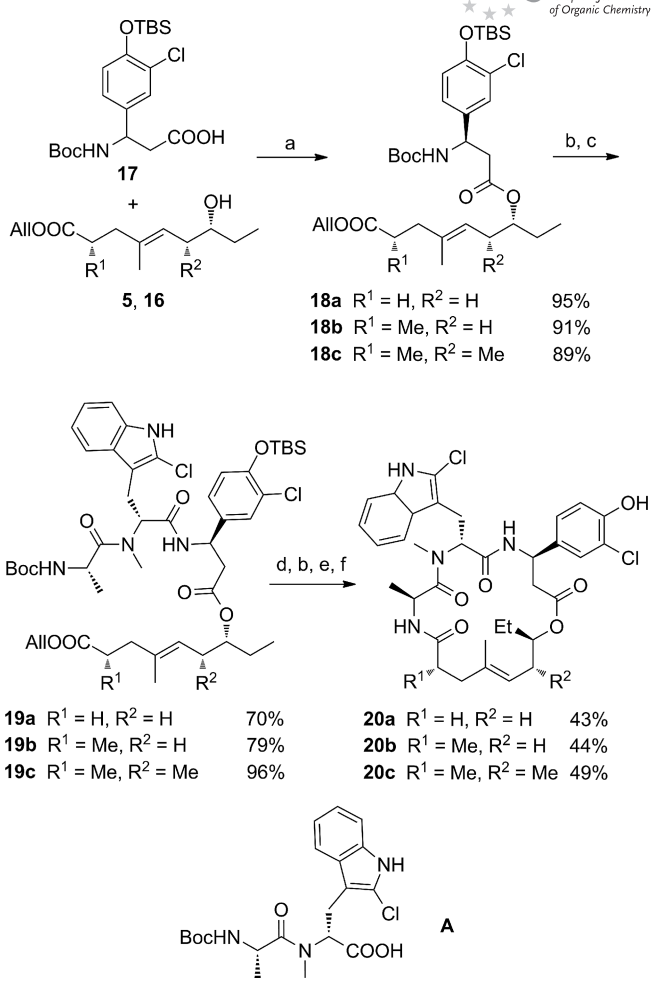


Scheme 4. Synthesis of ω-hydroxy esters **16a**. (a) DCC (*N*,*N*′-dicyclohexylcarbodiimide), DMAP (4-dimethylaminopyridine), Et_2O, 0 °C to room temp., 16 h; (b) LDA (lithium diisopropylamide), DMPU, TMSCl, THF, 1. –78 °C, 1 h; 2. –78 °C to r.t., 1 h; 3. 66 °C, 16 h; (c) K_2CO_3, allyl bromide, DMF, r.t., 16 h; (d) THF, H_2O/AcOH (1:3), 50 °C, 2 h; (e) LDA, $ZnCl_2$, THF, –78 °C to r.t., 16 h.

olide.[25] In general, HMPA (hexamethylphosphoramide) is used to generate the desired (*Z*)-enolate. To avoid the use of this rather toxic compound, we used DMPU (dimethylpropenylurea) as a surrogate.[26] But even when the silylketene acetal formed was heated to reflux, the required γ,δ-unsaturated acid (i.e., **15a**) was obtained only in poor yield, albeit with an acceptable diastereoselectivity [ratio (2*S*)/(2*R*) 9:1]. Unfortunately, attempts to improve the yield by variation of the amount of TMSCl (trimethylsilyl chloride) and base used (with or without DMPU) were unsuccessful. Allylic alcohol **12** could be isolated as a side-product, obviously formed by decomposition of the enolate. Subsequent reaction with allyl bromide gave the corresponding allyl ester, which was directly desilylated to give hydroxy ester **16a**.

With hydroxy esters **5** and **16a** in hand, we next focussed on the synthesis of the chondramide derivatives (Scheme 5). Esterification of the OH functionality with chlorinated β-tyrosine derivative **17**[12] using the Steglich protocol[27] gave the desired esters (i.e., **18**) in excellent yield. Cleavage of the *N*-Boc (*tert*-butoxycarbonyl) group and coupling with chlorinated tryptophan dipeptide **A** gave access to tripeptide esters **19**.

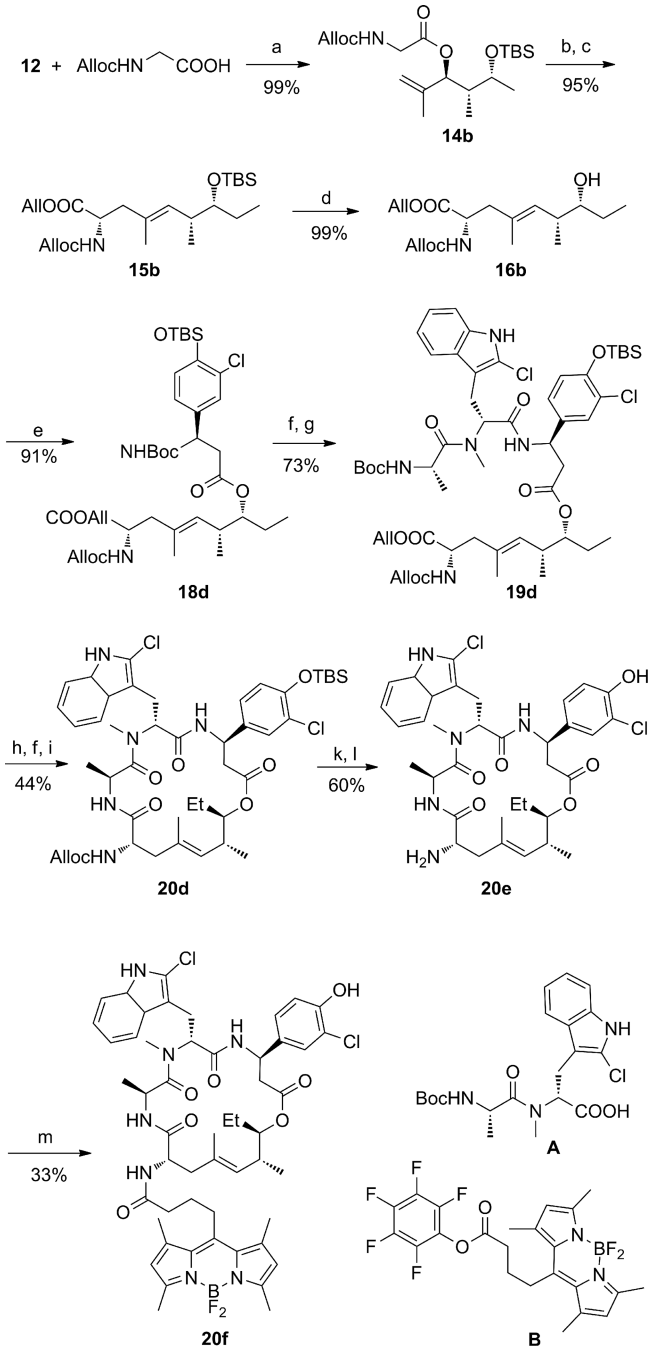
During the coupling step, a partial epimerization of the tryptophan was observed.[12] This was not a serious issue since the "wrong" diastereomer could be removed by chromatography of the cyclic peptide. The allyl ester was cleaved using $Pd(PPh_3)_4$/morpholine.[28] Trifluoroacetic acid was used to remove the *N*-Boc protecting group, and the terminal deprotected linear precursors were subjected to cyclization under high-dilution conditions using T3P® (propylphosphonic anhydride)[29] as coupling reagent. Finally, the silyl protecting group was removed to give the free chondramide derivatives (i.e., **20a**–**20c**). In all cases, acceptable yields of the cyclized products in the range of 43–52% (over three steps) were obtained. In the case of **5b**, which was used as a 1:1 diastereomeric mixture, the two diastereomeric cyclopeptides (i.e., **20b-1** and **20b-2**) could be separated by flash chromatography. The other peptides could also be obtained enantiomerically pure.



Scheme 5. Synthesis of modified chondramides **20**. (a) DCC, DMAP, Et_2O, 0 °C to room temp., 16 h; (b) CF_3COOH, CH_2Cl_2, –20 °C, 12 h; (c) **A**, *i*PrNEt$_2$, COMU® [(1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylaminomorpholinocarbenium hexafluorophosphate], CH_2Cl_2, 0 °C to r.t., 16 h; (d) $Pd(PPh_3)_4$, morpholine, THF, r.t., 2 h; (e) T3P®, *i*PrNEt$_2$, CH_2Cl_2, r.t., 16 h; (f) TBAF, THF, r.t., 1 h.

Since our group has been involved in Claisen rearrangements for a long time, especially for the synthesis of unsaturated amino acids,[30] we developed a protocol proceeding via chelated amino acid ester enolates.[31] To use this method for the introduction of an amine functionality (as anchor for the introduction of labels), we also coupled **12** to *N*-Alloc-protected (Alloc = allyloxycarbonyl) glycine (to give **14b**; Scheme 6). And indeed, much better results were obtained in the chelate enolate Claisen rearrangement of glycine ester **14b**.[32] The *N*-protected α-amino acid was formed in almost quantitative yield, and was then directly converted into allyl ester **15b**. The diastereoselectivity was also high, as a result of a chair-like transition state of the chelated (*Z*)-enolate. Cleavage of the silyl protecting group[33] gave hydroxy ester **16b**. The remainder of the synthesis proceeded as described for the other derivatives. It should be mentioned that in dichloromethane, the Pd-catalysed cleavage of the allyl ester was selective, proceeding without affecting the *N*-Alloc protecting group, whereas in THF the Alloc group was also cleaved.[34] After the cleavage of the silyl protecting group, the Alloc protecting group was also removed from the α-amino group to give **20e**. The amine was subsequently coupled with BODIPY-substituted (BODIPY = boron-dipyrromethene) pentafluorophenyl ester **B**[35] to give fluorescence-labelled chondramide **20f**.

After separation of the two diastereomeric peptides **20b-1** and **20b-2**, we wanted to assign the configuration of the α-methyl group by comparison of the NOESY spectra with those of derivatives of known configuration, e.g., **20c**. In **20c**, which has an (*S*) configuration at the α-C, a strong NOE was observed between NH_{Ala} and the α-H of the carboxylic acid, while only a weak NOE was observed between NH_{Ala} and the α-methyl group. The same situation was found for **20b-1**, while **20b-2** showed the opposite effects (strong NOE between NH_{Ala} and α-CH_3, weak NOE between NH_{Ala} and α-CH). Because the rest of the molecule was almost the same, we assigned the (*S*) configuration to **20b-1**, and the (*R*) configuration to **20b-2**. One



Scheme 6. Synthesis of fluorescence-labelled chondramide **20f**. (a) DCC, DMAP, Et_2O, 0 °C to room temp., 16 h; (b) LDA, $ZnCl_2$, THF, –78 °C to r.t., 16 h; (c) K_2CO_3, allyl bromide, DMF, r.t., 16 h; (d) THF, H_2O/AcOH (1:3), 50 °C, 2 h; (e) **17**, DCC, DMAP, Et_2O, 0 °C to r.t., 16 h; (f) CF_3COOH, CH_2Cl_2, –20 °C, 12 h; (g) **A**, *i*PrNEt$_2$, COMU® [(1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylaminomorpholinocarbenium hexafluorophosphate], CH_2Cl_2, 0 °C to r.t., 16 h; (h) $Pd(PPh_3)_4$, morpholine, THF, r.t., 2 h; (i) T3P®, *i*PrNEt$_2$, CH_2Cl_2, r.t., 16 h; (k) TBAF, THF, r.t., 1 h; (l) $Pd(OAc)_2$, $HNEt_2$, TPPTS [triphenylphosphine-3,3′,3′′-trisulfonic acid trisodium salt], MeCN/H_2O/EtOH (8:3:3), 1 h; (m) **B**, *i*PrNEt$_2$, CH_2Cl_2, DMSO, r.t., 16 h.

might expect that the configuration at this position should also be reflected in the biological activity of the peptides.

The activity of **20** towards a panel of tumor cell lines was investigated using the MTT-assay.[36] The results are summarized in Table 1. Also included for reference are data for chondramide C, chondramide C1, and dichlorodesmethyl chondramide C, a synthetic analogue in which all the substituents on the polyketide unit are removed. In previous studies, we found this derivative to have comparable activity to chondramide C (at least towards HCT-116 cells).[12]

Table 1. Cytotoxicity of chondramide derivatives **20** towards tumor cells.[11]

	GI_{50}[a] [nM] HCT-116[b]	KB-3.1[c]	RAW246.7[d]	U-2OS[e]
Chondramide C	34	37	26	26
Dichlorodesmethyl Chondramide C	30	376	197	67
Chondramide C1	42	56		15
20a	200	1100	800	600
20b-1	16	98	75	54
20b-2	800	1900	1800	1300
20c	83			30
20e	280			2500
20f				50000

[a] 50% of maximal inhibition of cell proliferation. [b] Human colon cancer. [c] Human cervical carcinoma. [d] Leukemic mouse macrophage. [e] Human bone osteosarcoma.

We observed previously that removal of the methyl groups causes a significant drop in biological activity, an effect that could be compensated by the introduction of two chlorine substituents. Therefore, dichlorodesmethyl chondramide C shows similar activity towards some cell lines, against others it was worse (KB-3.1). Interestingly, the introduction of an ethyl group at the ester functionality (**20a**) resulted in a significant drop of activity (by a factor of 10–30). Incorporation of the α-methyl group brought back the high cytotoxicity, but only for one stereoisomer. The excellent activity of **20b-1** indicates that our assignment as the natural (*S*) isomer was obviously correct. In contrast, the (*R*) isomer was less active by a factor of 20–40.[14b] The introduction of the "third" substituent (**20c**) brought no further improvement. We also investigated the activity of amine **20e**, since the NH_3^+ group that would probably form under physiological conditions, should be isosteric to the methyl group, but with an additional positive charge. Interestingly, the activity of **20e** towards HCT-116 cells was only slightly worse than that of desmethyl derivative **20a**, while a significant drop in activity was observed for U-2OS cells. The fluorescence-labelled derivative **20f** was found to be almost inactive.

Conclusions

In conclusion, we have shown that the structure of "ethyl chondramides" can be simplified by removing the methyl group at the ε-position (C-6). As long as both aromatic amino acids are chlorinated, antitumor activities comparable to those of chondramide C and C1 are observed. Removal of the α-methyl group results in a significant drop in

activity, a situation that is even worse if the configuration at this stereogenic centre is inverted. This is in contrast to results obtained with the dichlorinated desmethyl derivative.

Experimental Section

General Remarks: All air- or moisture-sensitive reactions were carried out in dried glassware (>100 °C) under an atmosphere of nitrogen or argon. Dried solvents were distilled before use; THF was distilled from $LiAlH_4$ or Na. Abs. dichloromethane and DMF were purchased from Sigma–Aldrich. The products were purified by flash chromatography on silica gel (0.063–0.2 mm). Mixtures of EtOAc and petroleum ether were generally used as eluents. Analytical TLC was carried out on precoated silica gel plates (Macherey–Nagel, Polygram® SIL G/UV254). Visualization was accomplished with UV light, $KMnO_4$ solution, or ninhydrin solution. Melting points were determined with a Dr. Tottoli (Büchi) melting point apparatus. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-400 instrument [400 MHz (^1H) and 100 MHz (^{13}C)]. Chemical shifts are reported in ppm, and spectra were calibrated using residual solvent signals. Diastereomeric ratios were determined by NMR spectroscopy or HPLC. Selected signals of minor isomers are extracted from the NMR spectra of the isomeric mixtures. Enantiomeric and diastereomeric ratios were determined by HPLC (Merck–Hitachi LaChrom D-7000, Merck's Multi-HSM-Manager) using a chiral column (Reprosil 100 Chiral-NR 8 µm or OD-H 250 × 4.6 mm). Gas chromatography (GC) was carried out using a GC-2010 Shimadzu gas chromatograph, and data were analysed using the Shimadzu GC Solution software. A Chirasil-Dex CB capillary column was used (25 m length, 0.25 mm internal diameter) as the stationary phase, and the carrier gas used was nitrogen. Preparative high-performance liquid chromatography (prep. HPLC) was carried out using an instrument from Merck–Hitachi (LaChrom D-7150, Interface D-700, UV Detector L-7400, Pump L-7150, Super Fraction Collector SF-3120, Merck's Multi-HSM-Manager) and a Reprosil 100 C-18 column (100 × 20 mm, 5 µm particle size; Altmann Analytics). HPLC–MS analysis was carried out with a Shimadzu system (LC: 10A-series + Autosampler, MS: LCMS-2020) and an achiral column (Luna 3µ C18, 50 × 4.6 mm). Mass spectra were recorded with a Finnigan MAT 95 spectrometer (quadrupole) using the CI technique. Elemental analyses were performed at the Saarland University.

(*R*)-Hex-5-en-3-ol (1):[17] Allylmagnesium bromide (1 M in diethyl ether; 32.9 mL, 23.9 mmol) was added to a solution of (–)-*B*-methoxydiisopinocamphenylborane (11.5 g, 36.4 mmol) in anhydrous diethyl ether (42 mL) at –78 °C, and the reaction mixture was allowed to warm up to room temperature overnight. The mixture was then cooled to –78 °C, and propionic aldehyde (2.61 mL, 36.4 mmol) was added. The reaction mixture was stirred for 3 h at this temperature. NaOH (3 M in H_2O; 14.5 mL) and H_2O_2 (30% aq.; 28.9 mL) were then added, and the mixture was heated at reflux for 3 h. The phases were separated, and the aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with HCl (1 M), H_2O, satd. aq. $NaHCO_3$, and brine, and dried with Na_2SO_4, and the solvent was removed by distillation. Purification by fractional distillation (125 mbar, b.p. 75–77 °C, micro distillery) gave **1** (2.59 g, 25.9 mmol, 79%, 84% *ee*) as a colourless oil. The *ee* value was determined by GC (Chirasil-Dex-CB) after conversion of the alcohol into the corresponding acetate [T_0 = 80 C (3 min), 2 °C/min, T_{end} = 200 °C (10 min): (*S*)-$\mathbf{1}_{Acetate}$: t_R = 5.63 min (*R*)-$\mathbf{1}_{Acetate}$: t_R = 6.05 min]. R_f: 0.41 (petroleum ether/ethyl acetate, 7:3). $[a]_D^{20}$ = +9.8 (*c* = 1.8, $CHCl_3$, 84% *ee*). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.5 Hz, 3 H), 1.50 (m, 2 H), 1.62 (br. s, 1 H), 2.14 (m, 1 H), 2.32 (m, 1 H), 3.58 (m, 1 H), 5.12 (m, 1 H), 5.15 (m, 1 H), 5.83 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.9, 29.5, 41.4, 72.0, 118.0, 134.9 ppm.

(*R*)-Hex-5-en-3-ol *tert*-Butyldimethylsilyl Ether (2):[17] TBSCl (4.17 g, 27.7 mmol) and imidazole (1.88 g, 27.7 mmol) were added to a solution of homoallylic alcohol (*R*)-**1** (2.31 g, 23.1 mmol, 84% *ee*) in anhydrous DMF (60 mL) at 0 °C. The mixture was allowed to warm to room temperature overnight. The solution was diluted with diethyl ether, washed with HCl (1 M aq.), satd. aq. $NaHCO_3$, and brine, and dried with Na_2SO_4, and the solvent was removed by distillation. Purification by fractional distillation (15 mbar, b.p. 74–84 °C) gave **2** (4.27 g, 19.9 mmol, 86%, 84% *ee*) as a colourless oil. R_f: 0.77 (petroleum ether/ethyl acetate, 9:1). $[a]_D^{20}$ = +13.2 (*c* = 2.1, $CHCl_3$, 84% *ee*). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.86 (t, *J* = 5.0 Hz, 3 H), 0.89 (s, 9 H), 1.46 (m, 2 H), 2.21 (m, 2 H), 3.62 (tt, *J* = 5.8 Hz, 1 H), 5.01 (m, 1 H), 5.04 (m, 1 H), 5.82 (ddt, *J* = 17.3, 10.3, 7.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6, 9.6, 18.2, 25.9, 29.5, 41.5, 73.2, 116.5, 135.6 ppm.

(5*R*)-5-(*tert*-Butyldimethylsilyloxy)-2-methylhept-1-en-3-ol (3): Ozone was bubbled through a solution of silyl ether **2** (0.98 g, 4.57 mmol, 84% *ee*) in anhydrous CH_2Cl_2 (45 mL) at –78 °C until the characteristic blue colour appeared. PPh_3 (1.21 g, 4.61 mmol) was added in one portion. The mixture was stirred for 1 h, then it was allowed to warm up to room temperature, and concentrated under reduced pressure (>500 mbar).

The crude aldehyde was slowly treated with a 2-propenylmagnesium bromide solution (0.5 M in THF; 10.9 mL, 5.46 mmol) at 0 °C. After the addition was complete, the mixture was allowed to warm to room temperature overnight. The reaction was quenched with satd. NH_4Cl, and the mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 95:5) gave allylic alcohol **3** (0.91 g, 3.52 mmol, 77%) as a colourless oil, a 1:1 diastereomeric mixture. R_f: 0.21 (petroleum ether/ethyl acetate, 95:5). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 1.5 H), 0.10 (s, 1.5 H), 0.10 (s, 1.5 H), 0.12 (s, 1.5 H), 0.81 (t, *J* = 7.5 Hz, 1.5 H), 0.86 (t, *J* = 7.5 Hz, 1.5 H), 0.90 (s, 4.5 H), 0.91 (s, 4.5 H), 1.51–1.68 (m, 4 H), 1.72 (s, 1.5 H), 1.73 (s, 1.5 H), 3.19 (d, *J* = 2.3 Hz, 0.5 H), 3.24 (d, *J* = 1.5 Hz, 0.5 H), 3.91 (m, 1 H), 4.18 (d, *J* = 9.0 Hz, 0.5 H), 4.33 (t, *J* = 5.5 Hz, 0.5 H), 4.91 (m, 1 H), 5.00 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8, –4.7, –4.5, –4.0, 8.8, 9.9, 18.0, 18.0, 18.1, 18.2, 25.8, 25.9, 29.1, 30.5, 39.9, 41.0, 72.1, 72.5, 74.2, 75.0, 109.9, 110.4, 147.4, 147.8 ppm. HRMS (CI): calcd. for $C_{14}H_{31}O_2Si$ $[M + H]^+$ 259.2088; found 259.2085. $C_{14}H_{30}O_2Si$ (258.47): calcd. C 65.06, H 11.70; found C 65.01, H 11.25.

Ethyl (*R*,*E*)-7-(*tert*-Butyldimethylsilyloxy)-4-methylnon-4-enoate (4a): Allylic alcohol **3** (1.10 g, 4.27 mmol) and propionic acid (10.0 µL, 0.13 mmol) were dissolved in triethyl orthoacetate (4.70 mL, 25.6 mmol), and the mixture was heated at reflux overnight. After the alcohol had been completely consumed, the solvent was removed under reduced pressure (40 mbar, 140 °C) with a Vigreux column. Purification by flash chromatography (petroleum ether/ethyl acetate, 95:5) gave **4a** (1.24 g, 3.77 mmol, 88%, 84% *ee*) as a colourless oil. R_f: 0.42 (petroleum ether/ethyl acetate, 95:5). $[a]_D^{20}$ = +7.4 (*c* = 0.9, $CHCl_3$, 84% *ee*). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6 H), 0.86 (t, *J* = 7.2 Hz, 3 H), 0.88 (s, 9 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.42 (m, 2 H), 1.61 (s, 3 H), 2.13 (m, 2 H), 2.31 (m, 2 H), 2.39 (m, 2 H), 3.56 (tt, *J* = 5.8, 5.8 Hz, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 5.18 (tq, *J* = 7.3, 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6, –4.5, 9.7, 14.2, 16.1, 18.1, 25.9,

29.5, 33.2, 34.8, 35.5, 60.2, 73.6, 121.8, 134.6, 173.5 ppm. HRMS (CI): calcd. for $C_{18}H_{37}O_3Si$ $[M + H]^+$ 329.2506; found 329.2478; calcd. for $C_{18}H_{36}O_3Si$ $[M]^+$ 328.2428; found 328.2440.

Ethyl (7*R*,*E*)-7-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylnon-4-enoate (4b): Ester **4b** was prepared analogously to ester **4a**, starting from allylic alcohol **3** (1.72 g, 6.65 mmol), propionic acid (15.0 μL, 0.20 mmol), and 1,1,1-triethoxypropane (7.98 mL, 39.8 mmol). Purification by flash chromatography (petroleum ether/ethyl acetate, 95:5) gave ester **4b** (2.15 g, 6.28 mmol, 94%) as a colourless oil, a 1:1 diastereomeric mixture. R_f: 0.66 (petroleum ether/ethyl acetate, 95:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3 H), 0.04 (s, 3 H), 0.86 (t, J = 7.5 Hz, 1.5 H), 0.86 (t, J = 7.5 Hz, 1.5 H), 0.88 (s, 9 H), 1.09 (d, J = 6.9 Hz, 1.5 H), 1.10 (d, J = 7.0 Hz, 1.5 H), 1.24 (t, J = 7.0 Hz, 1.5 H), 1.25 (t, J = 7.0 Hz, 1.5 H), 1.42 (m, 2 H), 1.59 (s, 3 H), 2.14 (m, 2 H), 2.30 (dd, J = 13.6, 7.8 Hz, 1 H), 2.38 (dd, J = 13.6, 7.3 Hz, 1 H), 2.59 (m, 1 H), 3.58 (tt, J = 5.0, 5.0 Hz, 1 H), 4.10 (q, J = 7.0 Hz, 1 H), 4.11 (q, J = 7.0 Hz, 1 H), 5.18 (t, J = 7.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6, –4.5, 9.7, 14.2, 15.9, 15.9, 16.6, 16.7, 18.1, 25.9, 29.4, 35.6, 35.6, 37.9, 37.9, 44.1, 44.1, 60.1, 73.5, 123.5, 123.5, 133.5, 176.6 ppm. HRMS (CI): calcd. for $C_{19}H_{39}O_3Si$ $[M + H]^+$ 343.2663; found 343.2647.

Allyl (*R*,*E*)-7-Hydroxy-4-methylnon-4-enoate (5a): NaOH (1 M aq.; 4.75 mL, 4.75 mmol) was added dropwise to a solution of unsaturated ethyl ester **4a** (1.20 g, 3.65 mmol, 84% *ee*) in EtOH (12 mL) at 0 °C. The mixture was allowed to warm to room temperature overnight, then the solvent was removed under reduced pressure, and H_2O was added to the residue. The aqueous solution was acidified to pH 2–3 with HCl (1 M aq.), and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo to give the crude acid as a colourless oil.

The crude acid was dissolved in anhydrous DMF (12 mL). The solution was cooled to 0 °C, and K_2CO_3 (1.01 g, 7.30 mmol) and allyl bromide (0.47 mL, 5.48 mmol) were added. The mixture was allowed to warm to room temperature overnight, then it was diluted with H_2O, and extracted with ethyl acetate. The combined organic layers were further washed with H_2O and brine, dried with Na_2SO_4, and concentrated under reduced pressure to give the allyl ester.

The crude allyl ester was dissolved[33] in THF (7 mL), AcOH (21 mL), and H_2O (7 mL). The reaction mixture was heated at 50 °C for 2 h, then it was diluted with diethyl ether, washed twice with H_2O and brine, dried with Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave hydroxy ester **5a** (0.76 g, 3.36 mmol, 92%, 84% *ee*) as a colourless oil. R_f: 0.08 (petroleum ether/ethyl acetate, 9:1). $[\alpha]_D^{20}$ = –5.5 (c = 1.0, $CHCl_3$, 84% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.5 Hz, 3 H), 1.46 (m, 2 H), 1.64 (s, 3 H), 1.71 (br. s, 1 H), 2.14 (m, 2 H), 2.35 (m, 2 H), 2.46 (m, 2 H), 3.51 (tt, J = 7.0, 5.3 Hz, 1 H), 4.55 (ddd, J = 5.8, 1.5, 1.5 Hz, 2 H), 5.18–5.24 (m, 2 H), 5.30 (ddt, J = 17.1, 1.5, 1.5 Hz, 1 H), 5.90 (ddt, J = 17.1, 10.5, 5.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.0, 16.1, 29.5, 32.9, 34.8, 35.6, 60.1, 72.9, 118.2, 121.3, 132.2, 136.7, 173.0 ppm. HRMS (CI): calcd. for $C_{13}H_{23}O_3$ $[M + H]^+$ 227.1642; found 227.1637.

Allyl (7*R*,*E*)-7-Hydroxy-2,4-dimethylnon-4-enoate (5b): Hydroxy ester **5b** was prepared analogously to hydroxy ester **5a**, starting from ester **4b** (2.14 g, 6.25 mmol), NaOH (1 M aq.; 8.11 mL, 8.11 mmol) in EtOH (20 mL); K_2CO_3 (1.73 g, 12.5 mmol) and allyl bromide (0.81 mL, 9.36 mmol) in anhydrous DMF (30 mL); and THF (12 mL), H_2O (12 mL), and AcOH (36 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave hydroxy ester **5b** (1.40 g, 5.82 mmol, 93%) as a colourless oil, a 1:1 diastereomeric mixture. R_f: 0.09 (petroleum ether/ethyl acetate, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.5 Hz, 1.5 H), 0.95 (t, J = 7.5 Hz, 1.5 H), 1.13 (d, J = 7.0 Hz, 1.5 H), 1.14 (d, J = 7.0 Hz, 1.5 H), 1.46 (m, 2 H), 1.59 (br. s, 0.5 H), 1.63 (s, 3 H), 1.70 (br. s, 0.5 H), 2.08–2.18 (m, 3 H), 2.40 (dd, J = 13.6, 8.0 Hz, 1 H), 2.67 (m, 1 H), 3.51 (tt, J = 6.5, 6.5 Hz, 1 H), 4.55 (m, 2 H), 5.17–5.24 (m, 2 H), 5.31 (ddt, J = 17.3, 1.5, 1.5 Hz, 1 H), 5.91 (ddt, J = 17.3, 10.3, 5.8 Hz, 0.5 H), 5.92 (ddt, J = 17.3, 10.3, 5.8 Hz, 0.5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.0, 16.0, 16.1, 16.8, 29.5, 35.5, 35.7, 38.18, 38.22, 44.1, 44.3, 64.94, 64.91, 72.8, 72.9, 118.0, 118.1, 122.7, 122.9, 132.3, 135.6, 135.7, 176.0 ppm. HRMS (CI): calcd. for $C_{14}H_{25}O_3$ $[M + H]^+$ 241.1798; found 241.1807.

(*S*)-4-Benzyl-3-[(2*S*,3*R*)-3-hydroxy-2-methylpentanoyl]-oxazolidin-2-one (6):[19] Bu_2BOTf (1 M in CH_2Cl_2; 35.4 mL, 35.4 mmol) and NEt_3 (5.52 mL, 39.7 mmol) were successively added to a solution of (*S*)-4-benzyl-3-propionyloxazolidin-2-one (7.00 g, 30.0 mmol) in anhydrous CH_2Cl_2 (67 mL) at 0 °C. (The internal temperature should not exceed 2 °C.) After the addition was complete, freshly distilled propionic aldehyde (2.39 mL, 33.3 mmol) was added at –78 °C. The reaction mixture was stirred for a further 30 min, and then it was allowed to warm up to 0 °C over a period of 1 h. After a further 1 h, the solution was quenched with aq. phospate buffer (pH 7; 33.0 mL) and MeOH (98.0 mL) (T_{intern} < 6 °C) and further treated with a mixture of MeOH and H_2O_2 (30% aq.) (2:1; 98.0 mL) (T_{intern} < 10 °C). After 45 min, the organic solvent was evaporated under reduced pressure, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed twice with satd. aq. $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated under reduced pressure. Purification by recrystallization (diethyl ether/pentane) gave **6** (8.52 g, 29.2 mmol, 97%) as a colourless solid, m.p. 75–77 °C. R_f: 0.35 (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = +46.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, J = 7.4 Hz, 3 H), 1.25 (d, J = 7.0 Hz, 3 H), 1.47 (m, 1 H), 1.58 (m, 1 H), 2.79 (dd, J = 13.4, 9.4 Hz, 1 H), 2.86 (br. s, 1 H), 3.26 (dd, J = 13.3, 3.3 Hz, 1 H), 3.79 (qd, J = 7.0, 2.8 Hz, 1 H), 3.87 (m, 1 H), 4.19 (dd, J = 9.3, 3.3 Hz, 1 H), 4.23 (dd, J = 9.0, 7.5 Hz, 1 H), 4.71 (dddd, J = 9.3, 7.3, 3.3, 3.3 Hz, 1 H), 7.21 (d, J = 6.8 Hz, 2 H), 7.29 (m, 1 H), 7.34 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.2, 10.4, 26.7, 37.8, 41.7, 55.1, 66.2, 72.9, 127.4, 128.9, 129.4, 135.0, 153.0, 177.6 ppm. HPLC (Reprosil; hexane/*i*-PrOH, 7:3; 1 mL/min): t_R = 6.68 min.

(2*S*,3*R*)-3-Hydroxy-*N*-methoxy-*N*,2-dimethylpentanamide (7):[20] $Al(CH_3)_3$ (2 M in hexane; 33.3 mL, 66.6 mmol) was added to a suspension of *N*,*O*-dimethylhydroxylamine·HCl (6.50 g, 66.6 mmol) in anhydrous CH_2Cl_2 (238 mL) at 0 °C over a period of 20 min. The reaction mixture was allowed to warm to room temperature, and was stirred for a further 2 h to give a clear solution. A solution of oxazolidinone **6** (9.70 g, 33.3 mmol) in anhydrous CH_2Cl_2 (60 mL) was then added at –15 °C. The mixture was stirred for a further 90 min at 0–10 °C, then it was cooled to –20 °C, and allowed to warm up to room temperature overnight. The reaction was quenched with Rochelle salt (1 M in H_2O; 200 mL), and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate, 7:3) gave Weinreb amide **7** (5.82 g, 33.2 mmol, 99%) as a colourless oil. R_f: 0.12 (petroleum ether/ethyl acetate, 7:3). $[\alpha]_D^{20}$ = +17.4 (c = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.4 Hz, 3 H), 1.16 (d, J = 7.0 Hz, 3 H), 1.40 (m, 1 H), 1.57 (m, 1 H), 2.91 (br. s, 1 H), 3.20 (s, 3 H), 3.70 (s, 3 H),

3.73–3.77 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.0, 10.3, 26.7, 31.9, 38.2, 61.5, 73.0, 178.4 ppm.

(4*S*,5*R*)-5-Hydroxy-2,4-dimethylhept-1-en-3-one (8): Following the Grignard addition procedure used for the synthesis of **3**, ketone **8** was prepared from **7** (1.62 g, 9.25 mmol) and 2-propenylmagnesium bromide solution (0.5 M in THF; 55.5 mL, 27.7 mmol) in anhydrous THF (19 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 8:2) gave **8** (0.90 g, 5.76 mmol, 62%) as a colourless oil. R_f: 0.26 (petroleum ether/ethyl acetate, 8:2). $[a]_D^{20}$ = +3.3 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.4 Hz, 3 H), 1.14 (d, J = 7.0 Hz, 3 H), 1.38 (m, 1 H), 1.54 (m, 1 H), 1.88 (s, 3 H), 2.99 (d, J = 3.0 Hz, 1 H), 3.24 (qd, J = 7.3, 3.0 Hz, 1 H), 3.78 (m, 1 H), 5.84 (q, J = 1.5 Hz, 1 H), 5.97 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.4, 11.2, 17.7, 27.1, 42.9, 73.0, 125.5, 143.6, 207.7 ppm. HRMS (CI): calcd. for $C_9H_{14}O$ $[M - H_2O]^+$ 139.1117; found 139.1086.

(3*R*,4*S*,5*R*)-2,4-Dimethylhept-1-ene-3,5-diol (9):[21] A solution of ketone **8** (236 mg, 1.51 mmol) in anhydrous acetonitrile (1.50 mL) was added to a solution of $(CH_3)_4NBH(OAc)_3$ (3.17 g, 12.1 mmol) in anhydrous acetonitrile (4.60 mL) and AcOH (4.60 mL) at –40 °C. The mixture was stirred for 1 h at this temperature, then it was stirred for 15 h at –35 °C, and for a further 24 h at –15 °C. The reaction was quenched with satd. aq. Rochelle salt, and the mixture was extracted with diethyl ether. The combined organic layers were washed with satd. aq. $NaHCO_3$, H_2O, and brine, dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate, 8:2) gave isomerically pure **9** (154 mg, 0.97 mmol, 64%) as a colourless oil. R_f: 0.15 (petroleum ether/ethyl acetate, 8:2 + 1% EtOH). $[a]_D^{20}$ = +7.7 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, J = 7.0 Hz, 3 H), 0.96 (t, J = 7.5 Hz, 3 H), 1.47 (m, 1 H), 1.58 (m, 1 H), 1.69 (s, 3 H), 1.72 (m, 1 H), 2.65 (br. s, 2 H), 3.79 (ddd, J = 7.8, 5.8, 2.0 Hz, 1 H), 4.27 (s, 1 H), 4.93 (q, J = 1.5 Hz, 1 H), 5.03 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.2, 10.5, 19.6, 28.3, 38.0, 77.9, 79.7, 110.2, 145.7 ppm. HRMS (CI): calcd. for $C_9H_{19}O_2$ $[M + H]^+$ 159.1380; found 159.1371.

(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,2-dimethylpentanamide (10):[37] TBSCl (5.49 g, 36.4 mmol) and imidazole (2.48 g, 36.4 mmol) were added to a solution of Weinreb amide **7** (5.80 g, 33.1 mmol) in anhydrous DMF (110 mL) at 0 °C, and the mixture was allowed to warm to room temperature overnight. The solution was diluted with ethyl acetate, washed with HCl (1 M aq.), satd. aq. $NaHCO_3$ and brine, and dried with Na_2SO_4, and the solvents were evaporated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave **10** (8.71 g, 30.1 mmol, 91%) as a colourless oil. R_f: 0.43 (petroleum ether/ethyl acetate, 9:1). $[a]_D^{20}$ = +2.6 (c = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.88 (t, J = 7.3 Hz, 3 H), 0.89 (s, 9 H), 1.14 (d, J = 7.0 Hz, 3 H), 1.46 (m, 1 H), 1.54 (m, 1 H), 2.99 (br. s, 1 H), 3.17 (s, 3 H), 3.69 (s, 3 H), 3.89 (dt, J = 8.0, 4.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, –4.2, 8.5, 14.7, 18.2, 25.9, 28.1, 32.1, 40.0, 61.4, 74.2, 176.8 ppm.

(4*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhept-1-en-3-one (11): Following the Grignard addition procedure used for the synthesis of **3**, ketone **11** was prepared from **10** (8.70 g, 30.1 mmol) and 2-propenylmagnesium bromide solution (0.5 M in THF; 120 mL, 60.0 mmol) in anhydrous THF (60 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 95:5) gave **11** (7.69 g, 28.4 mmol, 95%) as a colourless oil. R_f: 0.36 (petroleum ether/ethyl acetate, 8:2). $[a]_D^{20}$ = +24.4 (c = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.04 (s, 3 H), 0.85 (t, J = 7.5 Hz, 3 H), 0.88 (s, 9 H), 1.08 (d, J = 6.8 Hz, 3 H), 1.41 (m, 1 H), 1.48 (m, 1 H), 1.87 (s, 3 H), 3.56 (qd, J = 7.0, 7.0 Hz, 1 H), 3.90 (dt, J = 6.5, 5.3 Hz, 1 H), 5.78 (s, 1 H), 5.95 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5, –4.2, 8.9, 14.2, 17.9, 18.1, 25.9, 28.2, 44.2, 74.7, 124.3, 144.3, 205.1 ppm. HRMS (CI): calcd. for $C_{11}H_{21}O_2Si$ $[M - C_4H_9]^+$ 213.1305; found 213.1295.

(3*S*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhept-1-en-3-ol (12):[38] $CeCl_3 \cdot 7H_2O$ (0.81 g, 2.17 mmol) and $NaBH_4$ (117 mg, 3.09 mmol) were added to a solution of ketone **11** (0.56 g, 2.07 mmol) in anhydrous MeOH (21 mL) at –78 °C. After 16 h at this temperature, the resulting mixture was quenched with satd. NH_4Cl, and extracted with diethyl ether. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave isomerically pure **12** (0.48 g, 1.76 mmol, 85%) as a colourless oil. R_f: 0.43 (petroleum ether/ethyl acetate, 9:1). $[a]_D^{20}$ = +10.2 (c = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 3 H), 0.13 (s, 3 H), 0.70 (d, J = 7.3 Hz, 3 H), 0.92 (s, 9 H), 0.93 (t, J = 7.5 Hz, 3 H), 1.58 (m, 2 H), 1.71 (s, 3 H), 1.86 (m, 1 H), 3.76 (ddd, J = 7.8, 4.8, 2.5 Hz, 1 H), 4.01–4.04 (m, 2 H), 4.85 (m, 1 H), 4.89 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 11.3, 12.9, 16.2, 18.0, 24.6, 25.9, 39.4, 78.3, 79.3, 113.2, 145.9 ppm. HRMS (CI): calcd. for $C_{15}H_{33}O_2Si$ $[M + H]^+$ 273.2244; found 273.2259.

(4*R*,5*S*,6*S*)-4-Ethyl-2,2,5-trimethyl-6-(prop-1-en-2-yl)-1,3-dioxane (13):[39] TBAF (1 M in THF; 140 µL, 140 µmol) was added to a solution of ketone **12** (38.0 mg, 140 µmol) in anhydrous THF (1 mL), and the mixture was stirred for 16 h at room temperature. The resulting mixture was quenched with satd. NH_4Cl, and extracted with diethyl ether. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo.

The crude diol was dissolved in acetone (1 mL), and treated with 2,2-dimethoxypropane (1.29 mL, 10.5 mmol) and pyridinium *p*-toluenesulfonate (1 M in anhydrous CH_2Cl_2; 14.0 µL, 14.0 µmol) at room temperature. After stirring for 16 h, the resulting mixture was diluted with diethyl ether. The organic layer was washed twice with satd. aq. $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated in vacuo to give crude acetonide **13** (22.0 mg, 111 µmol, 80%) as a colourless oil. R_f: 0.56 (petroleum ether/ethyl acetate, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, J = 7.0 Hz, 3 H), 0.93 (t, J = 7.4 Hz, 3 H), 1.36 (s, 3 H), 1.38 (s, 3 H), 1.44 (m, 2 H), 1.77 (s, 3 H), 1.84 (m, 1 H), 3.71 (d, J = 8.0 Hz, 1 H), 3.74 (dt, J = 8.8, 5.0 Hz, 1 H), 4.85 (m, 1 H), 4.93 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.6, 11.7, 18.0, 23.7, 23.9, 24.9, 37.1, 70.9, 79.0, 100.5, 112.1, 144.2 ppm.

[(3*S*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhept-1-en-3-yl] Propionate (14a): DMAP (0.14 g, 1.15 mmol) and DCC (1.72 g, 8.34 mmol) were added to a solution of propionic acid (0.50 mL, 6.68 mmol) and allylic alcohol **12** (1.52 g, 5.58 mmol) in anhydrous diethyl ether (28.0 mL) at 0 °C, and the mixture was allowed to warm up to room temperature overnight. The precipitate was removed by filtration, and the filtrate was washed twice with $KHSO_4$ (1 M aq.), H_2O, satd. aq. $NaHCO_3$, and brine, dried with Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave allylic ester **14a** (1.83 g, 5.58 mmol, 99%) as a colourless oil. R_f: 0.67 (petroleum ether/ethyl acetate, 9:1). $[a]_D^{20}$ = –4.2 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.01 (s, 3 H), 0.02 (s, 3 H), 0.72 (d, J = 7.0 Hz, 3 H), 0.84 (t, J = 7.5 Hz, 3 H), 0.88 (s, 9 H), 1.13 (t, J = 7.5 Hz, 3 H), 1.53 (m, 2 H), 1.66 (s, 3 H), 1.81 (m, 1 H), 2.31 (q, J = 7.5 Hz, 2 H), 3.73 (ddd, J = 8.5, 5.8, 1.5 Hz, 1 H), 4.95–4.97 (m, 2 H, 6-H), 4.99 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1, –3.8, 8.3, 9.2, 10.2, 17.5, 18.2, 25.9, 27.9, 28.2, 37.5, 71.8, 79.4, 115.4,

142.4, 173.4 ppm. HRMS (CI): calcd. for $C_{14}H_{27}O_3Si$ $[M - C_4H_9]^+$ 271.1724; found 271.1706.

***N*-Allyloxycarbonylglycine-[(3*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-2,4-dimethylhept-1-en-3-yl] Ester (14b):** Following the method used for the synthesis of allylic ester **14a**, **14b** was prepared from *N*-Alloc-glycine (0.33 g, 2.07 mmol), allylic alcohol **12** (0.47 g, 1.72 mmol), DMAP (42.0 mg, 0.34 mmol), and DCC (0.53 g, 2.57 mmol) in anhydrous diethyl ether (12 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave allylic ester **14b** (0.70 g, 1.70 mmol, 99%) as a colourless oil. R_f: 0.19 (petroleum ether/ethyl acetate, 9:1). $[\alpha]_D^{20}$ = –9.1 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.03 (s, 3 H), 0.03 (s, 3 H), 0.73 (d, *J* = 7.0 Hz, 3 H), 0.84 (t, *J* = 7.5 Hz, 3 H), 0.88 (s, 9 H), 1.51 (m, 2 H), 1.66 (s, 3 H), 1.84 (m, 1 H), 3.69 (m, 1 H), 3.96 (d, *J* = 5.0 Hz, 2 H), 4.58 (d, *J* = 5.5 Hz, 2 H), 4.98 (m, 1 H), 5.01 (s, 1 H), 5.06 (d, *J* = 10.3 Hz, 1 H), 5.17–5.23 (m, 2 H), 5.31 (ddt, *J* = 17.3, 1.5, 1.5 Hz, 1 H), 5.91 (ddt, *J* = 17.1, 10.3, 5.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1, –3.7, 8.2, 10.2, 17.3, 18.2, 25.9, 27.9, 37.4, 42.9, 65.8, 71.7, 81.1, 116.3, 117.8, 132.6, 141.6, 155.9, 169.1 ppm. HRMS (CI): calcd. for $C_{17}H_{30}NO_5Si$ $[M - C_4H_9]^+$ 356.1888; found 356.1911. $C_{21}H_{39}NO_5Si$ (413.62): calcd. C 60.98, H 9.50, N 3.39; found C 61.09, H 9.49, N 3.36.

(2*S*,6*R*,7*R*,*E*)-7-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethylnon-4-enoic Acid (15a):[24–26] *n*-Butyllithium (2.5 M in hexane; 4.55 mL, 11.4 mmol) was added to a solution of freshly distilled diisopropylamine (1.70 mL, 11.9 mmol) in anhydrous THF (19 mL) in a dry Schlenk flask at –30 °C under nitrogen. After 5 min at this temperature, the mixture was stirred at room temperature for 30 min. DMPU (4.80 mL, 39.7 mmol, 19 vol.-%) was added, and the solution was cooled to –78 °C. In a second Schlenk flask, allylic ester **14a** (1.87 g, 5.69 mmol) was dissolved in anhydrous THF (19 mL) under nitrogen, and the solution was cooled to –78 °C. The base solution was slowly transferred to the substrate solution at –78 °C by cannula. After 30 min, TMSCl (2.55 mL, 19.9 mmol) was added, and stirring was continued for 60 min at this temperature. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. The mixture was then heated to 60 °C for 16 h, after which time it was allowed to cool to room temperature. The mixture was diluted with diethyl ether, and quenched with HCl (1 M aq.). The organic layer was further washed with HCl (1 M aq.) and brine, dried with Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave unsaturated acid **15a** (0.41 g, 1.25 mmol, 22%) as a colourless oil, and a 9:1 mixture of diastereomers. R_f: 0.25 (petroleum ether/ethyl acetate, 9:1). $[\alpha]_D^{20}$ = +2.4 (*c* = 0.9, $CHCl_3$). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6 H), 0.82 (t, *J* = 7.5 Hz, 3 H), 0.89–0.90 (m, 12 H), 1.12 (d, *J* = 7.0 Hz, 3 H), 1.43 (m, 2 H), 1.62 (s, 3 H), 2.03 (dd, *J* = 13.6, 8.0 Hz, 1 H), 2.39 (dd, *J* = 13.1, 6.5 Hz, 1 H), 2.45 (m, 1 H), 2.62 (m, 1 H), 3.39 (dt, *J* = 6.5, 5.0 Hz, 1 H), 5.04 (d, *J* = 9.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5, –4.2, 8.5, 15.8, 16.2, 16.9, 18.2, 25.9, 27.4, 36.8, 37.7, 43.8, 76.9, 130.4, 131.6, 182.8 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.83 (t, *J* = 7.5 Hz, 3 H), 1.67 (s, 3 H), 5.14 (d, *J* = 9.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.7, 27.3, 36.9, 37.8, 130.6, 131.3 ppm. HRMS (CI): calcd. for $C_{18}H_{35}O_3Si$ $[M - H]^-$ 327.2361; found 327.2348. $C_{18}H_{36}O_3Si$ (328.56): calcd. C 65.80, H 11.04; found C 65.36, H 10.73.

Allyl (2*S*,6*R*,7*R*,*E*)-2-(Allyloxycarbonylamino)-7-(*tert*-butyldimethylsilyloxy)-4,6-dimethylnon-4-enoate (15b):[32] *n*-Butyllithium (2.5 M in hexane; 8.44 mL, 21.1 mmol) was added to a solution of freshly distilled diisopropylamine (3.11 mL, 21.8 mmol) in anhydrous THF (21 mL) in a dry Schlenk flask at –30 °C under nitrogen. After 5 min at this temperature, the mixture was stirred at room temperature for 30 min, and was cooled to –78 °C. In a second Schlenk flask $ZnCl_2$ (1.19 g, 8.73 mmol) and allylic ester **14b** (3.01 g, 7.28 mmol) were dissolved successively in anhydrous THF (17 mL) under nitrogen, and the solution was cooled to –78 °C. The base solution was slowly transferred to the substrate solution at –78 °C by cannula. The reaction mixture was allowed to warm to room temperature overnight, then it was diluted with diethyl ether, quenched with HCl (1 M aq.), and extracted with diethyl ether. The organic layer was further washed with HCl (1 M aq.) and brine, dried with Na_2SO_4, and concentrated in vacuo to give the crude acid.

The crude acid was dissolved in anhydrous DMF (17 mL), and the solution was cooled to 0 °C. K_2CO_3 (1.21 g, 8.73 mmol) and allyl bromide (1.89 mL, 21.8 mmol) were added. The mixture was allowed to warm to room temperature overnight, then it was diluted with H_2O, and extracted with ethyl acetate. The combined organic layers were further washed with H_2O and brine, dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave unsaturated allylic ester **15b** (3.15 g, 6.94 mmol, 95%) as a colourless oil. R_f: 0.30 (petroleum ether/ethyl acetate, 9:1). $[\alpha]_D^{20}$ = +7.3 (*c* = 1.8, $CHCl_3$). 94:6 Mixture of diastereomers. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.03 (s, 3 H), 0.83 (t, *J* = 7.4 Hz, 3 H), 0.87–8.89 (m, 12 H), 1.43 (m, 2 H), 1.64 (d, *J* = 1.0 Hz, 3 H), 2.28 (dd, *J* = 13.6, 9.0 Hz, 1 H), 2.46 (m, 1 H), 2.54 (dd, *J* = 13.4, 4.9 Hz, 1 H), 3.40 (dt, *J* = 5.3, 5.3 Hz, 1 H), 4.45 (ddd, *J* = 8.5, 8.5, 5.3 Hz, 1 H), 4.53–4.63 (m, 4 H), 5.06–5.10 (m, 2 H), 5.18–5.36 (m, 4 H), 5.84–5.96 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5, –4.2, 8.9, 15.9, 16.4, 18.2, 25.9, 27.2, 36.9, 42.8, 52.2, 65.7, 65.9, 76.9, 117.7, 118.8, 128.5, 131.6, 132.6, 133.7, 155.6, 172.2 ppm. HRMS (CI): calcd. for $C_{24}H_{44}NO_5Si$ $[M + H]^+$ 454.2983; found 454.2972.

Allyl (2*S*,6*R*,7*R*,*E*)-7-Hydroxy-2,4,6-trimethylnon-4-enoate (16a): Following the method used for the esterification and deprotection of **5**, **16a** was prepared from **15a** (0.38 g, 1.16 mmol), K_2CO_3 (0.18 g, 1.29 mmol), and allyl bromide (0.20 mL, 2.29 mmol) in anhydrous DMF (12 mL) and THF (2.7 mL), H_2O (2.7 mL), and AcOH (8.1 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave **16a** (0.27 g, 1.06 mmol, 91%) as a colourless oil, a 9:1 mixture of diastereomers. R_f: 0.15 (petroleum ether/ethyl acetate, 9:1). $[\alpha]_D^{20}$ = +24.1 (*c* = 1.1, $CHCl_3$). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.5 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 1.12 (d, *J* = 6.8 Hz, 3 H), 1.26 (m, 1 H), 1.48 (br. s, 1 H), 1.54 (m, 1 H), 1.63 (d, *J* = 1.5 Hz, 3 H), 2.06 (dd, *J* = 13.4, 7.2 Hz, 1 H), 2.39 (dd, *J* = 13.6, 8.3 Hz, 1 H), 2.44 (m, 1 H), 2.65 (m, 1 H), 3.27 (ddd, *J* = 9.3, 6.3, 3.3 Hz, 1 H), 4.54 (m, 2 H), 5.01 (d, *J* = 9.8 Hz, 1 H), 5.22 (ddt, *J* = 10.5, 1.3, 1.3 Hz, 1 H), 5.31 (ddt, *J* = 17.1, 1.5, 1.5 Hz, 1 H), 5.90 (ddt, *J* = 17.3, 10.5, 5.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.4, 16.1, 16.3, 16.8, 26.9, 38.1, 38.3, 44.2, 64.9, 77.3, 117.9, 129.9, 132.3, 132.8, 176.1 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.3, 16.4, 16.7, 27.2, 38.4, 44.0, 77.4, 129.8, 132.3, 132.7 ppm. HPLC (OD-H; hexane/*i*PrOH, 95:5; 0.5 mL/min): (*R*)-**16a**: t_R = 10.19 min; (*S*)-**16a**: t_R = 10.83 min. HRMS (CI): calcd. for $C_{15}H_{27}O_3$ $[M + H]^+$ 255.1955; found 255.1925; calcd. for $C_{15}H_{26}O_3$ $[M]^+$ 254.1876; found 254.1870.

Allyl (2*S*,6*R*,7*R*,*E*)-2-(Allyloxycarbonylamino)-7-hydroxy-4,6-dimethylnon-4-enoate (16b): Following the method used for the de-

protection of **5**, **16b** was prepared from **15b** (3.03 g, 6.68 mmol), THF (16 mL), H_2O (16 mL), and AcOH (48 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 7:3) gave **16b** (2.24 g, 6.60 mmol, 99%) as a colourless oil, a 94:6 mixture of diastereomers. R_f: 0.23 (petroleum ether/ethyl acetate, 7:3). $[\alpha]_D^{20}$ = +17.7 (c = 1.2, $CHCl_3$). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93–0.97 (m, 6 H), 1.31 (m, 1 H), 1.49–1.58 (m, 2 H), 1.67 (d, J = 1.0 Hz, 3 H), 2.31 (dd, J = 13.6, 8.3 Hz, 1 H), 2.46 (m, 1 H), 2.54 (dd, J = 13.6, 5.5 Hz, 1 H), 3.31 (ddd, J = 9.0, 6.0, 3.3 Hz, 1 H), 4.48 (ddd, J = 8.3, 8.3, 5.5 Hz, 1 H), 4.54–4.67 (m, 4 H), 5.09 (d, J = 9.0 Hz, 1 H), 5.16 (br. s, 1 H), 5.18–5.36 (m, 4 H), 5.85–5.96 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.4, 15.9, 16.4, 27.0, 38.3, 42.9, 52.6, 65.8, 65.9, 77.2, 117.8, 118.9, 130.3, 131.5, 132.3, 132.6, 155.6, 171.9 ppm. HPLC (OD-H; hexane/*i*PrOH, 8:2; 0.5 mL/min): (*R*)-**16b**: t_R = 9.49 min; (*S*)-**16b**: t_R = 10.33 min. HRMS (CI): calcd. for $C_{18}H_{30}NO_5$ $[M + H]^+$ 340.2118; found 340.2112. $C_{18}H_{29}NO_5$ (339.43): calcd. C 63.69, H 8.61, N 4.13; found C 63.52, H 8.49, N 4.04.

***N*-*tert*-Butoxycarbonyl-(*R*)-3-chloro-4-*tert*-butyldimethylsilyloxy-β-phenylalanine-{[(*R*,*E*)-4-methylnon-4-enoic Acid Allyl Ester]-7-yl} Ester (18a):** DMAP (13.0 mg, 0.10 mmol) and DCC (116 mg, 0.56 mmol) were added to a solution of chlorinated β-tyrosine derivative **17** (0.21 g, 0.51 mmol) and ω-hydroxy ester **5a** (127 mg, 0.56 mmol, 84% *ee*) in anhydrous diethyl ether (3.4 mL) at 0 °C, and the mixture was allowed to warm up to room temperature overnight. The precipitate was removed by filtration. The filtrate was washed twice with $KHSO_4$ (1 M aq.), H_2O, satd. aq. $NaHCO_3$, and brine, dried with Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 8:2) gave β-tyrosine ester **18a** (309 mg, 0.48 mmol, 95%) as a colourless oil, a 92:8 mixture of diastereomers. R_f: 0.30 (petroleum ether/ethyl acetate, 8:2). $[\alpha]_D^{20}$ = +26.2 (c = 1.9, $CHCl_3$). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 6 H), 0.71 (t, J = 7.3 Hz, 3 H), 1.01 (s, 9 H), 1.42 (s, 9 H), 1.47 (m, 2 H), 1.60 (s, 3 H), 2.16 (m, 2 H), 2.31 (m, 2 H), 2.42 (m, 2 H), 2.74 (dd, J = 15.3, 6.0 Hz, 1 H), 2.81 (dd, J = 14.6, 6.0 Hz, 1 H), 4.56 (ddd, J = 5.8, 1.5, 1.5 Hz, 2 H), 4.71 (tt, J = 6.0, 6.0 Hz, 1 H), 4.99 (m, 1 H), 5.07 (t, J = 7.3 Hz, 1 H), 5.23 (ddt, J = 10.4, 1.3, 1.3 Hz, 1 H), 5.31 (ddt, J = 17.3, 1.5, 1.5 Hz, 1 H), 5.57 (br. s, 1 H), 5.90 (ddt, J = 17.3, 10.5, 5.8 Hz, 1 H), 6.81 (d, J = 8.5 Hz, 1 H), 7.05 (dd, J = 8.5, 2.3 Hz, 1 H), 7.27 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 9.6, 16.1, 18.3, 25.6, 26.2, 28.3, 32.0, 33.0, 34.6, 40.8, 50.4, 65.0, 75.9, 79.7, 118.2, 119.8, 120.6, 125.4, 125.6, 128.0, 132.2, 136.3, 136.3, 150.8, 154.9, 170.6, 172.9 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (t, J = 7.4 Hz, 3 H), 1.58 (s, 3 H), 6.76 (d, J = 8.5 Hz, 1 H) ppm. HPLC (OD-H; hexane/*i*PrOH, 95:5; 0.5 mL/min): (*S*)-**16b**: t_R = 10.16 min; (*R*)-**16b**: t_R = 10.89 min. HPLC–MS (H_2O/MeCN, 1:9; 0.6 mL/min): t_R = 8.51 min; m/z = 660 $[C_{33}H_{52}ClNO_7Si + Na]^+$. HRMS (CI): calcd. for $C_{33}H_{53}ClNO_7Si$ $[M + H]^+$ 638.3274; found 638.3237. $C_{33}H_{52}ClNO_7Si$ (638.31): calcd. C 62.09, H 8.21, N 2.19; found C 62.18, H 8.26, N 2.61.

***N*-*tert*-Butoxycarbonyl-(*R*)-3-chloro-4-*tert*-butyldimethylsilyloxy-β-phenylalanine-{[(7*R*,*E*)-2,4-dimethylnon-4-enoic Acid Allyl Ester]-7-yl} Ester (18b):** Following the method used for the synthesis of β-tyrosine ester **18a**, ester **18b** was prepared from chlorinated β-tyrosine derivative **17** (0.60 g, 1.39 mmol), ω-hydroxy ester **5b** (0.34 g, 1.41 mmol), DMAP (17.0 mg, 0.14 mmol), and DCC (0.32 g, 1.55 mmol) in anhydrous diethyl ether (9.4 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave ester **18b** (0.83 g, 1.27 mmol, 91%) as a colourless oil, a 92:8 mixture of diastereomers. R_f: 0.16 (petroleum ether/ethyl acetate, 9:1). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 6 H), 0.71 (t, J = 7.4 Hz, 3 H), 1.01 (s, 9 H), 1.09 (d, J = 7.0 Hz, 3 H), 1.42 (s, 9 H), 1.47 (m, 2 H), 1.57 (s, 3 H), 2.04 (dd, J = 13.6, 7.5 Hz, 1 H), 2.17 (m, 2 H), 2.38 (dd, J = 13.6, 7.3 Hz, 1 H), 2.63 (tq, J = 7.3, 7.3 Hz, 1 H), 2.74 (m, 1 H), 2.81 (dd, J = 15.3, 6.3 Hz, 1 H), 4.54 (ddd, J = 5.5, 1.5, 1.5 Hz, 2 H), 4.71 (tt, J = 6.5, 6.5 Hz, 1 H), 4.99 (m, 1 H), 5.07 (t, J = 7.3 Hz, 1 H), 5.22 (d, J = 11.0 Hz, 1 H), 5.30 (ddt, J = 17.3, 1.3, 1.3 Hz, 1 H), 5.58 (br. s, 1 H), 5.90 (ddt, J = 17.1, 10.3, 5.8 Hz, 1 H), 6.81 (d, J = 8.3 Hz, 1 H), 7.05 (dd, J = 8.4, 2.4 Hz, 1 H), 7.27 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 9.5, 15.9, 15.9, 16.6, 16.7, 18.3, 25.6, 26.2, 28.3, 31.9, 32.0, 37.9, 40.8, 43.8, 43.8, 50.4, 64.9, 75.9, 79.7, 118.0, 120.6, 121.4, 121.5, 125.4, 125.6, 128.0, 132.3, 135.2, 135.2, 150.8, 154.9, 170.6, 175.9 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (t, J = 6.5 Hz, 3 H), 1.56 (s, 3 H), 6.76 (d, J = 8.5 Hz, 1 H) ppm. HPLC (OD-H; hexane/*i*PrOH, 95:5; 0.5 mL/min): (*S*)-**18b**: t_R = 9.52 min; (*R*)-**18b**: t_R = 10.29/10.75 min. HPLC–MS (H_2O/MeCN, 1:9; 0.6 mL/min): t_R = 10.72 min; m/z = 674 $[C_{34}H_{54}ClNO_7Si + Na]^+$. HRMS (CI): calcd. for $C_{34}H_{55}ClNO_7Si$ $[M + H]^+$ 652.3431; found 652.3439. $C_{34}H_{54}ClNO_7Si$ (652.33): calcd. C 62.60, H 8.34, N 2.15; found C 62.35, H 8.38, N 2.37.

***N*-*tert*-Butoxycarbonyl-(*R*)-3-chloro-4-*tert*-butyldimethylsilyloxy-β-phenylalanine-{[(2*S*,6*S*,7*R*,*E*)-2,4,6-trimethylnon-4-enoic Acid Allyl Ester]-7-yl} ester (18c):** Following the method used for the synthesis of β-tyrosine ester **18a**, ester **18c** was prepared from chlorinated β-tyrosine derivative **17** (0.32 g, 0.74 mmol), ω-hydroxy ester **16a** (0.21 g, 0.82 mmol), DMAP (18.0 mg, 0.15 mmol), and DCC (0.23 g, 1.11 mmol) in anhydrous diethyl ether (5 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 8:2) gave ester **18c** (0.44 g, 0.66 mmol, 89%) as a colourless oil. R_f: 0.37 (petroleum ether/ethyl acetate, 8:2). $[\alpha]_D^{20}$ = +22.7 (c = 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 6 H), 0.63 (t, J = 7.3 Hz, 3 H), 0.80 (d, J = 6.5 Hz, 3 H), 1.01 (s, 9 H), 1.11 (d, J = 7.0 Hz, 3 H), 1.30 (m, 1 H), 1.41 (s, 9 H), 1.49 (m, 1 H), 1.57 (d, J = 1.3 Hz, 3 H), 2.02 (dd, J = 13.7, 6.9 Hz, 1 H), 2.39 (dd, J = 13.6, 7.5 Hz, 1 H), 2.51 (m, 1 H), 2.63 (m, 1 H), 2.77 (dd, J = 15.6, 6.0 Hz, 1 H), 2.85 (dd, J = 15.3, 6.0 Hz, 1 H), 4.54 (m, 2 H), 4.60 (ddd, J = 8.3, 8.3, 3.3 Hz, 1 H), 4.92 (d, J = 8.8 Hz, 1 H), 4.99 (br. s, 1 H), 5.22 (ddt, J = 10.3, 1.3, 1.3 Hz, 1 H), 5.30 (ddt, J = 17.3, 1.8, 1.8 Hz, 1 H), 5.59 (br. s, 1 H), 5.90 (ddt, J = 17.1, 10.3, 5.8 Hz, 1 H), 6.81 (d, J = 8.5 Hz, 1 H), 7.06 (dd, J = 8.4, 2.1 Hz, 1 H), 7.28 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 9.5, 16.1, 16.8, 16.9, 18.3, 24.6, 25.6, 28.3, 35.9, 37.9, 40.7, 43.8, 50.4, 64.9, 79.7, 79.7, 118.0, 120.6, 125.4, 125.6, 128.1, 128.8, 132.3, 132.9, 135.3, 150.8, 154.9, 170.8, 175.9 ppm. HPLC (OD-H; hexane/*i*PrOH, 95:5; 0.5 mL/min): (*S*)-**18c**: t_R = 9.84 min; (*R*)-**18c**: t_R = 11.43 min. HPLC–MS (H_2O/MeCN, 1:9; 0.6 mL/min): t_R = 7.88 min; m/z = 688 $[C_{35}H_{56}ClNO_7Si + Na]^+$. HRMS (CI): calcd. for $C_{35}H_{56}ClNO_7Si$ $[M + H]^+$ 666.3587; found 666.3589. $C_{35}H_{56}ClNO_7Si$ (666.36): calcd. C 63.09, H 8.47, N 2.10; found C 62.69, H 8.37, N 2.11.

***N*-*tert*-Butoxycarbonyl-(*R*)-3-chloro-4-*tert*-butyldimethylsilyloxy-β-phenylalanine-{[(2*S*,6*R*,7*R*,*E*)-2-(allyloxycarbonylamino)-4,6-dimethylnon-4-enoic Acid Allyl Ester]-7-yl} Ester (18d):** Following the method used for the synthesis of β-tyrosine ester **18a**, ester **18d** was prepared from chlorinated β-tyrosine derivative **17** (0.69 g, 1.60 mmol), ω-hydroxy ester **16b** (0.60 g, 1.77 mmol), DMAP (39.0 mg, 0.32 mmol), and DCC (0.49 g, 2.37 mmol) in anhydrous diethyl ether (11 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 8:2) gave ester **18d** (1.06 g, 1.41 mmol, 88%) as a colourless oil, a 94:6 mixture of diastereomers. R_f: 0.19 (petroleum ether/ethyl acetate, 8:2). $[\alpha]_D^{20}$ = +21.7 (c = 1.2, $CHCl_3$). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 6

H), 0.66 (t, J = 7.0 Hz, 3 H), 0.82 (d, J = 6.8 Hz, 3 H), 1.01 (s, 9 H), 1.33 (m, 1 H), 1.41 (s, 9 H), 1.49 (m, 1 H), 1.60 (s, 3 H), 2.32 (dd, J = 13.7, 7.9 Hz, 1 H), 2.49–2.58 (m, 2 H), 2.79 (dd, J = 15.1, 5.8 Hz, 1 H), 2.85 (dd, J = 15.1, 5.8 Hz, 1 H), 4.48 (m, 1 H), 4.54–4.66 (m, 5 H), 4.96 (d, J = 9.8 Hz, 1 H), 5.01 (br. s, 1 H), 5.18–5.36 (m, 5 H), 5.54 (br. s, 1 H), 5.95–5.95 (m, 2 H), 6.81 (d, J = 8.5 Hz, 1 H), 7.06 (dd, J = 8.4, 2.1 Hz, 1 H), 7.28 (d, J = 2.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 9.7, 16.2, 16.3, 18.3, 24.5, 25.6, 28.3, 35.9, 40.7, 42.7, 50.4*, 52.2, 65.8, 65.9, 79.3, 79.8, 117.8, 118.9, 120.6, 125.5, 125.6, 128.1, 130.7, 131.1, 131.5, 132.6, 135.3, 150.8, 154.9, 155.6, 170.8, 171.9 ppm (*determined from C,H-COSY). HPLC (Reprosil; hexane/*i*PrOH, 6:4; 1 mL/min): (*R*)-**18d**: t_R = 6.23 min; (*S*)-**18d**: t_R = 7.07 min. HPLC–MS (H_2O/MeCN, 2:8; 0.6 mL/min): t_R = 13.59 min; m/z = 773 $[C_{38}H_{59}ClN_2O_9Si + Na]^+$. HRMS (CI): calcd. for $C_{34}H_{50}ClN_2O_9Si$ $[M - C_4H_9]^+$ 693.2969; found 693.2935. $C_{38}H_{59}ClN_2O_9Si$ (751.42): calcd. C 60.74, H 7.91, N 3.73; found C 60.37, H 7.96, N 3.54.

***N*-*tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-2-chlorotryptophanyl-(*R*)-3-chloro-4-*tert*-butyldimethylsilyloxy-β-phenylalanine-{[(*R*,*E*)-4-methylnon-4-enoic Acid Allyl Ester]-7-yl} Ester (19a):** A solution of β-tyrosine ester **18a** (0.50 g, 0.78 mmol) in anhydrous CH_2Cl_2 (5.6 mL) was treated with TFA (trifluoroacetic acid; 2.40 mL, 31.5 mmol) at –20 °C, and the mixture was stirred for 16 h at this temperature. The mixture was poured into satd. aq. $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were further washed with brine, dried with Na_2SO_4, and concentrated in vacuo.

The resulting crude amine was dissolved in anhydrous CH_2Cl_2 (2.3 mL), and the solution was cooled to at 0 °C. Chlorinated dipeptide **A** (0.40 g, 0.94 mmol), *i*Pr_2NEt (0.25 mL, 1.42 mmol), and COMU® [(1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylaminomorpholinocarbenium hexafluorophosphate][40] (0.40 g, 0.94 mmol) were added. The mixture was allowed to warm up to room temperature overnight, then it was concentrated to dryness, and the residue was dissolved in ethyl acetate. The organic layer was washed with $KHSO_4$ (1 M aq.), H_2O, satd. aq. $NaHCO_3$, and brine, dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate, 7:3) gave **19a** (0.52 g, 0.55 mmol, 70%) as a slightly yellow foam, an 86:14 mixture of diastereomers. R_f: 0.17 (petroleum ether/ethyl acetate, 7:3). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.67 (d, J = 6.8 Hz, 3 H), 0.74 (t, J = 7.4 Hz, 3 H), 1.01 (s, 9 H), 1.37 (s, 9 H), 1.43 (m, 2 H), 1.60 (s, 3 H), 2.15 (m, 2 H), 2.32 (dd, J = 8.0, 8.0 Hz, 2 H), 2.43 (dd, J = 9.5, 8.0 Hz, 2 H), 2.78 (dd, J = 16.1, 7.0 Hz, 1 H), 2.89 (dd, J = 15.9, 7.7 Hz, 1 H), 2.95 (s, 3 H), 3.20 (dd, J = 15.2, 10.9 Hz, 1 H), 3.41 (dd, J = 15.3, 5.5 Hz, 1 H), 4.25 (dq, J = 6.8, 6.8 Hz, 1 H), 4.56 (ddd, J = 5.5, 1.3, 1.3 Hz, 2 H), 4.71 (tt, J = 5.8, 5.8 Hz, 1 H), 5.05–5.09 (m, 2 H), 5.22 (ddt, J = 10.3, 1.3, 1.3 Hz, 1 H), 5.30 (ddt, J = 17.2, 1.4, 1.4 Hz, 1 H), 5.36 (ddd, J = 7.3, 7.3 Hz, 1 H), 5.63 (dd, J = 10.5, 5.3 Hz, 1 H), 5.90 (ddt, J = 17.3, 10.5, 5.8 Hz, 1 H), 6.77 (d, J = 8.3 Hz, 1 H), 7.02–7.04 (m, 2 H), 7.07 (dd, J = 6.8, 6.8 Hz, 1 H), 7.11 (dd, J = 6.9, 6.9 Hz, 1 H), 7.19–7.23 (m, 2 H), 7.49 (d, J = 7.8 Hz, 1 H), 8.39 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 9.5, 16.1, 16.4, 18.3, 22.3, 25.6, 26.1, 28.3, 31.6, 31.9, 32.9, 34.6, 40.3, 46.4, 49.1, 56.3, 65.0, 75.8, 79.8, 107.3, 110.4, 118.2, 118.3, 119.7, 120.1, 120.6, 121.6, 122.3, 125.5, 125.8, 127.3, 128.3, 132.2, 134.4, 134.6, 136.3, 150.8, 155.7, 169.2, 170.2, 172.9, 174.3 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 6 H), 1.01 (s, 9 H), 1.39 (s, 9 H), 1.61 (s, 3 H), 2.71 (s, 3 H), 3.31 (dd, J = 15.6, 3.3 Hz, 1 H), 4.01 (m, 1 H), 4.77 (m, 1 H), 4.89 (d, J = 6.3 Hz, 1 H), 4.93 (dd, J = 10.9, 3.4 Hz, 1 H), 5.47 (m, 1 H), 6.78 (d, J = 8.3 Hz, 1 H), 7.49 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.5, 16.1, 80.6, 122.7, 128.5, 168.3 ppm. HPLC–MS (H_2O/MeCN, 1:9; 0.6 mL/min): t_R = 7.76 min; m/z = 965 $[C_{48}H_{68}Cl_2N_4O_9Si + Na]^+$. HRMS (CI): calcd. for $C_{48}H_{70}Cl_2N_4O_9Si$ $[M + 2H]^+$ 944.4284; found 944.4284.

***N*-*tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-2-chlorotryptophanyl-(*R*)-3-chloro-4-*tert*-butyldimethylsilyloxy-β-phenylalanine-{[(7*R*,*E*)-2,4-dimethylnon-4-enoic Acid Allyl Ester]-7-yl} Ester (19b):** Tripeptide **19b** was prepared following the method used for the synthesis of **19a**, starting from β-tyrosine ester **18b** (0.43 g, 0.66 mmol) and TFA (2.02 mL, 26.3 mmol) in anhydrous CH_2Cl_2 (4.7 mL), and chlorinated dipeptide **A** (0.33 g, 0.78 mmol), *i*Pr_2NEt (0.21 mL, 1.18 mmol), and COMU® (0.34 g, 0.79 mmol) in anhydrous CH_2Cl_2 (1.9 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 7:3) gave **19b** (0.50 g, 0.52 mmol, 79%) as a slightly yellow foam, an 82:18 mixture of diastereomers. R_f: 0.20 (petroleum ether/ethyl acetate, 7:3). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.68 (d, J = 6.8 Hz, 3 H), 0.74 (t, J = 7.4 Hz, 3 H), 1.02 (s, 9 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.37 (s, 9 H), 1.43 (m, 2 H), 1.58 (s, 3 H), 2.05 (dd, J = 13.6, 7.8 Hz, 1 H), 2.15 (m, 2 H), 2.39 (dd, J = 13.2, 6.9 Hz, 1 H), 2.63 (m, 1 H), 2.74 (dd, J = 16.1, 4.8 Hz, 1 H), 2.90 (dd, J = 15.8, 7.5 Hz, 1 H), 2.95 (s, 3 H), 3.21 (dd, J = 15.1, 10.8 Hz, 1 H), 3.41 (dd, J = 15.3, 5.8 Hz, 1 H), 4.26 (dq, J = 6.8, 6.8 Hz, 1 H), 4.54 (ddd, J = 5.8, 1.3, 1.3 Hz, 2 H), 4.71 (tt, J = 6.5, 6.5 Hz, 1 H), 5.05–5.09 (m, 2 H), 5.21 (ddt, J = 9.3, 1.0, 1.0 Hz, 1 H), 5.30 (ddt, J = 17.3, 1.0, 1.0 Hz, 1 H), 5.35 (ddd, J = 7.0, 7.0, 7.0 Hz, 1 H), 5.63 (dd, J = 10.5, 5.5 Hz, 1 H), 5.89 (ddt, J = 17.3, 10.5, 5.5 Hz, 1 H), 6.77 (d, J = 8.3 Hz, 1 H), 7.02–7.04 (m, 2 H), 7.07 (dd, J = 8.0, 8.0 Hz, 1 H), 7.12 (dd, J = 6.8, 6.8 Hz, 1 H), 7.19–7.23 (m, 2 H), 7.49 (d, J = 7.8 Hz, 1 H), 8.33 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 9.4, 15.9, 16.6, 16.6, 18.3, 22.3, 25.6, 26.0, 28.3, 31.6, 31.9, 37.9, 40.3*, 43.8, 46.4, 49.1, 56.3, 64.9, 75.8, 79.8, 107.3, 110.4, 118.0, 118.3, 120.2, 120.6, 120.7, 121.4, 122.3, 125.5, 125.8, 127.3, 128.3, 132.3, 134.4, 134.6, 136.1, 150.9, 155.6, 169.2, 170.2, 174.2, 176.1 ppm (*determined from C,H-COSY). Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 6 H), 1.01 (s, 9 H), 1.39 (s, 9 H), 1.59 (s, 3 H), 2.71 (s, 3 H), 3.31 (dd, J = 15.6, 3.8 Hz, 1 H), 4.01 (m, 1 H), 4.77 (m, 1 H), 4.86 (d, J = 6.3 Hz, 1 H), 4.93 (dd, J = 10.9, 3.4 Hz, 1 H), 5.47 (m, 1 H), 6.78 (d, J = 8.3 Hz, 1 H), 7.43 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 9.5, 16.5, 122.7, 128.5. 150.8, 154.9, 155.6, 170.8, 171.9 ppm. HPLC (OD-H; hexane/*i*PrOH, 9:1; 1 mL/min): (*R*/*S*)-**19b**: t_R = 14.08 min. HPLC–MS (H_2O/MeCN, 1:9; 0.6 mL/min): (*R*/*S*)-**19b**: t_R = 10.15 min; m/z = 979 $[C_{49}H_{70}Cl_2N_4O_9Si + Na]^+$. HRMS (CI): calcd. for $C_{49}H_{71}Cl_2N_4O_9Si$ $[M + H]^+$ 957.4362; found 957.4401.

***N*-*tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-2-chlorotryptophanyl-(*R*)-3-chloro-4-*tert*-butyldimethylsilyloxy-β-phenylalanine-{[(2*S*,6*S*,7*R*,*E*)-2,4,6-trimethylnon-4-enoic Acid Allyl Ester]-7-yl} Ester (19c):** Tripeptide **19c** was prepared following the method used for the synthesis of **19a**, starting from β-tyrosine ester **18c** (0.36 g, 0.54 mmol) and TFA (1.68 mL, 21.8 mmol) in anhydrous CH_2Cl_2 (3.9 mL), and chlorinated dipeptide **A** (0.28 g, 0.66 mmol), *i*Pr_2NEt (114 μL, 0.65 mmol), and COMU® (0.28 g, 0.65 mmol) in anhydrous CH_2Cl_2 (1.6 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 7:3) gave **19c** (0.51 g, 0.52 mmol, 96%) as a slightly yellow foam, an 89:11 mixture of diastereomers. R_f: 0.20 (petroleum ether/ethyl acetate, 7:3). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.64–0.69 (m, 6 H), 0.79 (d, J = 7.4 Hz, 3 H), 1.02 (s, 9 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.28 (m, 1 H), 1.37 (s, 9 H), 1.50 (m, 1 H), 1.57 (s, 3 H), 2.02 (dd, J = 13.7, 7.4 Hz, 1 H), 2.38 (dd, J = 13.7, 7.4 Hz, 1 H), 2.50 (m, 1

H), 2.62 (m, 1 H), 2.77 (dd, *J* = 15.8, 6.5 Hz, 1 H), 2.91–2.95 (m, 4 H), 3.21 (dd, *J* = 15.3, 10.8 Hz, 1 H), 3.41 (dd, *J* = 15.3, 5.5 Hz, 1 H), 4.26 (dq, *J* = 6.8, 6.8 Hz, 1 H), 4.54 (m, 2 H), 4.58 (m, 1 H), 4.91 (d, *J* = 9.8 Hz, 1 H), 5.07 (d, *J* = 6.3 Hz, 1 H), 5.21 (ddt, *J* = 10.5, 1.5, 1.5 Hz, 1 H), 5.30 (ddt, *J* = 16.8, 1.5, 1.5 Hz, 1 H), 5.34 (ddd, *J* = 7.3, 7.3, 7.3 Hz, 1 H), 5.62 (dd, *J* = 10.5, 5.5 Hz, 1 H), 5.89 (ddt, *J* = 17.3, 10.5, 5.5 Hz, 1 H), 6.77 (d, *J* = 8.3 Hz, 1 H), 7.01–7.05 (m, 2 H), 7.07 (dd, *J* = 6.8, 6.8 Hz, 1 H), 7.12 (dd, *J* = 6.9, 6.9 Hz, 1 H), 7.19–7.24 (m, 2 H), 7.49 (d, *J* = 7.5 Hz, 1 H), 8.27 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 9.5, 16.1, 16.6, 16.6, 17.1, 18.3, 22.3, 24.7, 25.6, 28.3, 31.6, 36.0, 37.9, 40.1, 43.8, 46.4, 49.1, 56.3, 64.9, 75.6, 79.8, 107.4, 110.4, 118.0, 118.4, 120.2, 120.7, 121.6, 122.4, 125.6, 125.9, 127.3, 128.3, 128.9, 132.3, 132.8, 134.4, 134.6, 150.9, 155.6, 169.2, 170.4, 174.2, 176.0 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 6 H), 1.01 (s, 9 H), 1.40 (s, 9 H), 1.59 (s, 3 H), 3.27 (dd, *J* = 10.0, 3.5 Hz, 1 H), 3.46 (m, 1 H), 4.01 (m, 1 H), 4.66 (m, 1 H), 4.85 (d, *J* = 6.0 Hz, 1 H), 4.93 (m, 1 H), 5.48 (m, 1 H), 6.78 (d, *J* = 8.3 Hz, 1 H), 7.31 (d, *J* = 2.3 Hz, 1 H), 7.43 (d, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.5, 36.0, 49.6, 118.0, 125.6 ppm. HPLC (OD-H; hexane/*i*-PrOH, 8:2; 0.5 mL/min): t_R = 8.16 min. HPLC–MS (H_2O/MeCN, 1:9; 0.6 mL/min): t_R = 6.51 min; *m*/*z* = 993 $[C_{50}H_{72}Cl_2N_4O_9Si + Na]^+$. HRMS (CI): calcd. for $C_{50}H_{73}Cl_2N_4O_9Si$ $[M + H]^+$ 971.4518; found 971.4569.

***N*-*tert*-Butoxycarbonyl-(*S*)-alanyl-*N*-methyl-(*R*)-2-chlorotryptophanyl-(*R*)-3-chloro-4-*tert*-butyldimethylsilyloxy-β-phenylalanine-{[(2*S*,6*R*,7*R*,*E*)-2-(Allyloxycarbonylamino)-4,6-dimethylnon-4-enoic Acid Allyl Ester]-7-yl} Ester (19d):** Tripeptide **19d** was prepared following the method used for the synthesis of **19a**, starting from β-tyrosine ester **18d** (1.02 g, 1.36 mmol) and TFA (4.20 mL, 54.6 mmol) in anhydrous CH_2Cl_2 (9.8 mL), and chlorinated dipeptide **A** (0.69 g, 1.63 mmol), *i*Pr_2NEt (0.29 mL, 1.64 mmol), and COMU® (0.70 g, 1.63 mmol) in anhydrous CH_2Cl_2 (3.9 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 7:3) gave **19d** (1.05 g, 0.99 mmol, 73%) as a slightly yellow foam, a 94:6 mixture of diastereomers. R_f: 0.28 (petroleum ether/ethyl acetate, 6:4). $[\alpha]_D^{20}$ = +20.2 (*c* = 1.5, $CHCl_3$). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.68–0.71 (m, 6 H), 0.81 (t, *J* = 6.5 Hz, 3 H), 1.02 (s, 9 H), 1.31–1.37 (m, 10 H), 1.50 (m, 1 H), 1.62 (s, 3 H), 2.31 (dd, *J* = 13.7, 8.7 Hz, 1 H), 2.50–2.56 (m, 2 H), 2.78 (dd, *J* = 15.3, 6.0 Hz, 1 H), 2.91–2.95 (m, 4 H), 3.19 (dd, *J* = 15.3, 10.8 Hz, 1 H), 3.40 (dd, *J* = 15.2, 5.7 Hz, 1 H), 4.27 (dq, *J* = 6.8, 6.8 Hz, 1 H), 4.45 (m, 1 H), 4.54–4.65 (m, 5 H), 4.96 (d, *J* = 9.5 Hz, 1 H), 5.08 (d, *J* = 6.3 Hz, 1 H), 5.17–5.33 (m, 5 H), 5.36 (m, 1 H), 5.63 (dd, *J* = 10.5, 5.5 Hz, 1 H), 5.83–5.94 (m, 2 H), 6.77 (d, *J* = 8.3 Hz, 1 H), 6.98–7.05 (m, 2 H), 7.08 (dd, *J* = 7.0, 7.0 Hz, 1 H), 7.13 (dd, *J* = 6.0, 6.0 Hz, 1 H), 7.19–7.24 (m, 2 H), 7.49 (d, *J* = 7.5 Hz, 1 H), 8.18 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 9.6, 16.1, 16.4, 16.6, 18.3, 22.3, 24.6, 25.6, 28.3, 31.5, 35.9, 40.2, 42.8, 46.4, 49.1, 52.3, 56.2, 65.7, 65.9, 79.2, 79.7, 107.4, 110.3, 117.8, 118.4, 119.9, 120.2, 120.7, 121.5, 122.4, 125.5, 125.9, 127.3, 128.3, 130.6, 131.2, 131.5, 132.6, 134.3, 134.6, 150.9, 155.6, 155.6, 169.2, 170.3, 171.9, 174.1 ppm. HPLC–MS (H_2O/MeCN, 1:9; 0.6 mL/min): t_R = 3.93 min; *m*/*z* = 1079 $[C_{53}H_{75}Cl_2N_5O_{11}Si + Na]^+$. HRMS (CI): calcd. for $C_{53}H_{76}Cl_2N_5O_{11}Si$ $[M + H]^+$ 1056.4682; found 1056.4769.

(4*R*,7*R*,10*S*,18*R*,*E*)-7-(2-Chloro-1*H*-indol-3-ylmethyl)-4-(3-chloro-4-hydroxyphenyl)-18-ethyl-8,10,15-trimethyl-1-oxa-5,8,11-triazacyclooctadec-15-en-2,6,9,12-tetraone (20a): $Pd(PPh_3)_4$ (44.0 mg, 40.0 μmol) and morpholine (66.0 μL, 0.76 mmol) were added to a solution of tripeptide **19a** (0.36 g, 0.38 mmol) in anhydrous THF (3.8 mL). The reaction mixture was stirred for 2 h, then it was diluted with ethyl acetate, washed twice with HCl (1 M aq.) and brine, dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate, 7:3 to 1:1 + 1% AcOH) gave acid **20a′** (0.34 g, 0.38 mmol, 99%) as a colourless solid, an 86:14 mixture of diastereomers. R_f: 0.16 (petroleum ether/ethyl acetate, 7:3 + 1% AcOH). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.67 (t, *J* = 7.4 Hz, 3 H), 0.73 (d, *J* = 6.8 Hz, 3 H), 1.02 (s, 9 H), 1.38 (s, 9 H), 1.40 (m, 2 H), 1.62 (s, 3 H), 2.18 (m, 2 H), 2.32 (m, 2 H), 2.48 (dd, *J* = 8.5, 6.0 Hz, 2 H), 2.74 (dd, *J* = 13.3, 5.5 Hz, 1 H), 2.85 (dd, *J* = 15.6, 7.0 Hz, 1 H), 3.02 (s, 3 H), 3.22 (dd, *J* = 15.1, 10.3 Hz, 1 H), 3.36 (dd, *J* = 15.1, 5.8 Hz, 1 H), 4.40 (dq, *J* = 7.0, 7.0 Hz, 1 H), 4.75 (tt, *J* = 6.5, 6.5 Hz, 1 H), 5.11 (t, *J* = 6.7 Hz, 1 H), 5.31–5.37 (m, 2 H), 5.59 (dd, *J* = 9.8, 5.8 Hz, 1 H), 6.76 (d, *J* = 8.5 Hz, 1 H), 7.01 (d, *J* = 9.0 Hz, 1 H), 7.07 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.13 (dd, *J* = 8.0, 8.0 Hz, 1 H), 7.19–7.23 (m, 2 H), 7.38 (d, *J* = 8.3 Hz, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 8.17 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 9.6, 16.2, 16.9, 18.3, 22.6, 25.6, 26.5, 28.3, 31.7, 32.0, 32.5, 34.4, 40.1, 46.5, 49.1, 56.4, 75.8, 79.8, 107.0, 110.4, 118.3, 119.9, 120.2, 120.6, 121.7, 122.3, 125.5, 125.7, 127.3, 128.3, 134.4, 134.5, 136.0, 150.8, 155.6, 169.4, 170.3, 174.4, 175.7 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 6 H), 1.01 (s, 9 H), 1.39 (s, 9 H), 1.64 (s, 3 H), 2.73 (s, 3 H), 4.03 (m, 1 H), 4.83 (m, 1 H), 4.99 (m, 1 H), 6.78 (d, *J* = 8.5 Hz, 1 H), 7.47 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.0, 49.1, 122.6, 175.7 ppm. HPLC–MS (H_2O/MeCN, 2:8; 0.6 mL/min): t_R = 3.26 min; *m*/*z* = 925 $[C_{45}H_{64}Cl_2N_4O_9Si + Na]^+$. HRMS (CI): calcd. for $C_{45}H_{63}Cl_2N_4O_9Si$ $[M - H]^-$ 901.3747; found 301.3768.

TFA (1.69 mL, 21.9 mmol) was added to a solution of acid **20a′** (0.33 g, 0.36 mmol) in anhydrous CH_2Cl_2 (3.6 mL) at –20 °C, and the mixture was stirred for 16 h at this temperature. The solvent was removed under reduced pressure.

The crude amine was dissolved in anhydrous CH_2Cl_2 (80 mL). *i*Pr_2NEt (0.51 mL, 2.92 mmol) and T3P® (50 wt.-% in ethyl acetate; 1.61 g, 2.56 mmol)[29] were added at 0 °C. The reaction mixture was allowed to warm up to room temperature overnight, then it was concentrated to dryness, and the residue was dissolved in ethyl acetate. The organic layer was washed with HCl (1 M), satd. aq. $NaHCO_3$, H_2O, and brine, dried with Na_2SO_4, and concentrated in vacuo.

The crude macrocycle was dissolved in anhydrous THF (3.6 mL), and TBAF (1 M in THF; 0.40 mL, 0.40 mmol) was added. The reaction mixture was stirred for 16 h, then it was diluted with ethyl acetate, washed twice with HCl (1 M aq.) and brine, dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate, 3:7) gave macrocycle **20a** (134 mg, 199 μmol, 55%; 78% purity of the major diastereomer) [equates to 105 mg of enantiomerically pure **20a** (156 μmol, 43%)] as a colourless solid. Removal of undesired diastereomers was achieved by further preparative RP-HPLC (acetonitrile/H_2O, 6:4) purification, m.p. 125–127 °C. $[\alpha]_D^{20}$ = +44.2 (*c* = 1.0, $CHCl_3$). R_f: 0.16 (petroleum ether/ethyl acetate, 3:7). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72 (t, *J* = 7.4 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H), 1.43 (m, 2 H), 1.61 (s, 3 H), 1.81 (br. s, 1 H), 2.17–2.26 (m, 3 H), 2.37–2.44 (m, 3 H), 2.77 (d, *J* = 5.3 Hz, 2 H), 2.96 (s, 3 H), 3.25 (dd, *J* = 15.1, 9.8 Hz, 1 H), 3.34 (dd, *J* = 15.1, 6.8 Hz, 1 H), 4.65 (dq, *J* = 7.0, 7.0 Hz, 1 H), 4.72 (tt, *J* = 5.8, 5.8 Hz, 1 H), 5.14 (t, *J* = 6.8 Hz, 1 H), 5.29 (dt, *J* = 9.5, 5.0 Hz, 1 H), 5.38 (dd, *J* = 9.2, 7.2 Hz, 1 H), 6.55 (d, *J* = 6.8 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 6.91 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.08 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.12–7.17 (m, 2 H), 7.18–7.25 (m, 2 H), 7.49 (d, *J* =

8.0 Hz, 1 H), 8.50 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7, 16.2, 17.8, 22.8, 26.5, 31.9, 31.9, 33.7, 34.5, 39.7, 45.8, 48.6, 56.7, 76.7*, 106.7, 110.6, 116.3, 118.1, 120.0, 120.2, 120.4, 121.7, 122.5, 126.0, 126.8, 127.0, 133.7, 134.4, 135.9, 150.7, 169.4, 170.9, 171.6, 173.9 ppm (*determined from C,H-COSY). HPLC–MS (H_2O/MeCN, 1:1; 0.6 mL/min): t_R = 4.31 min; m/z = 693 $[C_{34}H_{40}Cl_2N_4O_6 + Na]^+$. HRMS (CI): calcd. for $C_{34}H_{41}Cl_2N_4O_6$ $[M + H]^+$ 671.2398; found 671.2394. $C_{34}H_{40}Cl_2N_4O_6$ (671.61): calcd. C 60.80, H 6.00, N 8.34; found C 60.49, H 6.32, N 8.01.

(4*R*,7*R*,10*S*,13*S*,18*R*,*E*)-7-(2-Chloro-1*H*-indol-3-ylmethyl)-4-(3-chloro-4-hydroxyphenyl)-18-ethyl-8,10,13,15-tetramethyl-1-oxa-5,8,11-triazacyclooctadec-15-en-2,6,9,12-tetraone [(*S*)-20b-1] and (4*R*,7*R*,10*S*,13*R*,18*R*,*E*)-7-(2-Chloro-1*H*-indol-3-ylmethyl)-4-(3-chloro-4-hydroxyphenyl)-18-ethyl-8,10,13,15-tetramethyl-1-oxa-5,8,11-triazacyclooctadec-15-en-2,6,9,12-tetraone [(*R*)-20b-2]: Following the method used for the synthesis of acid **20a′**, **20b′** was prepared from tripeptide **19b** (0.43 g, 0.45 mmol), $Pd(PPh_3)_4$ (52.0 mg, 45.0 μmol), and morpholine (79.0 μL, 0.90 mmol) in anhydrous THF (4.5 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 7:3 to 1:1 + 1% AcOH) gave acid **20b′** (0.36 g, 0.39 mmol, 87%) as a colourless foam, an 82:18 mixture of diastereomers. R_f: 0.20 (petroleum ether/ethyl acetate, 7:3 + 1% AcOH). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 3 H), 0.21 (s, 3 H), 0.63–0.78 (m, 6 H), 1.01 (s, 4.5 H), 1.02 (s, 4.5 H), 1.22 (d, J = 6.8 Hz, 1.5 H), 1.27 (d, J = 7.0 Hz, 1.5 H), 1.37 (s, 9 H), 1.43 (m, 2 H), 1.61 (s, 1.5 H), 1.63 (s, 1.5 H), 2.01–2.40 (m, 4 H), 2.63–2.95 (m, 3 H), 3.04 (s, 1.5 H), 3.06 (s, 1.5 H), 3.31 (m, 2 H), 4.40 (dq, J = 7.3, 7.3 Hz, 1 H), 4.74 (m, 1 H), 4.91 (m, 1 H), 5.24–5.39 (m, 2 H), 5.62 (m, 1 H), 6.77 (d, J = 8.3 Hz, 1 H), 7.00–7.23 (m, 5 H), 7.32–7.63 (m, 2 H), 8.04 (br. s, 0.5 H), 8.07 (br. s, 0.5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, –4.4, 9.5, 9.7, 16.1, 16.3, 17.1, 17.8, 18.3, 22.6, 22.9, 25.6, 26.1, 26.5, 28.3, 31.4, 31.7, 31.9, 32.0, 38.3, 39.7, 40.5, 44.2, 46.5, 48.7, 49.4, 55.8, 56.7, 75.7, 75.9, 79.8, 110.0, 110.4, 118.3, 120.2, 120.5, 120.6, 120.6, 121.7, 121.7, 122.3, 125.5, 125.7, 125.7, 127.2, 127.3, 128.1, 128.4, 134.4, 135.2, 135.6, 150.9, 155.6, 169.5, 170.4, 174.2, 174.4, 178.6, 178.7 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.18 (s, 6 H), 1.00 (s, 9 H), 1.65 (s, 3 H), 2.72 (s, 3 H), 7.62 (d, J = 8.3 Hz, 1 H) ppm. HPLC–MS (H_2O/MeCN, 2:8; 0.6 mL/min): t_R = 2.89 min; m/z = 939 $[C_{46}H_{66}Cl_2N_4O_9Si + Na]^+$. HRMS (CI): calcd. for $C_{46}H_{68}Cl_2N_4O_9Si$ $[M + 2H]^+$ 918.4127; found 918.4153.

Following the method used for the synthesis of macrocycle **20a**, **20b** was prepared from **20b′** (0.27 g, 0.29 mmol) and TFA (1.37 mL, 17.8 mmol) in anhydrous CH_2Cl_2 (2.9 mL), iPr$_2$NEt (0.42 mL, 2.38 mmol) and T3P® (1.31 g, 2.08 mmol) in anhydrous CH_2Cl_2 (65 mL), and TBAF (1 M in THF; 0.33 mL, 0.33 mmol) in anhydrous THF (2.9 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 4:6) gave macrocycle (*S*)-**20b-1** (52 mg, 76 μmol, 26%; 84% purity of the major diastereomer) [equates to 44 mg enantiomerically pure **20b-1** (64 μmol, 22%)] and (*R*)-**20b-2** (69 mg, 100 μmol, 34%; 64% purity of the major diastereomer) [equates to 44 mg of enantiomerically pure **20b-2** (64 μmol, 22%)] as colourless solids. Removal of the undesired diastereomers was achieved by further preparative RP-HPLC (acetonitrile/H_2O, 6:4) purification.

Data for [(*S*)-**20b-1**]: m.p. 130–132 °C. $[\alpha]_D^{20}$ = +42.3 (c = 0.7, $CHCl_3$). R_f: 0.23 (petroleum ether/ethyl acetate, 4:6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, J = 7.4 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 1.16 (d, J = 6.8 Hz, 3 H), 1.48 (qd, J = 7.3, 7.3 Hz, 2 H), 1.65 (s, 3 H), 1.77 (br. s, 1 H), 1.94–2.06 (m, 2 H), 2.14–2.29 (m, 2 H), 2.42 (m, 1 H), 2.68 (dd, J = 15.6, 8.3 Hz, 1 H), 2.76 (dd, J = 15.6, 4.3 Hz, 1 H), 3.02 (s, 3 H), 3.25 (dd, J = 14.8, 9.0 Hz, 1 H), 3.32 (dd, J = 14.8, 7.3 Hz, 1 H), 4.61–4.68 (m, 2 H), 5.10 (t, J = 6.9 Hz, 1 H), 5.27–5.35 (m, 2 H), 6.48 (d, J = 6.8 Hz, 1 H), 6.85 (d, J = 8.5 Hz, 1 H), 6.89 (dd, J = 8.5, 1.8 Hz, 1 H), 6.96 (d, J = 8.8 Hz, 1 H), 7.08–7.11 (m, 2 H), 7.16 (dd, J = 7.3, 7.3 Hz, 1 H), 7.24 (d, J = 8.0 Hz, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 8.35 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7, 16.4, 18.2, 18.6, 23.5, 26.2, 31.9, 32.0, 39.8, 40.2, 44.3, 45.5, 48.9, 56.2, 76.8, 106.5, 110.6, 116.4, 118.0, 120.0, 120.1, 120.5, 121.8, 122.6, 126.1, 126.9, 127.0, 133.9, 134.4, 136.5, 150.7, 169.4, 170.8, 173.8, 174.8 ppm. HPLC–MS (H_2O/MeCN, 4:6, 0.6 mL/min): t_R = 3.13 min; m/z = 707 $[C_{35}H_{42}Cl_2N_4O_6 + Na]^+$. HRMS (CI): calcd. for $C_{35}H_{43}Cl_2N_4O_6$ $[M + H]^+$ 685.2554; found 685.2536.

Data for [(*R*)-**20b-2**]: m.p. 115–118 °C. $[\alpha]_D^{20}$ = +47.1 (c = 0.9, $CHCl_3$). R_f: 0.15 (petroleum ether/ethyl acetate, 4:6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (t, J = 7.5 Hz, 3 H), 0.78 (d, J = 6.8 Hz, 3 H), 1.17 (d, J = 7.0 Hz, 3 H), 1.27 (m, 1 H), 1.43 (m, 1 H), 1.60 (s, 3 H), 2.06–2.14 (m, 2 H), 2.19–2.29 (m, 2 H), 2.58 (m, 1 H), 2.69 (dd, J = 15.3, 3.8 Hz, 1 H), 2.76 (dd, J = 15.3, 8.3 Hz, 1 H), 2.95 (s, 3 H), 3.23 (dd, J = 15.1, 9.8 Hz, 1 H), 3.32 (dd, J = 15.3, 7.0 Hz, 1 H), 4.64 (dq, J = 6.8, 6.8 Hz, 1 H), 4.77 (m, 1 H), 5.08 (t, J = 6.0 Hz, 1 H), 5.31 (ddd, J = 8.3, 8.3, 3.5 Hz, 1 H), 5.54 (dd, J = 9.5, 7.0 Hz, 1 H), 6.11 (br. s, 1 H), 6.57 (d, J = 7.0 Hz, 1 H), 6.82–6.86 (m, 2 H), 6.92 (dd, J = 8.5, 2.3 Hz, 1 H), 7.09 (d, J = 7.0, 7.0 Hz, 1 H), 7.13–7.17 (m, 2 H), 7.23 (d, J = 8.0 Hz, 1 H), 7.48 (d, J = 7.5 Hz, 1 H), 8.48 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.8, 16.1, 17.9, 18.6, 22.7, 25.9, 31.1, 31.4, 40.9, 40.9, 45.6, 45.6, 49.1, 56.1, 76.8, 106.6, 110.6 116.5, 118.1, 120.1, 120.4, 120.9, 121.7, 122.5, 125.9, 126.6, 127.0, 133.9, 134.4, 135.4, 150.8, 169.1, 170.7, 173.9, 174.5 ppm. HPLC–MS (H_2O/MeCN, 4:6; 0.6 mL/min): t_R = 2.70 min; m/z = 707 $[C_{35}H_{42}Cl_2N_4O_6 + Na]^+$. HRMS (CI): calcd. for $C_{35}H_{43}Cl_2N_4O_6$ $[M + H]^+$ 685.2554; found 685.2558.

(4*R*,7*R*,10*S*,13*S*,17*R*,18*R*,*E*)-7-(2-Chloro-1*H*-indol-3-ylmethyl)-4-(3-chloro-4-hydroxyphenyl)-18-ethyl-8,10,13,15,17-pentamethyl-1-oxa-5,8,11-triazacyclooctadec-15-en-2,6,9,12-tetraone (20c): Following the method used for the synthesis of acid **20a′**, **20c′** was prepared from tripeptide **19c** (0.46 g, 0.47 mmol), $Pd(PPh_3)_4$ (55.0 mg, 48.0 μmol), and morpholine (83.0 μL, 0.95 mmol) in anhydrous THF (4.8 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 7:3 to 1:1 + 1% AcOH) gave **20c′** (0.40 g, 0.43 mmol, 91%) as a colourless foam, an 89:11 mixture of diastereomers. R_f: 0.22 (petroleum ether/ethyl acetate, 7:3 + 1% AcOH). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.21 (s, 6 H), 0.60 (t, J = 7.4 Hz, 3 H), 0.65 (d, J = 6.8 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 3 H), 1.02 (s, 9 H), 1.27 (d, J = 7.0 Hz, 3 H), 1.32 (m, 1 H), 1.38 (s, 9 H), 1.45 (m, 1 H), 1.61 (s, 3 H), 2.09 (dd, J = 12.9, 4.6 Hz, 1 H), 2.36 (dd, J = 11.0, 7.8 Hz, 1 H), 2.60–2.82 (m, 4 H), 3.07 (s, 3 H), 3.18 (d, J = 8.3 Hz, 2 H), 4.40 (dq, J = 7.0, 7.0 Hz, 1 H), 4.67 (m, 1 H), 5.06 (d, J = 10.0 Hz, 1 H), 5.24–5.29 (m, 2 H), 5.73 (t, J = 8.2 Hz, 1 H), 6.77 (d, J = 8.3 Hz, 1 H), 7.03–7.08 (m, 2 H), 7.13 (dd, J = 7.2, 7.2 Hz, 1 H), 7.19–7.23 (m, 2 H), 7.48 (d, J = 7.8 Hz, 1 H), 7.86 (d, J = 7.8 Hz, 1 H), 8.27 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 10.4, 15.8, 16.3, 17.4, 17.7, 18.3, 22.6, 23.4, 25.6, 28.3, 31.2, 35.2, 39.5, 41.0, 45.2, 46.4, 49.9, 55.1, 79.7, 79.9, 106.7, 110.4, 118.3, 120.1, 120.6, 121.7, 122.4, 125.5, 125.6, 127.2, 128.2, 129.0, 133.5, 134.3, 135.6, 150.8, 155.2, 169.2, 170.5, 174.1, 178.4 ppm. Minor diastereomer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.69 (m, 3 H), 0.81 (m, 3 H), 1.02 (s, 9 H), 1.59 (s, 3 H), 2.99 (s, 3 H), 4.32 (m, 1 H), 4.61 (m, 1 H), 4.96 (d, J = 8.3 Hz, 1 H), 5.58 (m, 1 H), 6.78 (d, J = 8.5 Hz, 1 H), 8.54 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.4, 51.8, 80.6 ppm. HPLC–MS (H_2O/

MeCN, 2:8; 0.6 mL/min): t_R = 2.70 min; m/z = 953 $[C_{47}H_{68}Cl_2N_4O_9Si + Na]^+$. HRMS (CI): calcd. for $C_{47}H_{69}Cl_2N_4O_9Si$ $[M + H]^+$ 931.4205; found 931.4256.

Following the method used for the synthesis of macrocycle **20a**, **20c** was prepared from **20c′** (355 mg, 381 μmol) and TFA (1.17 mL, 15.2 mmol) in anhydrous CH_2Cl_2 (2.7 mL), *i*Pr_2NEt (0.33 mL, 1.90 mmol) and T3P® (0.96 g, 1.52 mmol) in anhydrous CH_2Cl_2 (95 mL), and TBAF (1 M in THF; 0.42 mL, 0.42 mmol) in anhydrous THF (3.5 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 3:7) gave macrocycle **20c** (162 mg, 232 μmol, 61%; 81% purity of the major diastereomer) [equates to 131 mg of enantiomerically pure **20c** (188 μmol, 49%)] as a colourless solid. Removal of the undesired diastereomers was achieved by further preparative RP-HPLC (acetonitrile/H_2O, 6:4) purification, m.p. 135–137 °C. $[\alpha]_D^{20}$ = +68.8 (c = 1.0, $CHCl_3$). R_f: 0.26 (petroleum ether/ethyl acetate, 3:7). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72 (t, J = 7.5 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 1.20 (d, J = 7.0 Hz, 3 H), 1.48 (m, 2 H), 1.59 (s, 3 H), 2.07 (d, J = 14.1 Hz, 1 H), 2.38 (dd, J = 14.6, 10.8 Hz, 1 H), 2.48–2.54 (m, 2 H), 2.74 (s, 3 H), 2.77 (dd, J = 16.8, 5.5 Hz, 1 H), 2.89 (dd, J = 16.8, 4.5 Hz, 1 H), 3.40 (d, J = 7.3 Hz, 2 H), 4.54 (dq, J = 6.8, 6.8 Hz, 1 H), 4.65 (td, J = 8.0, 2.5 Hz, 1 H), 4.99 (t, J = 5.8 Hz, 1 H), 5.12 (d, J = 9.5 Hz, 1 H), 5.37 (ddd, J = 9.3, 4.8, 4.8 Hz, 1 H), 6.76 (d, J = 6.8 Hz, 1 H), 6.87 (d, J = 8.5 Hz, 1 H), 6.98 (dd, J = 8.5, 2.0 Hz, 1 H), 7.07 (dd, J = 7.2, 7.2 Hz, 1 H), 7.14 (dd, J = 7.7, 7.7 Hz, 1 H), 7.19 (d, J = 2.0 Hz, 1 H), 7.25 (d, J = 7.8 Hz, 1 H), 7.37 (d, J = 9.0 Hz, 1 H), 7.45 (d, J = 7.8 Hz, 1 H), 8.84 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.3, 14.5, 16.1, 17.9, 20.3, 22.2, 25.4, 33.8, 35.0, 38.8, 39.8, 43.8, 46.1, 48.1, 59.2, 79.8, 107.0, 110.7, 116.3, 117.9, 120.1, 120.3, 121.7, 122.5, 126.0, 126.9, 127.1, 128.9, 133.0, 133.6, 134.5, 150.8, 169.4, 171.4, 173.6, 174.7 ppm. HPLC–MS (H_2O/MeCN, 6:4; 0.6 mL/min): t_R = 3.32 min; m/z = 721 $[C_{36}H_{44}Cl_2N_4O_6 + Na]^+$. HRMS (CI): calcd. for $C_{36}H_{45}Cl_2N_4O_6$ $[M + H]^+$ 699.2711; found 699.2755.

Allyl-[(4*R*,7*R*,10*S*,13*S*,17*R*,18*R*,*E*)-4-(4-*tert*-butyldimethylsilyloxy-3-chlorophenyl)-7-(2-chloro-1*H*-indol-3-ylmethyl)-18-ethyl-8,10,15,17-tetramethyl-2,6,9,12-tetraoxo-1-oxa-5,8,11-triazacyclooctadec-15-en-13-yl]carbamate (20d): Morpholine (55.0 μL, 0.58 mmol) was added to a solution of tripeptide **19d** (0.55 g, 0.52 mmol), $Pd(PPh_3)_4$ (30.0 mg, 26.0 μmol), and PPh_3 (28.0 mg, 107 μmol) in anhydrous CH_2Cl_2 (1.5 mL) at 0 °C.[34] The reaction mixture was stirred for 1 h, then it was diluted with CH_2Cl_2. The organic phase was washed twice with HCl (1 M aq.) and brine, dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate, 6:4 to 1:1 + 1% AcOH) gave **20d′** (0.36 g, 0.44 mmol, 84%) as a colourless solid, a 94:6 mixture of diastereomers, m.p. 64–64 °C. R_f: 0.26 (petroleum ether/ethyl acetate, 6:4 + 1% AcOH). $[\alpha]_D^{20}$ = +24.8 (c = 2.6, $CHCl_3$). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.21 (s, 6 H), 0.65–0.68 (m, 6 H), 0.87 (d, J = 6.8 Hz, 3 H), 1.02 (s, 9 H), 1.38–1.47 (m, 11 H), 1.60 (s, 3 H), 2.41 (dd, J = 12.8, 8.0 Hz, 1 H), 2.52–2.63 (m, 2 H), 2.75 (dd, J = 15.3, 6.5 Hz, 1 H), 2.93–2.99 (m, 4 H), 3.18 (dd, J = 14.8, 10.3 Hz, 1 H), 3.26 (dd, J = 15.1, 6.0 Hz, 1 H), 4.42–4.49 (m, 2 H), 4.61 (d, J = 5.3 Hz, 2 H), 4.66 (td, J = 8.7, 8.7 Hz, 1 H), 5.04 (d, J = 9.8 Hz, 1 H), 5.22–5.36 (m, 4 H), 5.52 (d, J = 8.3 Hz, 1 H), 5.65 (dd, J = 9.2, 6.2 Hz, 1 H), 5.95 (ddd, J = 17.1, 10.5, 5.5 Hz, 1 H), 6.76 (d, J = 8.3 Hz, 1 H, 23-H), 7.02 (d, J = 8.5 Hz, 1 H), 7.05 (dd, J = 7.0, 7.0 Hz, 1 H), 7.12 (dd, J = 7.2, 7.2 Hz, 1 H), 7.19–7.22 (m, 2 H), 7.46 (d, J = 7.8 Hz, 1 H), 8.29 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, 10.3, 15.7, 16.2, 17.2, 18.3, 22.7, 22.7, 25.6, 28.3, 31.1, 35.2, 40.1, 43.1, 46.5, 49.6, 52.5, 55.5, 65.7, 79.3, 80.1, 106.9, 110.4, 117.9, 118.2, 120.2, 120.7, 121.7, 122.4, 125.6, 125.9, 127.2, 128.4, 130.4, 131.2, 132.7, 134.3, 135.5, 150.9, 155.6, 155.6, 169.2, 170.3, 173.7, 174.4 ppm. HPLC–MS (H_2O/MeCN, 1:9; 0.6 mL/min): t_R = 2.56 min; m/z = 1038 $[C_{50}H_{71}Cl_2N_5O_{11}Si + Na]^+$. HRMS (CI): calcd. for $C_{50}H_{72}Cl_2N_5O_{11}Si$ $[M + H]^+$ 1016.4369; found 1016.4399.

Following the method used for the synthesis of macrocycle **20a**, **20d** was prepared from **20d′** (405 mg, 398 μmol) and TFA (1.23 mL, 15.9 mmol) in anhydrous CH_2Cl_2 (2.9 mL), and *i*Pr_2NEt (0.35 mL, 1.99 mmol) and T3P® (1.00 g, 1.59 mmol) in anhydrous CH_2Cl_2 (100 mL). Purification by flash chromatography (petroleum ether/ethyl acetate, 1:1) gave macrocycle **20d** (185 mg, 206 μmol, 52%) as a colourless solid, m.p. 142–144 °C. $[\alpha]_D^{20}$ = –10.4 (c = 1.7, $CHCl_3$). R_f: 0.28 (petroleum ether/ethyl acetate, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.23 (s, 3 H), 0.24 (s, 3 H), 0.80–0.84 (m, 6 H), 0.88 (d, J = 6.8 Hz, 3 H), 1.04 (s, 9 H), 1.48 (m, 1 H), 1.56–1.62 (m, 4 H), 2.24 (dd, J = 13.7, 2.4 Hz, 1 H), 2.43–2.51 (m, 3 H), 2.85 (dd, J = 16.8, 12.3 Hz, 1 H), 2.91 (dd, J = 14.0, 7.0 Hz, 1 H), 3.18 (dd, J = 14.2, 8.2 Hz, 1 H), 3.33 (s, 3 H), 4.38 (dd, J = 13.3, 4.0 Hz, 1 H), 4.47 (dd, J = 13.6, 5.0 Hz, 1 H), 4.69 (d, J = 9.3 Hz, 1 H), 4.79 (t, J = 7.5 Hz, 1 H), 4.83 (br. s, 1 H), 5.03 (dq, J = 6.3, 6.3 Hz, 1 H), 5.18 (ddt, J = 10.5, 1.3, 1.3 Hz, 1 H), 5.24–5.32 (m, 2 H), 5.60 (dd, J = 7.8, 7.8 Hz, 1 H), 5.82–5.91 (m, 2 H), 6.74 (d, J = 8.3 Hz, 1 H), 6.94 (dd, J = 7.5, 7.5 Hz, 1 H), 7.07–7.13 (m, 2 H), 7.21 (d, J = 8.0 Hz, 1 H), 7.25 (d, J = 2.0 Hz, 1 H), 7.37 (d, J = 7.8 Hz, 1 H), 8.04 (br. s, 1 H), 8.18 (br. s, 1 H), 8.31 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3, 10.3, 13.2, 18.3, 18.6, 18.7, 24.9, 25.6, 27.4, 30.9, 35.1, 41.9, 43.9, 46:7, 49.4, 54.1, 55.2, 65.9, 79.0, 106.2, 110.4, 117.1, 117.4, 120.1, 120.4, 121.9, 122.5, 125.3, 126.6, 126.9, 127.5, 130.4, 131.9, 132.5, 134.3, 136.7, 150.5, 155.1, 168.8, 168.8, 169.1, 173.9 ppm. HPLC–MS (H_2O/MeCN, 3:7; 0.6 mL/min): t_R = 8.54 min; m/z = 920 $[C_{45}H_{61}Cl_2N_5O_8Si + Na]^+$. HRMS (CI): calcd. for $C_{45}H_{61}ClN_5O_8Si$ $[M – Cl]^+$ 862.3972; found 862.3934.

(4*R*,7*R*,10*S*,13*S*,17*R*,18*R*,*E*)-13-Amino-7-(2-chloro-1*H*-indol-3-ylmethyl)-4-(3-chloro-4-hydroxyphenyl)-18-ethyl-8,10,15,17-tetramethyl-1-oxa-5,8,11-triazacyclooctadec-15-en-2,6,9,12-tetraone (20e): TBAF (1 M in THF; 0.12 mL, 0.12 mmol) was added to a solution of **20d** (98.0 mg, 109 μmol) in anhydrous THF (1.1 mL). The mixture was stirred for 1 h at room temperature, then it was diluted with ethyl acetate, washed twice with HCl (1 M aq.) and brine, dried with Na_2SO_4, and concentrated under reduced pressure.

The crude product was dissolved in acetonitrile (0.8 mL), H_2O (0.3 mL), and EtOH (0.3 mL), and was treated with $Pd(OAc)_2$ (1.0 mg, 4.45 μmol), $NHEt_2$ (57.0 μL, 0.55 mmol) and TPPTS [Triphenylphosphine-3,3′,3′′-trisulfonic acid trisodium salt] (3.0 mg, 5.28 μmol) at room temperature.[41] The reaction mixture was stirred for 1 h (complete consumption, TLC control), and then it was concentrated to dryness under reduced pressure. Purification by preparative RP-HPLC (acetonitrile/H_2O) gave macrocycle **20e′** (46.0 mg, 66 μmol, 60%) as a colourless solid, m.p. 134–136 °C. $[\alpha]_D^{20}$ = 24.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80–0.85 (m, 6 H), 0.90 (d, J = 7.0 Hz, 3 H), 1.40 (m, 1 H), 1.54 (m, 1 H), 1.63 (s, 3 H), 2.26 (m, 2 H), 2.59–2.65 (m, 2 H), 2.90 (dd, J = 15.4, 9.2 Hz, 1 H), 2.95 (s, 3 H), 3.18 (dd, J = 15.1, 10.8 Hz, 1 H), 3.41–3.49 (m, 2 H), 4.33 (dq, J = 5.5, 5.5 Hz, 1 H), 4.63 (ddd, J = 7.8, 4.0, 4.0 Hz, 1 H), 4.96 (d, J = 9.3 Hz, 1 H), 5.21 (ddd, J = 8.5, 8.5, 2.8 Hz, 1 H), 5.61 (dd, J = 10.2, 5.4 Hz, 1 H), 6.71 (d, J = 8.3 Hz, 1 H), 6.87 (dd, J = 8.4, 1.6 Hz, 1 H), 7.06 (dd, J = 7.4, 7.4 Hz, 1 H), 7.12 (dd, J = 7.4, 7.4 Hz, 1 H), 7.16 (d, J = 4.8 Hz, 1 H), 7.19–7.21 (m, 2 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.74 (d, J = 7.5 Hz, 1 H), 8.81 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 11.2, 15.5, 16.3, 16.9, 22.1, 23.8, 31.9, 35.5, 40.9, 45.6, 46.9, 50.1, 54.1, 56.7, 80.4, 106.9, 110.6, 116.6, 118.1, 120.1, 120.1, 121.6, 122.2, 125.3, 127.2, 127.3, 128.9, 132.8, 134.4, 134.5, 151.4, 169.7, 171.0, 173.9, 174.0 ppm. HPLC–MS (H_2O/MeCN, 1:1; 0.6 mL/min): t_R = 2.18 min; *m*/*z* = 722 $[C_{35}H_{43}Cl_2N_5O_6 + Na]^+$. HRMS (CI): calcd. for $C_{35}H_{44}Cl_2N_5O_6$ $[M + H]^+$ 700.2663; found 700.2673.

10-(4-{[(4*R*,7*R*,10*S*,13*S*,17*R*,18*R*,*E*)-7-(2-Chloro-1*H*-indol-3-ylmethyl)-4-(3-chloro-4-hydroxyphenyl)-18-ethyl-8,10,15,17-tetramethyl-2,6,9,12-tetraoxo-1-oxa-5,8,11-triazacyclooctadec-15-en-13-yl]amino}-4-oxobutyl)-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*][1,3,2]diazaborinin-4-ium-5-ide (20f): BODIPY **B**[34] (15.0 mg, 30.0 μmol) and *i*Pr_2NEt (7.0 μL, 40 μmol) were added to a solution of macrocycle **20e**·HCl (20.0 mg, 27.0 μmol) in anhydrous CH_2Cl_2 (1.0 mL) and anhydrous DMSO (0.3 mL). The reaction mixture was stirred overnight at room temperature, and then the solvent was removed under reduced pressure. Purification by preparative RP-HPLC (acetonitrile/H_2O) gave macrocycle **20e** (9.0 mg, 8.90 μmol, 33%) as a reddish solid, m.p. 180–182 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81–0.84 (m, 6 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 1.49 (m, 2 H), 1.59 (s, 3 H), 1.80 (m, 1 H), 1.94 (m, 1 H), 2.22–2.54 (m, 12 H), 2.56 (s, 6 H), 2.81–3.03 (m, 4 H), 3.17 (dd, *J* = 13.7, 8.7 Hz, 1 H), 3.36 (s, 3 H), 4.69 (br. s, 1 H), 4.77 (m, 1 H), 5.03 (br. s, 1 H), 5.14 (br. s, 1 H), 5.20 (t, *J* = 9.0 Hz, 1 H), 5.53 (t, *J* = 7.3 Hz, 1 H), 5.97 (s, 2 H), 6.12 (s, 1 H), 6.21 (s, 1 H), 6.64 (s, 1 H), 6.83–6.89 (m, 2 H), 6.93 (dd, *J* = 8.5, 1.8 Hz, 1 H), 6.99 (m, 1 H), 7.15 (d, *J* = 1.8 Hz, 1 H), 7.27 (s, 1 H), 7.78 (s, 1 H), 8.41 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.3, 13.2, 14.6, 16.4, 16.6, 18.7, 18.9, 22.7, 24.8, 27.1, 27.5, 29.7, 30.9, 35.2, 35.8, 41.2, 42.0, 43.9, 49.3, 53.9, 53.9, 78.8, 106.1, 110.3, 115.9, 117.6, 119.4, 120.1, 121.7, 122.2, 125.4, 126.9, 127.5, 129.9, 131.2, 132.4, 134.2, 135.3, 139.7, 140.9, 145.2, 153.8, 168.6, 168.9, 169.2, 169.7, 173.8 ppm. HPLC–MS (H_2O/MeCN, 2:8; 0.6 mL/min): t_R = 1.99 min; *m*/*z* = 1038 $[C_{52}H_{62}BCl_2F_2N_7O_7 + Na]^+$. HRMS (CI): calcd. for $C_{52}H_{63}BCl_2F_2N_7O_7$ $[M + H]^+$ 1016.4222; found 1016.4273.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra as well as HPLC and LC–MS data of all new compounds.

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[1] a) B. Kunze, R. Jansen, F. Sasse, G. Höfle, H. Reichenbach, *J. Antibiot.* **1995**, *48*, 1262–1266; b) R. Jansen, B. Kunze, H. Reichenbach, G. Höfle, *Liebigs Ann.* **1996**, 285–290.

[2] a) P. Crews, L. V. Manes, M. Boehler, *Tetrahedron Lett.* **1986**, *27*, 2797–2800; b) J. C. Braekman, D. Daloze, B. Moussiaux, R. Riccio, *J. Nat. Prod.* **1987**, *50*, 994–995.

[3] a) W. R. Chan, W. F. Tinto, P. S. Manchand, L. J. Todaro, *J. Org. Chem.* **1987**, *52*, 3091–3093; b) E. D. De Silva, R. J. Andersen, T. M. Allen, *Tetrahedron Lett.* **1990**, *31*, 489–492.

[4] a) P. Wipf, *Chem. Rev.* **1995**, *95*, 2115–2134; b) Y. Hamada, T. Shioiri, *Chem. Rev.* **2005**, *105*, 4441–4482; c) F. von Nussbaum, M. Brands, B. Hinzen, S. Weigand, D. Häbich, *Angew. Chem. Int. Ed.* **2006**, *45*, 5072–5129; *Angew. Chem.* **2006**, *118*, 5194–5254; d) F. Desriac, C. Jégou, E. Balnois, B. Brillet, P. Le Chevalier, Y. Fleury, *Mar. Drugs* **2013**, *11*, 3632–3660.

[5] a) S. C. Posey, B. E. Bierer, *J. Biol. Chem.* **1999**, *274*, 4259–4265; b) X. Zhang, X. Cui, L. Cheng, X. Guan, H. Li, X. Li, M. Cheng, *PLoS One* **2012**, *7*, e50899.

[6] L. Xie, A. Forer, *Cell Motil. Cytoskel.* **2008**, *65*, 876–889.

[7] a) C. Odaka, M. L. Sanders, P. Crews, *Clin. Diagn. Lab. Immunol.* **2000**, *7*, 947–952; b) D. P. Cioca, K. Kitano, *Cell. Mol. Life Sci.* **2002**, *59*, 1377–1387; c) M. Matsuki-Fukushima, S. Hashimoto, M. Murakami, Y. Ogata, J. Fujita-Yoshigaki, T. Narita, H. Sugiya, *Arch. Oral Biol.* **2012**, *57*, 567–576.

[8] a) T. Iizuka, R. Fudou, Y. Jojima, S. Ogawa, S. Yamanaka, Y. Inukai, M. Ojika, *J. Antibiot.* **2006**, *59*, 385–391; b) M. Ojika, Y. Inukai, Y. Kito, M. Hirata, T. Iizuka, R. Fudou, *Chem. Asian J.* **2008**, *3*, 126–133.

[9] a) E. Sumiya, H. Shimogawa, H. Sasaki, M. Tsutsumi, K. Yoshita, M. Ojika, K. Suenaga, M. Uesugi, *ACS Chem. Biol.* **2011**, *6*, 425–431; b) L. Karmann, K. Schulz, J. Herrmann, R. Müller, U. Kazmaier, DOI: *Angew. Chem.* **2015**, *127*, DOI:10.1002/ange.201411212.

[10] S. Rachid, D. Krug, B. Kunze, I. Kochems, M. Scharfe, T. M. Zabriskie, H. Blöcker, R. Müller, *Chem. Biol.* **2006**, *13*, 667–681.

[11] J. Herrmann, S. Hüttel, R. Müller, *ChemBioChem* **2013**, *14*, 1573–1580.

[12] D. Becker, U. Kazmaier, *Eur. J. Org. Chem.* **2015**, *12*, 2591–2602.

[13] U. Eggert, R. Diestel, F. Sasse, R. Jansen, B. Kunze, M. Kalesse, *Angew. Chem. Int. Ed.* **2008**, *47*, 6478–6482; *Angew. Chem.* **2008**, *120*, 6578–6582.

[14] a) H. Waldmann, T. S. Hu, S. Renner, S. Menninger, R. Tannert, T. Oda, H. D. Arndt, *Angew. Chem. Int. Ed.* **2008**, *47*, 6473–6477; *Angew. Chem.* **2008**, *120*, 6573–6577; b) R. Tannert, L.-G. Milroy, B. Ellinger, T.-S. Hu, H. D. Arndt, H. Waldmann, *J. Am. Chem. Soc.* **2010**, *132*, 3063–3077.

[15] a) A. Schmauder, L. D. Sibley, M. E. Maier, *Chem. Eur. J.* **2010**, *16*, 4328–4336; b) A. Zhdanko, A. Schmauder, C. I. Ma, L. D. Sibley, D. Sept, F. Sasse, M. E. Maier, *Chem. Eur. J.* **2011**, *17*, 13349–13357.

[16] a) A. Ullrich, Y. Chai, D. Pistorius, Y. A. Elnakady, J. E. Herrmann, K. J. Weissman, U. Kazmaier, R. Müller, *Angew. Chem. Int. Ed.* **2009**, *48*, 4422–4425; *Angew. Chem.* **2009**, *121*, 4486–4489; b) A. Ullrich, J. Herrmann, R. Müller, U. Kazmaier, *Eur. J. Org. Chem.* **2009**, 6367–6378; c) J. Herrmann, R. M. Wiedmann, Y. A. Elnakady, A. Ullrich, M. Rohde, U. Kazmaier, A. M. Vollmar, R. Müller, *PLoS One* **2012**, *7*, e37416, 1–12; d) J. Hoffmann, U. Kazmaier, *Angew. Chem. Int. Ed.* **2014**, *53*, 11356–11360; *Angew. Chem.* **2014**, *126*, 11538–11542.

[17] a) P. K. Jadhav, K. S. Bhat, P. T. Perumal, H. C. Brown, *J. Org. Chem.* **1986**, *51*, 432–439; b) H. C. Brown, R. S. Randad, K. S. Bhat, M. Zaidlewicz, U. S. Racherla, *J. Am. Chem. Soc.* **1990**, *112*, 2389–2392; c) H. C. Brown, K. S. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 5919–5923.

[18] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

[19] a) D. A. Evans, H. P. Ng, J. S. Clark, D. L. Rieger, *Tetrahedron* **1992**, *48*, 2127–2142; b) J. Willwacher, N. Kausch-Busies, A. Fürstner, *Angew. Chem. Int. Ed.* **2012**, *51*, 12041–12076; *Angew. Chem.* **2012**, *124*, 12207–12212.

[20] D. E. Came, T. Weitian, W. R. Ott, *J. Am. Chem. Soc.* **1993**, *115*, 527–553.

[21] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3561–3578.

[22] A. L. Gemal, J.-L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

[23] a) S. D. Rychnovsky, D. J. Skalitxky, *Tetrahedron Lett.* **1990**, *31*, 945–948; b) S. D. Rychnovsky, J. B. Rogers, G. Yang, *J. Org. Chem.* **1993**, *58*, 3511–3515.

[24] R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.

[25] S. Marimganti, R. Wieneke, A. Geyer, M. E. Maier, *Eur. J. Org. Chem.* **2007**, *17*, 2779–2790.
[26] T. Mukhopadhyay, D. Seebach, *Helv. Chim. Acta* **1982**, *65*, 385–391.
[27] B. Neises, W. Steglich, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522–524; *Angew. Chem.* **1978**, *90*, 556–557.
[28] K. Narita, T. Kikuchi, K. Watanabe, T. Takizawa, T. Oguchi, K. Kudo, K. Matsuhara, H. Abe, T. Yamori, M. Yoshida, T. Katoh, *Chem. Eur. J.* **2009**, *15*, 11174–11186.
[29] J. K. Augustine, R. N. Atta, B. K. Ramappa, C. Boodappa, *Synlett* **2009**, 3378–3382.
[30] a) U. Kazmaier, C. Schneider, *Synthesis* **1998**, 1321–1326; b) U. Kazmaier, S. Maier, *Org. Lett.* **1999**, *1*, 1763–1766; c) H. Mues, U. Kazmaier, *Synthesis* **2001**, 487–498.
[31] a) U. Kazmaier, S. Maier, *Tetrahedron* **1996**, *52*, 941–954; b) U. Kazmaier, *J. Org. Chem.* **1996**, *61*, 3694–3699; c) A. Krebs, U. Kazmaier, *Tetrahedron Lett.* **1996**, *37*, 7945–7946; d) U. Kazmaier, H. Mues, A. Krebs, *Chem. Eur. J.* **2002**, *8*, 1850–1855.
[32] a) U. Kazmaier, *Amino Acids* **1996**, *11*, 283–299; b) U. Kazmaier, C. Schneider, *Synlett* **1996**, 975–977; c) U. Kazmaier, C. Schneider, *Tetrahedron Lett.* **1998**, *39*, 817–818.
[33] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis* 2nd ed., John Wiley & Sons, **1991**.
[34] N. Shibata, J. E. Baldwin, A. Jacobs, M. E. Wood, *Tetrahedron* **1996**, *52*, 12839–12852.
[35] C. Prandi, G. Ghigo, E. G. Occhiato, D. Scarpi, S. Begliomini, B. Lace, G. Alberto, E. Artuso, M. Blangetti, *Org. Biomol. Chem.* **2014**, *12*, 2960–2968.
[36] T. Mosmann, *J. Immunol. Methods* **1983**, *65*, 55–63; M. V. Berridge, A. S. Tan, K. D. McCoy, R. Wang, *Biochemica* **1996**, *4*, 14–19.
[37] R. A. Pilli, C. K. Z. de Andrade, C. R. O. Souto, A. de Meijere, *J. Org. Chem.* **1998**, *63*, 7811–7819.
[38] a) D. L. Boger, T. T. Curran, *J. Org. Chem.* **1992**, *57*, 2235–2244; b) P. A. Roethle, I. T. Chen, D. Trauner, *J. Am. Chem. Soc.* **2007**, *129*, 8960–8961; c) C. Roche, N. Desroy, M. Haddad, P. Phansavath, J.-P. Genet, *Org. Lett.* **2008**, *10*, 3911–3914.
[39] R. K. Mann, J. G. Parsons, M. A. Rizzacasa, *J. Chem. Soc. Perkin Trans. 1* **1998**, *7*, 1283–1294.
[40] A. El-Faham, R. S. Funosas, R. Prohens, F. Albericio, *Chem. Eur. J.* **2009**, *15*, 9404–9416.
[41] J. P. Genêt, E. Blart, M. Savignac, S. Lemeune, S. Lemaire-Audoire, J.-M. Paris, J.-M. Bernard, *Tetrahedron* **1994**, *50*, 497–503.

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