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A Matteson Homologation-Based Synthesis of Doliculide and Derivatives

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In memory of Klaus Hafner

Doliculide belongs to a group of marine cyclodepsipeptides with interesting biological properties. Apart from a halogenated dipeptide, a polyketide fragment containing 5 stereogenic centers is the most eye-catching element. This building block can be synthesized in a highly stereoselective fashion using only one key reaction: the Matteson homologation. This straightforward protocol allows for the introduction of a wide range of substituents at almost any position of a growing carbon chain and it is therefore perfectly suited for the synthesis of derivatives for structure-activity relationship studies

Introduction

Cytoskeletal elements such as microtubules and microfilaments play a key role in important cellular processes such as intracellular transport, motion, or cell division. The microfilaments, also called filamentous actin (F-actin) are polymers of a 43 kDa protein named globular actin (G-actin).[1] Approximately 50% of the actin in cells is G-actin. The polymerization is a dynamic process and has to be well balanced for correct cell functioning.[2] Compounds influencing or disturbing this balance are often cytotoxic and suitable candidates for the development of, e.g., anti-cancer drugs. Natural products perturbing the structures and function of the cytoskeleton a therefore powerful tools in chemical biology and lead structures for drug discovery.[3] Although microtubule-targeting compounds have been used in clinical applications for decades,[4] so far no actin-binding compound has made its way into an anticancer drug. One reason might be missing pharmacological data on the mode of action.[1]

A series of cyclodepsipeptides, related to jasplakinolide, have been identified as strong actin-targeting compounds. Jasplakinolide and the structurally closely related geodiamolides were isolated from sponges (Figure 1).[5] The chondramides are the product of terrestrial myxobacteria,[6] while marine myxobacteria are the producers of the miuraenamides.[7] Finally, doliculide was isolated from the sea hare *dolabella auricularia*,[8]

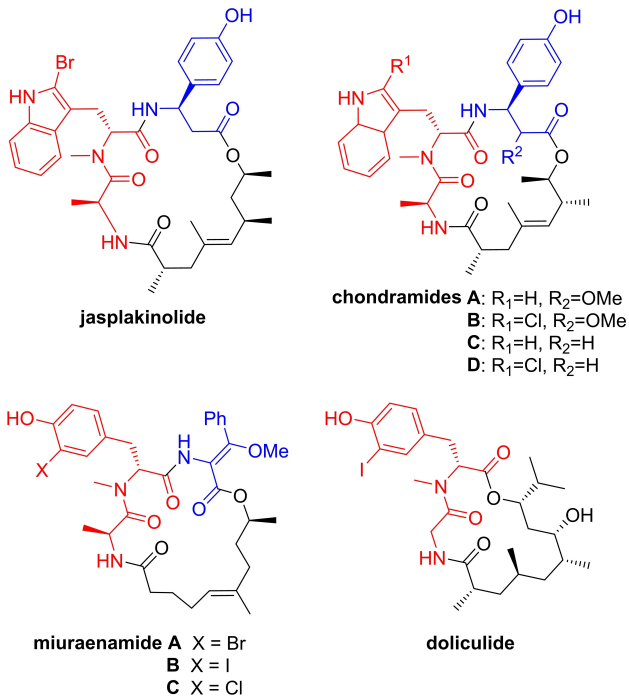

Figure 1. Actin stabilizing natural products.

but probably doliculide is not produced by the nudibranch itself, but by the cyanobacteria it shelters or which it feeds.[9]

All these cyclodepsipeptides show cytotoxicities in the low nM range towards a wide range of tumor cell lines and by far the most biological studies have been carried out with jasplakinolide. Most effects can be explained by stabilization of the actin skeleton,[10] altering e.g. anaphase chromosome movement[11] which finally leads to apoptosis.[12]

The mode of action of the other natural products seems to be very similar. For all these natural products total syntheses have been developed, which allow the synthesis of derivatives for structure-activity-relationship (SAR) studies.[13]

All the cyclodepsipeptides are hybrids of a small peptide fragment and a more or less substituted polyketide unit. The

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peptide fragment is rather conserved, at least at the *N*-terminus (red). In most examples an *N*-terminal alanine is bound to an *N*-methylated halogenated aromatic amino acid, either a tryptophan (jaspamide and chondramides) or a tyrosine (miuraenamide and doliculide). There are also aromatic amino acids (blue) located at the *C*-terminus of the tripeptides, but this position is varied significantly. Here, α- or β-amino acid can be incorporated, which might be substituted or unsaturated. Even the double bound geometry in the miuraenamides has no significant effect on cytotoxicity.[14] In contrast, halogenation at the central amino acid seems to be essential, since biological activity dramatically drops for (natural) derivatives missing this substituent.[15]

Since a couple of years, our group is involved in the synthesis of (modified) natural products addressing the cytoskeleton, either the microtubule[16] or the actin filaments.[17] Recently, we developed flexible syntheses for the miuraenamides, allowing modifications at the flexible *C*-terminus of the tripeptide *via* late-stage peptide modification, which allowed us to synthesize a library with >50 members of this natural product for SAR studies.[14,18]

The dehydroamino acid can be easily replaced by other nonpolar side chains or can even be removed completely without significant loss of activity, which was very surprising. Based on these SAR studies molecular dynamic simulations suggest that the bromophenol side chain interacts in a specific orientation with three aromatic amino acids in a binding pocket of actin, initiating polymerization.[19] Obviously, the *C*-terminal amino acid is not involved in binding and sticks out of the binding pocket. This nicely explains the high variability at this position and the non-variability of the conserved central amino acid. Interestingly, miuraenamide also influences cancer cell migration at 20 nM concentration, a concentration where no other cytotoxic effects are observed.[20]

Comparing the structures of the different cyclodepsipeptides (Figure 1) it is obvious, that one compound, doliculide, is significantly different from all the others. While the "conserved peptide part" (red) is almost the same as in the other examples, the flexible *C*-terminal amino acid (blue) is completely missing. Instead, a prolonged, more complex polyketide chain is incorporated. The biological activities are nevertheless very similar to the other natural products. It is reported that doliculide exhibits potent cytotoxicity towards HeLa-S_3 cells with an IC_{50} value of 1 ng/ml.[21] It is found to destroy actin stress fibers in cells and to initiate actin aggregation leading to inhibition of proliferation and finally to apoptosis.[22] Detailed studies at subtoxic doses showed that doliculide leads to a transient change in reversible cytoskeleton dynamics and induction of premature senescence.[23] There is also evidence that doliculide acts as a subtype-selective antagonist of prostaglandin E receptor 3.[24] It is not surprising, that this compound also got into the focus of synthetic chemistry.

So far seven different routes towards doliculide are described. The synthesis of the rather small peptide is not a serious issue, but the polyketide fragment with its five stereogenic centers is not trivial. The first synthesis was reported by the group of Yamada, which also isolated the natural product.[21] They used a combination of Evans aldol reaction and Barton deoxygenations to remove undesired OH-groups. This reliable protocol was used to confirm the configuration of the stereogenic centers but resulted in a rather long linear synthetic sequence (28 steps) for the polyketide fragment. The synthesis of Ghosh and Liu using asymmetric cyclopropanations/Sharpless epoxidations and ring opening reactions as key steps required a similar number of steps.[25] Hanessian et al. used more or less stereoselective iterative substrate-controlled cuprate additions onto α,β-unsaturated esters to generate the *syn/syn* methylation pattern of the polyketide.[26] Hirsch and Minaard in cooperation with the Waldmann group synthesized doliculide *via* a similar approach using Josiphos as a chiral ligand to control the stereochemical outcome of the cuprate additions.[27] They also carried out molecular modelling studies to determine the binding mode toward actin. The iodo tyrosine binds into a cavity formed by aromatic amino acids of G-actin and the iodine probably undergoes lipophilic interactions. The isopropyl group is not involved in binding and sticks out of the cavity. The binding mode seems to be similar to that of the miuraenamides. The shortest syntheses so far for the polyketide fragment were reported by Chen and Altmann, who developed two independent routes. A key step herein is a hydroxyl-directed catalytic hydrogenation of a trisubstituted double bond, which was obtained either *via* a modified Suzuki-Miyaura coupling or *via* Ireland Claisen rearrangement.[28] This allowed the synthesis of a suitably protected polyketide fragment in only 11 or 9 steps respectively. Zhou et al reported a synthetic route using asymmetric hydrogenations to introduce the stereogenic centers in the polyketide chain.[29] Very recently Yadar et al. reported an approach based on asymmetric Evans alkylations and Sharpless epoxidations.[30]

Results and Discussion

Because of the obvious similarities in the binding mode of doliculide and the miuraenamides, especially with the assumption that the C-terminus of the polyketide might be variable we became interested in the development of a synthesis that gives us high flexibility at exactly this position. Replacing the isopropyl group with other functionalities might influence the pharmacological properties of doliculide without affecting the biological activity and mode of action significantly. While most reported syntheses prepare the polyketide from the C-terminus toward the carboxyl functionality we wanted to go the opposite way, introducing the isopropyl group preferentially in the (almost) last step.

Recently, we developed a synthesis for lagunamides, members of the aurilide family,[31] also containing an interesting polyketide fragment. The whole alkyl chain was synthesized from the C-terminus via six consecutive Matteson homologations (Scheme 1).[32] This stereoselective prolongation of chiral boronic esters was introduced by Donald Matteson in the early 1980's.[33] A key step in this protocol is the highly stereoselective formation of an α-chloro boronic ester **A** (Scheme 1) which can be subjected to nucleophilic substitution under S_N2-conditions.

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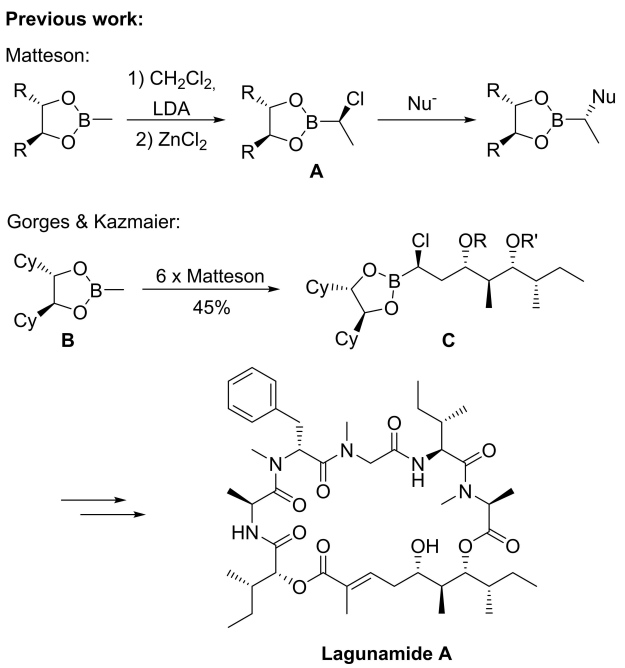
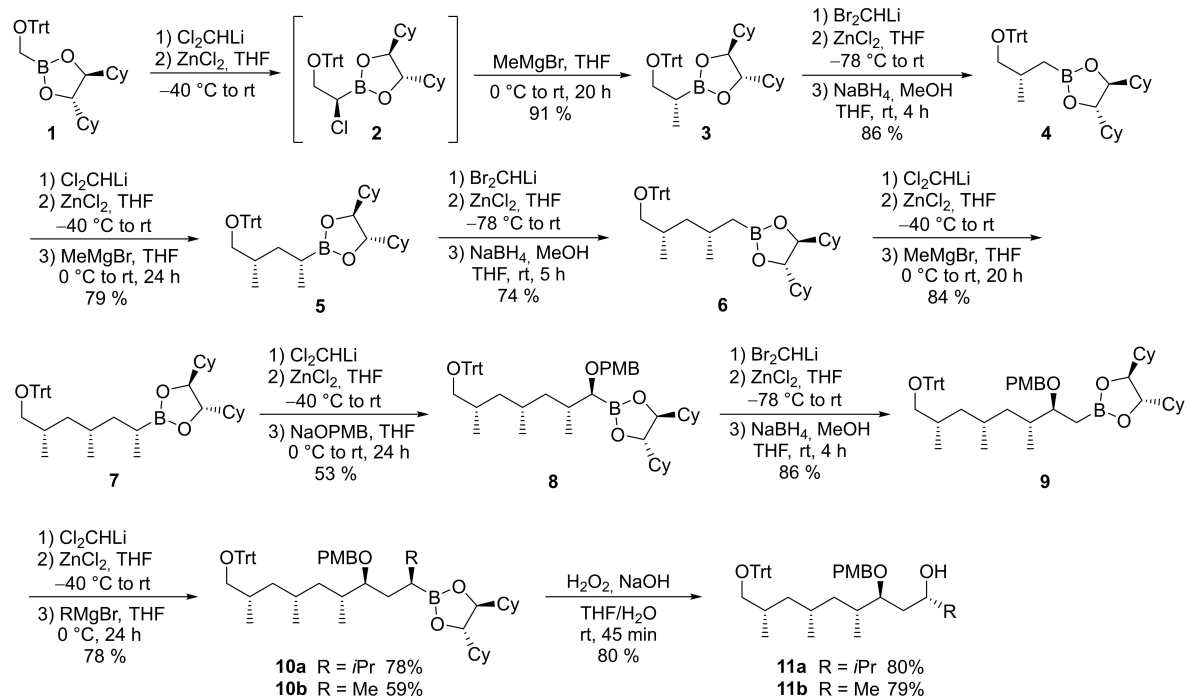


Scheme 1. Matteson homologation and application.

A wide range of nucleophiles can be used,[34] such as Grignard reagents, alkoxides or certain enolates.[35] This allows the stepwise stereoselective incorporation of all kinds of substituents and functionalities into a growing carbon chain and is therefore especially suited for natural product modifications. For example, apratoxin A and B, two highly cytotoxic marine cyclodepsipeptides have been synthesized in an analogues fashion.[36]

To apply this protocol to the synthesis of the desired polyketide from the carboxyl terminus toward the end of the alkyl chain, we started with trityl-protected boronic ester **1** (Scheme 2).[37] Reaction with deprotonated methylene chloride and the addition of zinc chloride provided α-chloro boronic ester **2** which was directly subjected to a Grignard addition as a one-pot reaction. The next prolongation step was carried out with lithiated dibromomethane. In this case an analogous α-bromo boronic ester is formed which is more reactive than the chloro derivative, but also more sensitive to epimerization.[38] For the introduction of a CH_2-group, this problem is not relevant. The bromo intermediate was directly reduced with $NaBH_4$ to **4**. Repeating these steps finally gave rise to boronic ester **7**. Next, we had to introduce the *O*-functionality. Although alcoholates are versatile nucleophiles in Matteson reactions, in this case the yields are often lower. In general, migration of an alkoxy group is slower compared to a *C*-nucleophile, but DMSO was found to be a useful additive, accelerating this migration step.[39]

The next CH_2-incorporation onto **8** proceeded nicely, while the introduction of the isopropyl group required some optimizations. In this case, the direct reaction of the α-chloro boronic ester in a one pot protocol resulted in a mixture of several products. Better results were obtained if the α-chloro boronic ester was isolated before further use. Final oxidation of boronic ester **10a** led to the desired protected polyketide precursor **11a**. Similarly, boronic ester **9** was converted to the boronic ester **10b** and then oxidized to the modified polyketide



Scheme 2. Synthesis of polyketide precursors **11**.

11 b in which the isopropyl group was replaced by a methyl group.

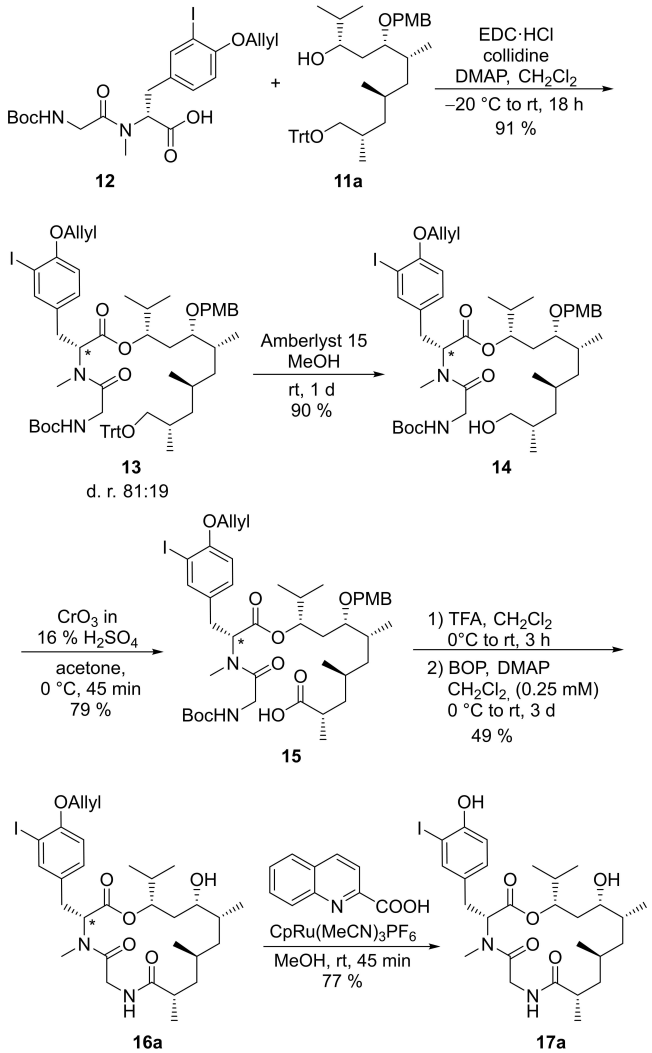
With alcohol **11 a** in hand we next tried to finalize the synthesis of doliculide (Scheme 3). Steglich esterification[40] with the modified peptide **12** using EDC gave the desired product **13** in good yield, but unfortunately partial epimerization of the tyrosine moiety was observed. An allyl protecting group was used on the phenolic OH since it can easily be removed under Ru-catalyzed conditions[41] and it is more stable towards basic reaction conditions than the commonly used silyl protecting groups. Nevertheless, we wanted to finalize the synthesis and determine which final steps are suitable to get the desired products.

With Amberlyst 15 the trityl protecting group could be removed selectively without effecting the Boc- and the PMB protecting group and Jones oxidation didn't cause any problems. The subsequent cyclization step was more critical. First of all we used Schmidt's pentafluorophenyl ester protocol[42] for cyclization. **15** was activated first before the acid labile Boc- and PMB protecting groups were removed. The ammonium salt was added dropwise to a vigorously stirred suspension of saturated $NaHCO_3$ and $CHCl_3$, simulating high dilution conditions, but the yield could not be increased to more than 18 %. Similar results were obtained if the protecting groups were removed first and coupling agents such as HATU/HOAt[43] or PyBOP[44] were added. To the present, the best results were obtained with BOP[45] in 0.25 mM solutions, as reported by Chen and Altmann.[28] Finally, the allyl protecting group was removed from **16 a** using $CpRu(MeCN)_3PF_6$,[41] and on the stage of the natural product **17 a** the epimer formed in the peptide coupling step could be separated by preparative HPLC.

To increase the yield and to circumvent the problem of peptide epimerization we decided to also investigate a ring closure between the glycine and the *N*-methyl tyrosine (Scheme 4). Although, peptide couplings with *N*-alkylated amino acids are sometimes critical, in this case this approach makes sense, because the glycine cannot epimerize in the cyclization step and activation of *N*-methylated amino acids is less critical than in the case of peptides.

Since in many marine depsipeptides common halogens (Cl, Br, I) are incorporated (Figure 1) and often best activities in SAR studies are obtained with iodinated and brominated derivatives, we decided to couple **11 a** with both, the brominated and the iodinated tyrosines **18** (Scheme 4), while **11 b** was only coupled with the original iodinated tyrosine **18 a**. No epimerizations were observed in these cases. Selective trityl-deprotection and Jones oxidation were as successful as in the previous case. Subsequent coupling with glycine *tert*-butylester provided peptides **21**, which were subjected to cyclization. Indeed, under the conditions using BOPCl for activation the doliculide precursors could be obtained in good yields.[29] To our surprise, while measuring the NMR spectra in non-stabilized $CDCl_3$, doliculide was chlorinated at the tyrosine moiety to the derivative **17 d**.

With these doliculide derivatives **17** in hand we undertook the first SAR studies to determine if the halogenation pattern of the tyrosine derivative and the substituent at the end of the polyketide chain plays a significant role. The cytotoxicity of our compounds was investigated with five cancer cell lines, and the results are summarized in Table 1.



Scheme 3. Synthesis of doliculide (**17 a**) (first generation).

Table 1. IC_{50}-values (in nM) of doliculide derivatives towards different human tumor cell lines.[a]

Derivative	HCT-116	U-2 OS	HepG2	KB3.1	CHO-K1
17a	8.8 ±0.5	25.1 ±1.8	16.4 ±4.2	38.0 ±9.9	110.8 ±4.5
17b	7.5 ±0.3	35.7 ±5.9	13.3 ±1.0	35.9 ±7.3	137.0 ±12.4
17c	6.7 ±0.7	40.7 ±4.2	10.9 ±0.2	35.3 ±11.4	115.5 ±16.5
17d	2350.3 ±506.9	1981.6 ±537.7	>5683.7	1797.3 ±445.5	10369.0 ±414.8
16a	10662.5 ±3306.4	9834.0 ±2040.8	6306.7 ±2161.1	6539.8 ±3103.9	19951.3 ±654.9

[a] HCT-116: human colon carcinoma; U-2 OS: human bone osteosarcoma; HepG2: human hepatocellular carcinoma; CHO-K1: mutagenized Chinese hamster ovary; KB3.1: human epidermoid carcinoma cell line.

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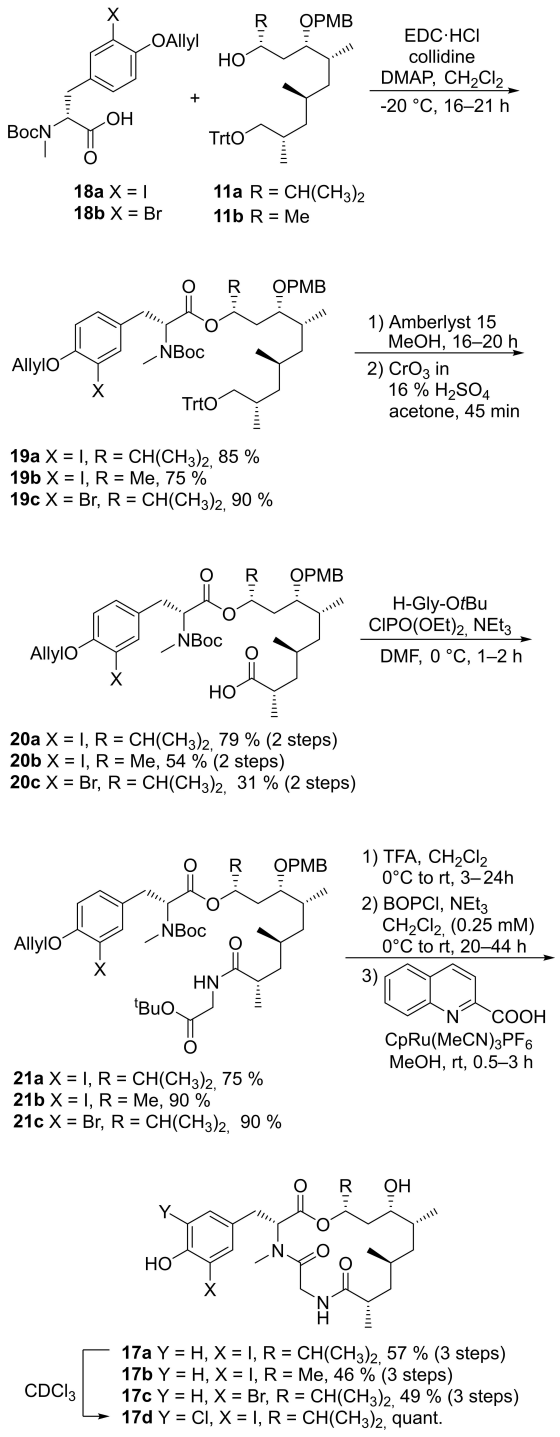

Scheme 4. Syntheses of doliculides (second generation).

Although cytotoxicity varied, depending on the sensitivity of the cancer cell line, a general trend was obvious. Replacing the iodine on the tyrosine with a bromine (**17a**/**17c**) had no significant effect. Also, the replacement of the isopropyl group by a small methyl substituent (**17b**) provided an almost equipotent derivative. The introduction of a second halogen atom (**17d**) resulted in a significant drop in activity, and the *O*-protected derivative **16a** was not active at all. These results are in good agreement with observations made with the miuraenamide derivatives earlier,[18,19] and with the calculations made by Minaard, Hirsch and Waldmann.[27]

Conclusions

In summary, we showed that doliculides are easily accessible via Matteson homologation. With this single reaction all stereogenic centers of the polyketide fragment can be obtained in a highly stereoselective fashion. This protocol should also allow for the synthesis of all kinds of derivatives by the proper choice of the nucleophiles used in the homologation steps. The substituent at the stereogenic center introduced last obviously does not play a significant role in binding, which shows the potential of this method. Syntheses of further derivatives for SAR studies are currently in progress.

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. THF was distilled over Na/benzophenone prior to use. Dry MeOH was prepared by distillation over Mg prior to use. $ZnCl_2$ was fused in vacuo at 0.1 mbar prior to use, ethyl acetate and petroleum ether (petroleum ether) were distilled prior to use. Reactions were monitored by analytical TLC, which was performed on precoated silica gel on TLC PET-foils by *Macherey Nagel*. Visualization was accomplished with UV-light (254 nm), $KMnO_4$ solution or Ce(IV) / ammonium molybdate solution. The products were purified by flash chromatography on silica gel columns (*Macherey-Nagel* 60, 0.063–0.2 mm or 0.04–0.063 mm) or by automated flash chromatography (*Büchi Reveleris Prep*, *Teledyne Isco RediSep* R_f silica cartridges or *Kinesis* silica C18 cartridges). Preparative HPLC was performed on a *Büchi Reveleris* Prep Chromatography System using a *Phenomenex Luna* C18(2) 100 Å column (250× 21.1 mm, 5 μm). Melting points were determined with a melting point apparatus *MEL-TEMP II* by *Laboratory Devices* and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a *Bruker AV II 400* [400 MHz (^1H), 100 MHz (^{13}C)], a Bruker *AV 500* [500 MHz, (^1H), 125 MHz (^{13}C)] or a *Bruker AV 500 Neo* [500 MHz, (^1H), 125 MHz (^{13}C)] spectrometer. NMR spectra were evaluated using *NMR Processor* Version 12.01 from *ACD*. Chemical shifts are reported in ppm relative to $Si(CH_3)_4$ and the solvent residual peak was used as the internal standard. Multiplicities are reported as bs (broad signal), s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Signals marked with * in ^{13}C NMR give broad signals. High resolution mass spectra were recorded with a *Finnigan MAT 95* spectrometer using the CI technique (CI), a *Bruker Daltonics maXis 4G hr-ToF* using the ESI technique (ESI-ToF) or a *Bruker solariX* using the ESI technique (ESI-FTICR). HPLC analyses were performed on a *Shimadzu LC-2030* chromatograph with a diode array detector and *Shimadzu LCMS-2020* mass spectrometer using the ESI technique on a *Phenomenex Onyx Monolithic* C18 column (50×4.6 mm). Optical rotations were measured with a *Perkin-Elmer* polarimeter (*Model 341*) or a *Jasco P-2000* polarimeter in thermostated (20 °C±1 °C) cuvettes and are given in 10^{-1} deg cm^2 g^{-1}. The radiation source used was a sodium vapor lamp (λ = 589 nm). The concentrations are given in g/100 mL.

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General procedures (GPs)

GP 1: Matteson homologation with $CHCl_2Li$ and reaction with nucleophiles: A solution of 1.35–1.45 equiv. of diisopropylamine (DIPA) in anhydrous THF (0.2 mL/mmol) was cooled to –40 °C and 1.25–1.35 equiv. *n*-BuLi (1.6 M or 2.5 M in hexane) were added slowly. The mixture was stirred at this temperature for 10 min and further 20 min at room temperature. In another flask 1.0 equiv. of the boronic ester and 3.0–3.25 equiv. of dichloromethane was dissolved in anhydrous THF (1.4 mL/mmol) and cooled to −40 °C. The previously prepared LDA solution was added slowly, and the mixture stirred for 10 min at this temperature. A solution of freshly fused 2.0–4.0 equiv. $ZnCl_2$ in anhydrous THF (0.6 mL/mmol) was then added and the mixture stirred at room temperature for 2 h. After homologation, the resulting chloroboronic ester solution was cooled to 0 °C and 1.0–2.5 equiv. of the nucleophile was added. The reaction mixture was warmed to room temperature and stirred for 20–24 h before it was treated with saturated NH_4Cl and pentane. The organic phase was separated, and the aqueous phase was extracted twice with pentane. The combined organic layers were dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified using column chromatography.

For compounds **10a**–**10b** the procedure was slightly modified. The chloroboronic ester was isolated after the homologation step. The reaction mixture was treated with saturated NH_4Cl and pentane. The organic phase was separated, and the aqueous phase extracted twice with pentane. The combined organic phases were dried over Na_2SO_4 and the solvent removed in vacuo. The crude chloroboronic ester was dissolved in anhydrous THF (4 mL/mmol) and then the nucleophile (1.2–1.5 equiv.) was added at 0 °C, warmed to room temperature and stirred for 90 min.

GP 2: Matteson-homologation with $CHBr_2Li$ and reduction with $NaBH_4$: A solution of 1.35–1.45 equiv. of DIPA in anhydrous THF (0.2 mL/mmol) was cooled to −40 °C and 1.25–1.35 equiv. *n*-BuLi (1.6 M or 2.5 M in hexane) were added slowly. The mixture was stirred at this temperature for 10 min and further 20 min at room temperature. In another flask 1.0 equiv. of the boronic ester and 3.0 equiv. of dibromomethane were dissolved in anhydrous THF (1.4 mL/mmol) and cooled to −78 °C. The previously prepared LDA solution was added slowly, and the mixture stirred for 1 h at this temperature. A solution of freshly fused 2.0–4.0 equiv. $ZnCl_2$ in anhydrous THF (0.6 mL/mmol) was then added and the mixture slowly warmed to room temperature overnight. After homologation, the mixture was treated with saturated NH_4Cl and pentane. The organic phase was separated, and the aqueous phase was extracted twice with pentane. The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was dissolved in MeOH/THF 3:1 (10 mL/mmol) and 1.0–1.7 equiv. $NaBH_4$ was added at room temperature. The mixture was stirred for 4–5 h and then treated with saturated NH_4Cl and pentane. The organic phase was separated, and the aqueous phase extracted twice with pentane. The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was then purified using column chromatography.

GP 3: Oxidation of boronic esters: 1.0 equiv. of the boronic ester was dissolved in THF (2 mL/mmol) and cooled to 0 °C. 5.0 equiv. of 33% H_2O_2 solution and 5.0 equiv. of NaOH in water (2 mL/mmol) were added. The mixture was warmed to room temperature and stirred for 45 min. Sat. NaCl was added and the mixture extracted three times with diethyl ether. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by chromatography to separate the desired alcohol and the chiral auxiliary (*S*,*S*)-DICHED.

GP 4: Steglich esterification: 1.0 equiv. of the alcohol and 3.0 equiv. of the free carboxylic acid were dissolved in anhydrous dichloromethane (20 mL/mmol) and cooled to −20 °C. To this solution 0.35 equiv. DMAP, 3.0 equiv. EDC·HCl and 3.0 equiv. collidine were added. The reaction mixture was stirred for 16–21 h at −20 °C and then diluted with ethyl acetate. The organic phase was washed with 1 M $KHSO_4$, saturated $NaHCO_3$ and saturated NaCl solution. The organic phase was dried over Na_2SO_4 and the solvent removed in vacuo. The crude product was then purified using column chromatography.

GP 5: Trityl deprotection: A solution of 1.0 equiv. trityl ether was dissolved in MeOH (20 mL/mmol) and 100 wt% of Amberlyst 15 were added at room temperature. The mixture was stirred for 16–20 h and then diluted with ethyl acetate. The solid Amberlyst 15 was removed by filtration and then stirred in ethyl acetate for 1 h. Amberlyst was again removed by filtration and the combined organic phases were washed with water. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified using column chromatography.

GP 6: Jones oxidation: A 3 M Jones reagent solution in 16% H_2SO_4 was prepared by dissolving 100 mg of CrO_3 in 316 µl H_2O and 60 µl conc. H_2SO_4. 1.0 equiv. of the alcohol was dissolved in acetone (10 mL/mmol) and cooled to 0 °C. To this solution 2.5 equiv. of the Jones reagent was added and stirred for 45 min. The reaction was quenched with *iso*-propanol and the solvent removed in vacuo. The residue was diluted with water and ethyl acetate and the organic phase was separated. The aqueous phase was extracted twice with ethyl acetate and the combined organic extract were washed with saturated NaCl solution and dried over Na_2SO_4. The solvent was removed in vacuo and the residue subjected to chromatography.

GP 7: Coupling with glycine *tert*-butylester: To a solution of 1.0 equiv. carboxylic acid and 1.33 equiv. glycine *tert*-butylester hydrochloride in anhydrous DMF (5 mL/mmol) was added 2.5 equiv. triethylamine and 2.3 equiv. diethyl cyanophosphonate at 0 °C. The mixture was stirred for 1 h and diluted with brine and diethyl ether. The aqueous layer was extracted twice with diethyl ether and the combined organic extracts were dried over Na_2SO_4. The solvent was removed in vacuo and the residue subjected to chromatography.

GP 8: Macrocyclization with BOP-Cl: A solution of 1.0 equiv. of the linear precursor in anhydrous dichloromethane (45 mL/mmol) was treated with trifluoroacetic acid (30 mL/mmol) at 0 °C. The cooling bath was removed, and the mixture stirred for another 3 h at room temperature. The solvent was removed in N_2 stream and azeotropically distilled with benzene. The residue was further dried in high vacuum for 3 h and then dissolved in dichloromethane (0.25 mM). The solution was cooled to 0 °C and 10.0 equiv. NEt_3 and 5.0 equiv. BOP-Cl were added. The mixture was slowly warmed to room temperature and stirred for 20–44 h, before it was washed with 0.1 M HCl, sat. $NaHCO_3$, sat. NH_4Cl and sat. NaCl solutions. The organic phase was dried over Na_2SO_4 und the solvent removed in vacuo. The residue was dissolved in MeOH (60 mL/mmol), aqueous ammonia was added (1 drop/4 mmol) and the solution was stirred at room temperature for 1 h to saponify the trifluoroacetate that originated during deprotection step. The solvent was removed in vacuo and the residue purified by reversed-phase flash chromatography and lyophilized.

GP 9: Allyl ether deprotection:

Method A: 1.0 equiv. of the allyl ether was dissolved in anhydrous MeOH (15 mL/mmol) under N_2-atmosphere and 0.2 equiv. quinaldic acid (0.05 M in anhydrous MeOH) and 0.2 equiv. of $[CpRu(NCMe)_3]PF_6$ (0.025 M in *anhydrous* MeOH) were added at

room temperature. After 45 min – 3 h the solvent was removed in vacuo and the residue purified by reversed-phase flash chromatography. The compound was further purified by preparative HPLC.

Method B: Freshly dried MeOH was degassed via 3 freeze-pump-thaw cycles. A 0.01 M stock solution of $[CpRu(NCMe)_3]PF_6$ and quinaldic acid was prepared in degassed MeOH and stirred for 30 min at room temperature. 1.0 equiv. of the allyl ether was dissolved in degassed anhydrous MeOH (15 mL/mmol) and 0.05 equiv. of the Ru-catalyst stock solution was added at room temperature. After 25–90 min the solvent was removed in vacuo and the residue purified by reversed-phase chromatography. The compound was further purified by preparative HPLC and lyophilized.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-[(*R*)-1-(trityloxy)propan-2-yl]-1,3,2-dioxaborolane (3): According to GP 1 boronic ester **1** (11.7 g, 23.1 mmol), dichloromethane (4.82 mL, 74.9 mmol), diisopropylamine (4.76 mL, 33.2 mmol), *n*-butyllithium (12.5 mL, 31.1 mmol, 2.5 M in hexane), zinc chloride (9.42 g, 69.1 mmol) and methylmagnesium bromide (19.2 mL, 57.6 mmol, 3 M in diethyl ether) were reacted to give boronic ester **3** in 91% yield (11.2 g, 20.9 mmol) as a colorless solid after column chromatography (petroleum ether:ethyl acetate 98:2). M.p. 91 °C. R_f (**3**) = 0.35 (silica, petroleum ether:ethyl acetate 98:2). $[\alpha]_D^{20} = -36.4$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (m, 2 H), 1.01 (d, *J* = 7.5 Hz, 3 H), 1.06 (m, 2 H), 1.11–1.26 (m, 6 H), 1.32 (m, 2 H), 1.47 (ddq, *J* = 7.5, 7.2, 6.7 Hz, 1 H), 1.55–1.68 (m, 4 H), 1.68–1.80 (m, 6 H), 3.04 (dd, *J* = 8.2, 7.2 Hz, 1 H), 3.18 (dd, *J* = 8.2, 6.7 Hz, 1 H), 3.85 (m, 2 H), 7.20 (m, 3 H), 7.26 (m, 6 H), 7.46 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.0, 18.3*, 25.9, 26.0, 26.4, 27.3, 28.3, 43.0, 66.6, 83.3, 86.1, 126.7, 127.5, 128.8, 144.6 ppm. HRMS (CI) calcd. for $C_{36}H_{45}O_3{}^{11}B^+$ $[M]^+$: 536.3456 found 536.3483.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-[(*S*)-2-methyl-3-(trityloxy)propyl]-1,3,2-dioxaborolane (4): According to GP 2 boronic ester **3** (7.77 g, 14.5 mmol), dibromomethane (3.04 mL, 43.5 mmol), diisopropylamine (2.99 mL, 21.0 mmol), *n*-butyllithium (7.83 mL, 19.6 mmol, 2.5 M in hexane), zinc chloride (5.93 g, 43.5 mmol) and sodium borohydride (548 mg, 14.5 mmol) were reacted to give boronic ester **4** in 86% yield (6.84 g, 12.4 mmol) as a colorless solid after column chromatography (petroleum ether:ethyl acetate 98:2). M.p. 60 °C. R_f (**4**) = 0.27 (silica, petroleum ether:ethyl acetate 98:2). $[\alpha]_D^{20} = -16.7$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69 (dd, *J* = 15.7, 8.7 Hz, 1 H), 0.91–0.98 (m, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 1.05 (m, 2 H), 1.11–1.23 (m, 6 H), 1.25–1.31 (m, 2 H), 1.56 (m, 2 H), 1.67 (m, 2 H), 1.70–1.79 (m, 6 H), 2.08 (m, 1 H), 2.82 (dd, *J* = 8.6, 7.1 Hz, 1 H), 2.91 (dd, *J* = 8.6, 6.1 Hz, 1 H), 3.78 (m, 2 H), 7.21 (m, 3 H), 7.28 (m, 6 H), 7.45 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8*, 19.9, 25.9, 26.0, 26.5, 27.5, 28.5, 30.5, 43.0, 70.3, 83.3, 86.1, 126.7, 127.6, 128.8, 144.6 ppm. HRMS (CI) calcd. for $C_{37}H_{47}O_3{}^{11}B^+$ $[M]^+$: 550.3613 found 550.3583.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-[(2*R*,4*S*)-4-methyl-5-(trityloxy)pentan-2-yl]-1,3,2-dioxaborolane (5): According to GP 1 boronic ester **4** (8.80 g, 16.0 mmol), dichloromethane (3.09 mL, 48.0 mmol), diisopropylamine (3.08 mL, 21.8 mmol), *n*-butyllithium (8.00 mL, 20.0 mmol, 2.5 M in hexane), zinc chloride (6.54 g, 48.0 mmol) and methylmagnesium bromide (13.3 mL, 48.0 mmol, 3 M in diethyl ether) were reacted to give boronic ester **5** in 82% yield (7.55 g, 13.1 mmol) as a colorless solid after column chromatography (petroleum ether:ethyl acetate 98:2). M.p. 55–60 °C. R_f (**5**) = 0.40 (silica, petroleum ether:ethyl acetate 98:2). $[\alpha]_D^{20} = -7.4$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91–1.00 (m, 8 H), 1.01–1.12 (m, 4 H), 1.13–1.25 (m, 6 H), 1.33 (m, 2 H), 1.61 (m, 2 H), 1.63–1.70 (m, 3 H), 1.71–1.82 (m, 6 H), 1.90 (m, 1 H), 2.82 (dd, *J* = 8.5, 6.9 Hz, 1 H), 2.96 (dd, 1 H), 3.83 (m, 2 H), 7.22 (m, 3 H), 7.29 (m, 6 H), 7.46 (m, *J* = 8.5, 5.5 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9*, 16.5, 17.8, 25.9, 26.0, 26.5, 27.4, 28.3, 32.9, 37.7, 43.1, 68.5, 83.1, 85.9, 126.7, 127.6, 128.8, 144.6 ppm. HRMS (CI) calcd. for $C_{39}H_{52}O_3{}^{11}B^+$ $[M]^+$: 579.4004 found 579.4020.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-[(2*S*,4*S*)-2,4-dimethyl-5-(trityloxy)pentyl]-1,3,2-dioxaborolane (6): According to GP 2 boronic ester **5** (7.03 g, 12.1 mmol), dibromomethane (2.54 mL, 36.4 mmol), diisopropylamine (2.34 mL, 16.4 mmol), *n*-butyllithium (6.07 mL, 15.2 mmol, 2.5 M in hexane), zinc chloride (4.96 g, 36.4 mmol) and sodium borohydride (459 mg, 12.1 mmol) were reacted to give boronic ester **6** in 71% yield (5.14 g, 8.70 mmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 98:2). R_f (**6**) = 0.25 (silica, petroleum ether:ethyl acetate 98:2). $[\alpha]_D^{20} = -10.7$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61 (dd, *J* = 15.7, 8.8 Hz, 1 H), 0.84–0.92 (m, 6 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 1.00–1.12 (m, 3 H), 1.14–1.25 (m, 6 H), 1.27–1.35 (m, 4 H), 1.61 (m, 2 H), 1.68 (m, 2 H), 1.73–1.80 (m, 6 H), 1.84 (m, 1 H), 2.81 (dd, *J* = 8.7, 7.1 Hz, 1 H), 2.99 (dd, *J* = 8.7, 5.1 Hz, 1 H), 3.80 (m, 2 H), 7.22 (m, 3 H), 7.29 (m, 6 H), 7.46 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0, 18.5, 23.0, 25.9, 26.0, 26.5, 26.8, 27.5, 28.5, 31.6, 43.1, 44.0, 68.7, 83.2, 86.1, 126.7, 127.6, 128.8, 144.6 ppm. HRMS (CI) calcd. for $C_{40}H_{53}O_3{}^{11}B^+$ $[M]^+$: 592.4082 found 592.4076.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-[(2*S*,4*S*)-2,4-dimethyl-5-(trityloxy)pentyl]-1,3,2-dioxaborolane (7): According to GP 1 boronic ester **6** (4.51 g, 7.60 mmol), dichloromethane (1.47 mL, 22.8 mmol), diisopropylamine (1.46 mL, 10.3 mmol), *n*-butyllithium (5.94 mL, 9.5 mmol, 1.6 M in hexane), zinc chloride (3.11 g, 22.8 mmol) and methylmagnesium bromide (6.33 mL, 19.0 mmol, 3 M in diethyl ether) were reacted to give boronic ester **7** in 84% yield (3.98 g, 6.41 mmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 98:2). R_f (**7**) = 0.21 (silica, petroleum ether:ethyl acetate 97:3). $[\alpha]_D^{20} = -20.1$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.5 Hz, 3 H), 0.86–0.92 (m, 2 H), 0.92–1.00 (m, 8 H), 1.05 (m, 2 H), 1.12–1.14 (m, 7 H), 1.29 (m, 3 H), 1.46 (m, 1 H), 1.56–1.63 (m, 3 H), 1.67 (m, 2 H), 1.72–1.81 (m, 6 H), 1.86 (m, 1 H), 2.80 (dd, *J* = 8.7, 7.2 Hz, 1 H), 2.96 (dd, *J* = 8.7, 5.4 Hz, 1 H), 3.81 (m, 2 H), 7.22 (m, 3 H), 7.29 (m, 6 H), 7.45 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1*, 16.9, 16.2, 20.9, 25.9, 26.0, 26.5, 27.4, 28.3, 29.4, 31.4, 40.9, 42.0, 43.1, 68.9, 83.1, 86.1, 126.7, 127.6, 128.8, 144.6 ppm. HRMS (CI) calcd. for $C_{42}H_{57}O_3{}^{11}B^+$ $[M]^+$: 620.4395 found 620.4357.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-{(1*S*,2*R*,4*R*,6*S*)-1-[(4-methoxybenzyl)oxy]-2,4,6-trimethyl-7-(trityloxy)heptyl}-1,3,2-dioxaborolane (8): According to GP 1 boronic ester 7 (3.85 g, 6.21 mmol), dichloromethane (1.20 mL, 18.6 mmol), diisopropylamine (1.19 mL, 8.38 mmol), *n*-butyllithium (4.85 mL, 7.76 mmol, 1.6 M in hexane), zinc chloride (2.54 g, 18.6 mmol), sodium hydride (323 mg, 8.07 mmol) and 4-methoxybenzyl alcohol (1.81 mL, 14.6 mmol) were reacted to give boronic ester **8** in 62% yield (2.95 g, 3.82 mmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 100:0–95:5). R_f (**8**) = 0.21 (silica, petroleum ether:ethyl acetate 97:3). $[\alpha]_D^{20} = -9.1$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.4 Hz, 3 H), 0.81–0.84 (m, 4 H), 0.93–0.99 (m, 5 H), 1.05 (m, 2 H), 1.12–1.23 (m, 6 H), 1.25–1.33 (m, 3 H), 1.33–1.44 (m, 2 H), 1.59 (m, 2 H), 1.67 (m, 2 H), 1.72–1.85 (m, 7 H), 1.94 (m, 1 H), 2.78 (dd, *J* = 8.8, 7.0 Hz, 1 H), 2.95 (dd, *J* = 8.7, 5.0 Hz, 1 H), 3.17 (d, *J* = 5.4 Hz, 1 H), 3.78 (s, 3 H), 3.86 (m, 2 H), 4.40 (d, *J* = 11.7 Hz, 1 H), 4.47 (d, *J* = 11.7 Hz, 1 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 7.20 (m, 3 H), 7.23–7.30 (m, 8 H), 7.44 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 18.5, 21.1, 25.9, 26.0, 26.4, 27.6, 27.7, 28.5, 31.3, 32.3, 41.3, 41.8, 43.0, 48.7, 55.2, 68.6, 71.9, 72.0*, 83.6, 86.1, 113.5, 126.7, 127.6, 128.8, 129.2, 131.5, 144.6, 158.9 ppm. HRMS (ESI-FTICR) calcd. for $C_{51}H_{71}{}^{10}BNO_5{}^+$ $[M+NH_4]^+$: 787.54841 found 787.54561.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-{(2*S*,3*R*,5*R*,7*S*)-2-[(4-methoxybenzyl)oxy]-3,5,7-trimethyl-8-(trityloxy)octyl}-1,3,2-dioxaborolane (9): According to GP 2 boronic ester **8** (2.50 g, 3.24 mmol), dibromomethane (0.68 mL, 9.72 mmol), diisopropylamine (623 µl, 4.37 mmol), *n*-butyllithium (2.53 mL, 4.05 mmol, 1.6 M in hexane), zinc chloride (1.77 g, 13.0 mmol) and sodium borohydride (208 mg, 5.51 mmol) were reacted to give boronic ester **9** in 89% yield (2.28 g, 2.90 mmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 96:4). R_f (**9**) = 0.22 (silica, petroleum ether:ethyl acetate 95:5). $[\alpha]_D^{20} = -13.3$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.7 Hz, 3 H), 0.80 (d, *J* = 6.4 Hz, 3 H), 0.83–0.95 (m, 4 H), 0.94–1.00 (m, 5 H), 1.05 (m, 2 H), 1.11–1.21 (m, 7 H), 1.24–1.33 (m, 3 H), 1.38 (m, 1 H), 1.58 (m, 2 H), 1.65 (m, 2 H_i), 1.69–1.81 (m, 7 H), 1.87 (m, 1 H), 2.80 (dd, *J* = 8.8, 7.1 Hz, 1 H), 2.97 (dd, *J* = 8.8, 5.0 Hz, 1 H), 3.56 (dt, *J* = 8.8, 4.5 Hz, 1 H), 3.78 (s, 3 H), 3.81 (m, 2 H), 4.43 (s, 2 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 7.18–7.24 (m, 5 H), 7.29 (m, 6 H), 7.45 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 18.7*, 18.8, 21.3, 25.9, 26.0, 26.4, 27.5, 27.9, 28.4, 31.4, 33.4, 40.9, 41.5, 43.0, 55.3, 68.4, 70.4, 80.1, 83.4, 86.1, 113.5, 126.8, 127.7, 128.7, 128.8, 131.6, 144.6, 158.8 ppm. HRMS (ESI-FTICR) calcd. for $C_{52}H_{69}{}^{11}BO_5Na^+$ $[M+Na]^+$: 807.51303 found 807.51359.

((4*S*,5*S*)-4,5-Dicyclohexyl-2-{(3*S*,5*S*,6*R*,8*R*,10*S*)-5-[(4-methoxybenzyl)oxy]-2,6,8,10-tetramethyl-11-(trityloxy)undecan-3-yl}-1,3,2-dioxaborolane (10a): According to the modified GP 1 boronic ester **9** (1.53 g, 1.95 mmol), dichloromethane (376 µl, 5.85 mmol), diisopropylamine (375 µl, 2.63 mmol), *n*-butyllithium (1.52 mL, 2.44 mmol, 1.6 M in hexane), zinc chloride (1.06 g, 7.80 mmol) and isopropylmagnesium chloride (1.46 mL, 2.92 mmol, 2 M in THF) were reacted to give boronic ester **10a** in 65% yield (1.07 g, 1.27 mmol) as a colorless resin after column chromatography (petroleum ether: ethyl acetate 97:3). R_f (**10a**) = 0.29 (silica, petroleum ether:ethyl acetate 97:3). $[\alpha]_D^{20} = -32.2$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.7 Hz, 3 H), 0.81 (d, *J* = 6.5 Hz, 3 H), 0.84 (m, 2 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 0.92 (m, 2 H), 0.94–1.10 (m, 10 H), 1.12–1.21 (m, 8 H), 1.32–1.50 (m, 5 H), 1.58 (m, 2 H), 1.67 (m, 2 H), 1.71–1.88 (m, 7 H), 1.93 (m, 1 H), 2.82 (dd, *J* = 8.6, 6.9 Hz, 1 H), 2.99 (dd, *J* = 8.6, 4.9 Hz, 1 H), 3.26 (m, 1 H), 3.75 (m, 2 H), 3.78 (s, 3 H), 4.31 (d, *J* = 11.1 Hz, 1 H), 4.46 (d, *J* = 11.1 Hz, 1 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 7.19–7.26 (m, 5 H, 6 H), 7.29 (m, 6 H), 7.46 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 18.8, 21.5, 21.5, 22.3, 25.9, 26.0, 26.5, 27.3, 27.7, 27.9, 28.8, 28.9, 30.8, 31.1, 31.9, 41.1, 41.3, 43.2, 55.2, 68.3, 70.9, 82.1, 83.5, 86.1, 113.6, 126.8, 127.6, 128.8, 129.4, 131.4, 144.5, 158.9 ppm. HRMS (ESI-FTICR) calcd. for $C_{56}H_{77}{}^{11}BNO_5{}^+$ $[M+Na]^+$: 863.57563 found 863.57430.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-{(2*R*,4*S*,5*R*,7*R*,9*S*)-4-[(4-methoxybenzyl)oxy]-5,7,9-trimethyl-10-(trityloxy)decan-2-yl}-1,3,2-dioxaborolane (10b): According to modified GP 1 boronic ester **9** (581 mg, 740 µmol), dichloromethane (143 µl, 2.22 mmol), diisopropylamine (142 µl, 1.00 mmol), *n*-butyllithium (578 µl, 925 µmol, 1.6 M in hexane), zinc chloride (403 mg, 2.96 mmol) and methylmagnesium bromide (296 µl, 740 µmol, 2.5 M in diethyl ether) were reacted to give boronic ester **10b** in 51% yield (305 mg, 375 µmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 98:2). R_f (**10b**) = 0.09 (silica, petroleum ether:ethyl acetate 97:3). $[\alpha]_D^{20} = -37.5$ (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.9 Hz, 3 H), 0.81–0.86 (m, 3 H), 0.91–0.98 (m, 3 H), 0.99–1.08 (m, 8 H), 1.10–1.24 (m, 9 H), 1.35–1.49 (m, 5 H), 1.58 (m, 2 H), 1.68 (m, 2 H), 1.72–1.80 (m, 6 H), 1.84 (m, 1 H), 1.93 (m, 1 H), 2.83 (dd, *J* = 8.7, 6.7 Hz, 1 H), 2.99 (dd, *J* = 6.8, 4.9 Hz, 1 H), 3.34 (m, 1 H), 3.77–3.81 (m, 5 H), 4.34 (d, *J* = 11.1 Hz, 1 H), 4.48 (d, *J* = 11.1 Hz, 1 H), 6.84 (, *J* = 8.7 Hz d, 2 H), 7.20–7.26 (m, 5 H, 6-H), 7.29 (m, 6 H), 7.47 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3*, 14.3, 17.3, 18.8, 21.4, 25.9, 26.0, 26.4, 27.4, 27.7, 28.5, 31.4, 31.7, 33.4, 41.0, 41.5, 55.2, 68.4, 70.8, 81.9, 83.2, 86.1, 113.6, 126.8, 127.6, 128.8, 129.4, 131.4, 144.5, 158.9 ppm. HRMS (ESI-FTICR) calcd. for $C_{54}H_{77}{}^{11}BNO_5{}^{28}Si^+$ $[M+NH_4]^+$: 831.59398 found 831.59662.

(3*R*,5*S*,6*R*,8*R*,10*S*)-5-[(4-Methoxybenzyl)oxy]-2,6,8,10-tetramethyl-11-(trityloxy)-undecan-3-ol (11a): According to GP 3 boronic ester **10a** (684 mg, 813 µmol), hydrogen peroxide (377 µl, 4.06 mmol) and sodium hydroxide (163 mg, 4.06 mmol) were reacted to give the alcohol **11a** in 80% yield (403 mg, 647 µmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 95:5–9:1). R_f (**11a**) = 0.56 (silica, petroleum ether:ethyl acetate 8:2). $[\alpha]_D^{20} = -12.2$ (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.7 Hz, 3 H), 0.82–0.86 (m, 6 H), 0.87–0.90 (m, 2 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 1.25 (m, 1 H), 1.35 (m, 1 H), 1.38–1.45 (m, 2 H), 1.52–1.61 (m, 2 H), 1.82 (m, 1 H), 1.99 (m, 1 H), 2.14 (d, *J* = 4.4 Hz, 1 H), 2.82 (dd, *J* = 8.8, 6.9 Hz, 1 H), 2.99 (dd, *J* = 8.8, 5.1 Hz, 1 H), 3.47–3.55 (m, 2 H), 3.79 (s, 3 H), 4.37 (d, *J* = 11.1 Hz, 1 H), 4.49 (d, *J* = 11.1 Hz, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 7.17–7.26 (m, 5 H), 7.28 (m, 6 H), 7.45 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 17.9, 18.8, 18.8, 21.1, 27.8, 31.4, 31.6, 32.3, 33.8, 41.3, 41.6, 55.3, 68.4, 70.8, 73.5, 79.4, 86.2, 113.8, 126.8, 127.6, 126.8, 129.5, 130.7, 144.5, 159.2 ppm. HRMS (CI) calcd. for $C_{42}H_{54}O_4{}^+$ $[M]^+$: 622.4017 found 622.4008.

(2*R*,4*S*,5*R*,7*R*,9*S*)-4-[(4-Methoxybenzyl)oxy]-5,7,9-trimethyl-10-(trityloxy)decan-2-ol (11b): According to GP 3 boronic ester **10b** (264 mg, 325 µmol), hydrogen peroxide (151 µl, 1.62 mmol) and sodium hydroxide (65.0 mg, 1.62 mmol) were reacted to give the alcohol **11b** in 79% yield (152 mg, 256 µmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 95:5–8:2). R_f (**11b**) = 0.16 (silica, petroleum ether:ethyl acetate 8:2). $[\alpha]_D^{20} = -22.4$ (c = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80 (d, J = 6.9 Hz, 3 H), 0.85 (d, J = 6.3 Hz, 3 H), 0.87–0.91 (m, 2 H), 0.99 (d, J = 6.6 Hz, 3 H), 1.15 (d, J = 6.3 Hz, 3 H), 1.21 (m, 1 H), 1.34–1.39 (m, 2 H), 1.41 (m, 1 H, 14 H), 1.60 (ddd, J = 14.5, 9.5, 2.5 Hz, 1 H), 1.82 (m, 1 H), 2.02 (m, 1 H), 2.23 (bs, 1 H), 2.83 (dd, J = 8.8, 6.6 Hz, 1 H), 2.99 (dd, J = 8.8, 5.0 Hz, 1 H), 3.53 (m, 1 H), 3.79 (s, 3 H), 4.00 (m, 1 H), 4.36 (d, J = 11.0 Hz, 1 H), 4.51 (d, J = 11.0 Hz, 1 H), 6.86 (d, J = 8.8 Hz, 2 H), 7.20–7.26 (m, 5 H), 7.29 (m, 6 H), 7.46 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6, 18.8, 21.1, 23.6, 27.7, 31.2, 31.4, 36.9, 41.2, 41.6, 55.2, 65.0, 68.3, 70.6, 78.8, 86.1, 113.8, 126.8, 127.6, 128.7, 130.5, 144.5, 159.2 ppm. HRMS (ESI-ToF) calcd. for $C_{21}H_{37}O_4{}^+$ $[M\text{-}Trt+H]^+$: 353.2686 found 353.2673.

(3*S*,5*S*,6*R*,8*R*,10*S*)-5-[(4-Methoxybenzyl)oxy]-2,6,8,10-tetramethyl-11-(trityloxy)undecan-3-yl (*R*)-3-[4-(allyloxy)-3-iodophenyl]-2-{2-[(*tert*-butoxycarbonyl)amino]-*N*-methylacetamido}propanoate (13): According to GP 4 the alcohol **11a** (297 mg, 477 µmol), dipeptide **12** (741 mg, 1.43 mmol), DMAP (20.0 mg, 167 µmol), EDC·HCl (274 mg, 1.43 mmol) and collidine (190 µl, 1.43 mmol) were reacted to give the ester **13** in 91% yield (490 mg, 436 µmol, *d. r.* = 81:19 according to HPLC analysis) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 9:1–8:2). R_f (**13**) = 0.18 (silica, petroleum ether:ethyl acetate 8:2). HPLC (Phenomenex Onyx Monolithic C18, 50×4.6 mm, MeCN:H_2O + 0.1% HCOOH, 0–5 min 80:20, 5–15 min 90:10, 4.3 mL/min, 40 °C): t_R (**13**) = 10.04 min. t_R (***epi*-13**) = 10.63 min. $[\alpha]_D^{20} = -11.9$ (c = 1.0, $CHCl_3$). *Major rotamer* **13**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.6 Hz, 3 H), 0.81–0.88 (m, 11 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 1.08 (m, 1 H), 1.35 (m, 2 H), 1.43 (s, 9 H), 1.50 (m, 2 H), 1.78–1.90 (m, 2 H), 2.00 (m, 1 H), 2.78 (s, 3 H), 2.81–2.90 (m, 2 H), 2.97 (dd, *J* = 8.8, 5.0 Hz, 1 H), 3.13 (m, 1 H), 3.20 (dd, *J* = 14.5, 6.0 Hz, 1 H), 3.79 (s, 3 H), 3.85 (m, 2 H), 4.18 (d, *J* = 10.4 Hz, 1 H), 4.40 (d, *J* = 10.4 Hz, 1 H), 4.50 (d, *J* = 5.0 Hz, 2 H), 5.09–5.24 (m, 2 H), 5.29 (dd, *J* = 10.7, 1.6 Hz, 1 H), 5.43 (m, 1 H), 5.48 (dd, *J* = 1.6, 17.3 Hz, 1 H), 6.01 (ddt, *J* = 17.3, 10.7, 5.0 Hz, 1 H), 6.64 (d, *J* = 8.5 Hz, 1 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 7.05 (dd, *J* = 8.5, 2.2 Hz, 1 H), 7.21 (m, 3 H), 7.25–7.31 (m, 8 H), 7.44 (m, 6 H), 7.58 (d, *J* = 2.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$):

δ = 14.1, 17.5, 18.1, 18.6, 21.3, 27.6, 28.3, 30.4, 31.0, 31.4, 31.6, 32.0, 33.2, 40.7, 41.3, 42.5, 55.3, 58.7, 66.4, 69.7, 71.0, 77.1, 78.1, 79.6, 86.1, 86.6, 112.3, 113.7, 117.6, 126.8, 127.6, 128.7, 129.5, 129.7, 130.9, 131.0, 132.5, 139.6, 144.5, 155.6, 156.0, 159.1, 168.9, 169.8 ppm. *Minor rotamer* **13** *(selected signals)*: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.91 (s, 3 H), 4.27 (d, *J* = 10.8 Hz, 1 H) ppm. *Major rotamer* **epi-13** *(selected signals)*: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.76 (s, 3 H), 4.14 (d, *J* = 10.3 Hz, 1 H), 4.54 (m, 2 H), 6.65 (d, *J* = 8.4 Hz, 1 H) ppm. HRMS (ESI-ToF) calcd. for $C_{43}H_{66}IN_2O_9^+$ $[M–Trt+H]^+$: 881.3808 found 881.3807.

(3*S*,5*S*,6*R*,8*R*,10*S*)-11-Hydroxy-5-[(4-methoxybenzyl)oxy]-2,6,8,10-tetramethylundecan-3-yl (*R*)-3-[4-(allyloxy)-3-iodophenyl]-2-{2-[(*tert*-butoxycarbonyl)amino]-*N*-methylacetamido}propanoate (14): According to GP 5 the trityl ether **13** (578 mg, 515 μmol) and Amberlyst 15 (578 mg) were reacted to give the alcohol **14** in 90% yield (406 mg, 461 μmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 8:2–6:4). R_f (**14**) = 0.28 (silica, petroleum ether:ethyl acetate 6:4). $[\alpha]_D^{20} = -4.3$ (c = 1.0, $CHCl_3$). *Major rotamer* **14**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.89 (m, 12 H), 0.89–0.96 (m, 5 H), 1.15 (m, 1 H), 1.29 (m, 1 H), 1.44 (s, 9 H), 1.47–1.57 (m, 3 H), 1.70 (m, 1 H), 1.84 (m, 1 H), 2.05 (m, 1 H), 2.77–2.96 (m, 4 H), 2.86 (dd, *J* = 14.6, 9.8 Hz, 1 H), 3.09–3.31 (m, 2 H), 3.22 (dd, *J* = 14.6, 6.6 Hz, 1 H), 3.40 (dd, *J* = 10.4, 6.6 Hz, 1 H), 3.50 (dd, *J* = 10.4, 5.0 Hz, 1 H), 3.78–3.98 (m, 5 H), 4.13 (d, *J* = 10.7 Hz, 1 H), 4.38 (d, *J* = 10.7 Hz, 1 H), 4.50 (m, 2 H), 5.12–5.20 (m, 2 H), 5.29 (ddt, *J* = 10.5, 1,6, 1.6 Hz, 1 H), 5.45–5.55 (m, 2 H), 6.01 (m, 1 H), 6.65 (d, *J* = 8.2 Hz, 1 H), 6.88 (m, 2 H), 7.09 (dd, *J* = 8.4, 2.2 Hz, 1 H), 7.29 (m, 2 H), 7.62 (d, *J* = 2.2 H, 1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 17.4, 17.9, 18.3, 20.5, 27.8, 28.3, 30.1, 31.0, 31.5, 32.0, 33.1, 33.2, 41.3, 41.5, 42.5, 55.3, 55.7, 67.7, 69.7, 71.0, 77.1, 77.4, 79.7, 86.6, 112.3, 113.8, 117.6, 129.6, 129.7, 130.9, 131.0, 132.5, 139.7, 155.6, 156.1, 159.1, 169.1, 169.7 ppm. *Minor rotamer* **14** *(selected signals)*: 2.78 (s, 3 H), 3.80 (s, 3 H), 3.93 (m, 2 H), 4.57 (m, 2 H), 6.71 (d, *J* = 8.2 Hz, 1 H), 7.60 (d, *J* = 2.2 Hz, 1 H) ppm. *Major rotamer* **epi-14** *(selected signals)*: 2.92 (s, 3 H), 3.81 (s, 3 H), 7.14 (d, *J* = 8.8 Hz, 1 H), 7.66 (d, *J* = 2.2 Hz, 1 H) ppm. HRMS (ESI-ToF) calcd. for $C_{43}H_{66}IN_2O_9^+$ $[M+H]^+$: 881.3808 found 881.3804.

(9*R*,12*S*,14*S*,15*R*,17*S*,19*S*)-9-[4-(Allyloxy)-3-iodobenzyl]-12-isopropyl-14-[(4-methoxybenzyl)oxy]-2,2,8,15,17,19-hexamethyl-4,7,10-trioxo-3,11-dioxa-5,8-diazaicosan-20-oic acid (15): According to GP 6 the alcohol **14** (406 mg, 461 μmol) and Jones reagent (384 μl, 1.15 mol, 3 M) were reacted to give the acid **15** in 79% yield (325 mg, 363 μmol) as a colorless resin after column chromatography (H_2O:MeCN 9:1–0:1). R_f (**15**) = 0.33 (silica, petroleum ether:ethyl acetate 6:4). $[\alpha]_D^{20} = +6.4$ (c = 1.0, $CHCl_3$). *Major rotamer* **15**: ^{1}H NMR (500 MHz, 373 K, DMSO-D_6): δ = 0.81–0.86 (m, 9 H), 0.84 (d, *J* = 6.3 Hz, 3 H), 0.93–1.05 (m, 4 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 1.19 (m, 1 H), 1.39 (s, 9 H), 1.49–1.54 (m, 3 H), 1.68 (m, 1 H), 1.83 (m, 1 H), 1,94 (m, 1 H), 2.42 (m, 1 H), 2.84 (s, 3 H), 2.95 (dd, *J* = 14.1, 8.8 Hz, 1 H), 3.14–3.24 (m, 2 H), 3.20 (dd, *J* = 14.2, 8.2 Hz, 1 H), 3.69–3.87 (m, 5 H), 4.24 (, *J* = 11.0 Hz d, 1 H), 4.40 (d, *J* = 11.0 H, 1 H z), 4.58 (m, 2 H), 4.90–5.11 (m, 3 H), 5.30 (m, 1 H), 5.46 (m, 1 H), 5.64 (t, *J* = 4.4 Hz, 1 H), 6.03 (ddt, *J* = 16.0, 10.4, 5.0 Hz, 1 H), 6.12 (bs, 1 H), 6.89 (m, 2 H), 7.19 (m, 1 H), 7.24 (m, 2 H), 7.67 (m, 1 H), 11.6 (bs, 1 H) ppm. ^{13}C NMR (125 MHz, 373 K, DMSO-D_6): δ = 13.8, 16.7, 17.5, 19.9, 27.7, 27.9, 30.7, 30.9, 31.4, 31.4, 32.4, 36.4, 40.0, 40.3, 41.7, 54.7, 58.9, 54.7, 58.9, 69.1, 70.3, 76.0, 76.7, 78.3, 86.0, 112.7, 113.3, 116.5, 128.5, 129.5, 130.8, 131.1, 132.8, 138.8, 154.8, 155.2, 158.4, 168.8, 176.7, 190.3 ppm. *Major rotamer* **epi-15** *(selected signals)*: ^{1}H NMR (500 MHz, 373 K, DMSO-D_6): δ = 3.89 (s, 3 H) ppm. ^{13}C NMR (125 MHz, 373 K, DMSO-D_6): δ = 16.8, 20.2, 30.9, 31.5, 36.0, 55.2, 70.1 ppm. HRMS (ESI-ToF) calcd. for $C_{43}H_{63}IN_2O_{10}^+$ $[M+H]^+$: 895.3600 found 895.3600.

(3*R*,9*S*,11*S*,13*R*,14*S*,16*S*)-3-[4-(Allyloxy)-3-iodobenzyl]-14-hydroxy-16-isopropyl-4,9,11,13-tetramethyl-1-oxa-4,7-diazacyclohexadecane-2,5,8-trione (16a): The acid **15** (18.0 mg, 20.0 μmol) was dissolved in dichloromethane (42 μl/μmol) and trifluoroacetic acid (30 μmol/μl) was added at 0 °C. The solution was warmed to room temperature and stirred for 3 h. The solvents were removed in N_2 stream and the residue was azeotropically dried with benzene and under high vacuum. The residue was dissolved in dichloromethane (0.25 mM) and the solution cooled to 0 °C. BOP (43 mg, 97 μmol) and DMAP (21 mg, 171 μmol) was added. The solution was slowly warmed to room temperature and stirred for 3 d. The mixture was washed with 0.1 M HCl, saturated $NaHCO_3$, saturated NH_4Cl and brine. The organic layer was dried over Na_2SO_4 and the solvent removed in vacuo. The residue was dissolved in 1.5 mL MeOH and 9 drops of 35% ammonia were added at room temperature. After 1 h, the solvent was removed in vacuo and the residue purified by reversed phase chromatography (H_2O:MeCN 9:1–0:1). The obtained colorless powder was further purified by preparative HPLC (*Phenomenex Luna C18(2)*, H_2O:MeCN 75:25–0:100) to give **16a** in 49% yield (6.4 mg, 9.8 μmol) as single diastereomer and as colorless amorphous powder. $[\alpha]_D^{20} = -13$ (c = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.9 Hz, 3 H), 0.87 (d, *J* = 6.3 Hz, 3 H), 0.93–0.98 (m, 9 H), 1.03–1.09 (m, 3 H), 1.12 (d, *J* = 6.6 Hz, 3 H), 1.18 (m, 1 H), 1.29 (m, 1 H), 1.43 (m, 1 H), 1.50 (m, 1 H), 1.85 (dqq, *J* = 5.4, 5.4, 5.4 Hz, 1 H), 2.03 (m, 1 H), 2.40 (ddq, *J* = 13.2, 6.6, 3.5 Hz, 1 H), 2.63 (d, *J* = 3.8 Hz, 1 H), 2.88 (dd, *J* = 15.8, 12.3 Hz, 1 H), 2.93 (s, 3 H), 3.28 (dd, *J* = 17.0, 1.9 Hz, 1 H), 3.44 (dd, *J* = 15.8, 4.4 Hz, 1 H), 3.57 (ddd, *J* = 13.6, 4.1, 1.9 Hz, 1 H), 4.57 (m, 2 H), 4.79 (dd, *J* = 17.0, 9.1 Hz, 1 H), 5.04 (ddd, *J* = 11.7, 5.4, 1.9 Hz, 1 H), 5.31 (ddt, *J* = 10.4, 1.6, 1.6 Hz, 1 H), 5.44 (dd, *J* = 12.3, 4.4 Hz, 1 H), 5.51 (ddt, *J* = 17.0, 1.6, 1.6 Hz, 1 H), 6.04 (ddt, *J* = 17.0, 10.4, 4.7 Hz, 1 H), 6.15 (d, *J* = 9.1 Hz, 1 H), 6.72 (d, *J* = 8.2 Hz, 1 H), 7.10 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.61 (d, *J* = 1.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4, 17.7, 18.0, 18.3, 18.9, 27.0, 30.3, 30.7, 32.4, 32.8, 34.2, 39.2, 43.0, 45.0, 58.1, 65.6, 69.7, 77.3, 86.8, 112.4, 117.7, 128.9, 130.7, 132.4, 139.1, 156.2, 171.7, 171.9, 177.7 ppm. HRMS (CI) calcd. for $C_{30}H_{46}O_6N_2^+$ $[M]^+$: 656.2317 found 656.2299.

(−)-Doliculide (17a): According to GP 9 Method A the cyclized allyl ether **16a** (3.3 mg, 5.0 μmol), quinaldic acid (20.0 μl, 1.0 μmol, 0.05 M in dry MeOH) and $CpRu(MeCN)_3PF_6$ (40.0 μl, 1.0 μmol, 0.025 M in dry MeOH) were reacted. After reversed phase chromatography (H_2O:MeCN 9:1–0:10) the obtained white powder was further purified by preparative HPLC (*Phenomenex Luna C18(2)*, H_2O + 0.1% HCOOH:MeCN 90:10–5:95) to give **17a** in 77% yield (2.4 mg, 3.9 μmol) as amorphous, colorless powder.

Alternatively, according to GP 8 the linear precursor **21a** (76.4 mg, 80.0 μmol) was deprotected and then reacted with triethylamine (112 μl, 803 μmol) and BOP-Cl (102 mg, 402 μmol) to give the cyclized allyl ether **16a** in 70% yield (36.8 mg, 56.0 μmol) as a colorless powder after reversed phase chromatography (H_2O:MeCN 9:10–0:10). According to GP 9 *Method A* the allyl ether **16a** (56.2 mg, 86.0 μmol), quinaldic acid (342 μl, 17.0 μmol, 0.05 M in MeOH) and CpRu(MeCN)PF_6 (685 μl, 17.0 μmol, 0.025 M in MeOH) were reacted. After reversed phase chromatography (H_2O:MeCN 9:1–0:10) the obtained powder was further purified by preparative HPLC (*Phenomenex Luna C18(2)*, H_2O:MeCN 7:3–0:10) to give (−)-Doliculide **17a** in 81% yield (42.5 mg, 69.0 μmol) as colorless, amorphous powder. $[\alpha]_D^{20} = -27$ (c = 0.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.7 Hz, 3 H), 0.93–0.98 (m, 9 H), 1.02–1.10 (m, 3 H), 1.13 (d, *J* = 6.7 Hz, 3 H), 1.16 (m, 1 H), 1.31 (m, 1 H), 1.44 (m, 1 H), 1.51 (m, 1 H), 1.87 (m, 1 H), 2.03 (m, 1 H), 2.42 (ddq, *J* = 12.2, 6.7, 3.4 Hz, 1 H), 2.57 (bs, 1 H), 2.88 (dd, *J* = 15.5, 12.4 Hz, 1 H), 2.94 (s, 3 H), 3.25 (dd, *J* = 16.8, 1.8 Hz, 1 H), 3.44 (dd, *J* = 15.5, 4.4 Hz, 1 H), 3.57 (m, 1 H), 4.80 (dd, *J* = 17.0, 9.0 Hz, 1 H), 5.05 (ddd, *J* = 11.6, 5.1, 2.0 Hz, 1 H), 5.47 (dd, *J* = 12.4, 4.4 Hz, 1 H), 6.19–6.27 (m, 2 H), 6.86 (d, *J* = 8.3 Hz, 1 H), 7.07 (dd, *J* = 8.3, 1.8 H, 1 H z), 7.49 (d, *J* = 1.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4, 17.6, 18.0, 18.3, 18.9,

27.0, 30.1, 30.8, 32.3, 32.8, 34.2, 39.2, 39.7, 43.1, 44.9, 58.1, 65.7, 77.3, 85.5, 115.2, 129.6, 130.3, 137.9, 154.1, 171.6, 171.9, 177.8 ppm. HRMS (CI) calcd. for $C_{27}H_{42}O_6N_2{}^{127}I^+$ $[M+H]^+$: 617.2082 found 617.2098.

(3*R*,9*S*,11*S*,13*R*,14*S*,16*R*)-14-Hydroxy-3-(4-hydroxy-3-iodobenzyl)-4,9,11,13,16-pentamethyl-1-oxa-4,7-diazacyclohexadecane-2,5,8-trione (17b): According to GP 8 the linear precursor **21b** (46.1 mg, 50.0 μmol) was deprotected and then reacted with triethylamine (70.0 μl, 500 μmol) and BOP–Cl (64 mg, 250 μmol) to give the cyclized allyl ether **16b** in 65% yield (20.3 mg, 32.0 μmol) as a colorless powder after reversed phase chromatography (H_2O:MeCN 9:10–0:10). $[\alpha]_D^{20} = -20$ (c = 0.3, $CHCl_3$) ppm. HRMS (CI) calcd. for $C_{28}H_{42}{}^{127}IN_2O_6$ $[M+H]^+$: 629.2082 found 629.2104.

According to GP 9 *Method A* the allyl ether **16b** (19.7 mg, 86.0 μmol), quinaldic acid (125 μl, 6.3 μmol, 0.05 M in MeOH) and CpRu(MeCN)PF_6 (251 μl, 6.3 μmol, 0.025 M in MeOH) were reacted. After reversed phase chromatography (H_2O:MeCN 9:1–0:10) the obtained powder was further purified by preparative HPLC (*Phenomenex Luna C18(2)*, H_2O:MeCN 7:3–0:10) to give **17b** in 70% yield (12.9 mg, 22.0 μmol) as colorless, amorphous powder. $[\alpha]_D^{20} = -23.1$ (c = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 6.0 Hz, 3 H), 1.02–1.10 (m, 3 H), 1.12 (d, *J* = 6.6 Hz, 3 H), 1.19 (m, 1 H), 1.28 (d, *J* = 6.0 Hz, 3 H), 1.40 (m, 2 H), 1.54 (m, 1 H), 1.95 (m, 1 H), 2.10 (bs, 1 H), 2.45 (m, 1 H), 2.83 (dd, *J* = 15.1, 12.0 Hz, 1 H), 2.91 (s, 3 H), 3.15 (d„ *J* = 16.4 Hz 1 H), 3.40 (dd, *J* = 15.1, 4.1 Hz, 1 H), 3.68 (m, 1 H), 4.78 (dd, *J* = 16.4, 8.5 Hz, 1 H), 5.24 (m, 1 H), 5.57 (dd, *J* = 12.0, 4.7 Hz, 1 H), 6.45 (m, 1 H), 6.81 (d, *J* = 8.2 Hz, 1 H), 7.05 (d, *J* = 8.2 Hz, 1 H), 7.47 (d, *J* = 1.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.5, 18.5, 20.8, 27.0, 30.7, 32.3, 34.6, 35.0, 39.0, 39.4, 42.8, 44.8, 57.5, 66.1, 69.6, 85.0, 115.1, 129.5, 130–2, 138.4, 154.3, 170.4, 171.9, 177.6 ppm. HRMS (ESI-ToF) calcd. for $C_{25}H_{38}{}^{127}IN_2O_6$ $[M+H]^+$: 589.1769 found 589.1750.

(3*R*,9*S*,11*S*,13*R*,14*S*,16*S*)-3-(3-Bromo-4-hydroxybenzyl)-14-hydroxy-16-isopropyl-4,9,11,13-tetramethyl-1-oxa-4,7-diazacyclohexadecane-2,5,8-trione (17c): According to GP 8 the linear precursor **21c** (53.0 mg, 59.0 μmol) was deprotected and then reacted with triethylamine (82.0 μl, 586 μmol) and BOP–Cl (75 mg, 293 μmol) to give the cyclized allyl ether **16c** in 72% yield (25.6 mg, 42.0 μmol) as a colorless powder after reversed phase chromatography (H_2O:MeCN 9:10–0:10). $[\alpha]_D^{20} = -39.6$ (c = 0.5, $CHCl_3$) ppm. HRMS (ESI) calcd. for $C_{30}H_{46}{}^{79}BrN_2O_6{}^+$ $[M+H]^+$: 609.2534 found 609.2530.

According to GP 9 *Method B* the allyl ether **16c** (16.5 mg, 27.0 μmol) and the Ru-catalyst stock solution (135 μl, 1.35 μmol, 0.01 M in MeOH) were reacted. After reversed phase chromatography (H_2O:MeCN 9:1–0:10) the obtained powder was further purified by preparative HPLC (*Phenomenex Luna C18(2)*, H_2O:MeCN 7:3–0:10) to give **17c** in 68% yield (10.5 mg, 18.0 μmol) as colorless, amorphous powder. $[\alpha]_D^{20} = -46$ (c = 0.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.9 Hz, 3 H), 0.93–0.95 (m, 9 H), 1.02–1.10 (m, 3 H), 1.13 (d, *J* = 6.6 Hz, 3 H), 1.18 (m, 1 H), 1.30 (m, 1 H), 1.43 (m, 1 H), 1.51 (m, 1 H), 1.86 (m, 1 H), 2.03 (m, 1 H), 2.41 (ddq, *J* = 12.2, 6.6, 3.3 Hz, 1 H), 2.58 (bs, 1 H), 2.88 (dd, *J* = 15.6, 12.5 Hz, 1 H), 2.93 (s, 3 H), 3.28 (dd, *J* = 16.9, 1.7 Hz, 1 H), 3.45 (dd, *J* = 15.4, 4.4 Hz, 1 H), 3.57 (m, 1 H), 4.80 (dd, *J* = 17.0, 8.8 Hz, 1 H), 5.05 (ddd, *J* = 11.6, 5.3, 2.0 Hz, 1 H), 5.46 (dd, *J* = 12.5, 4.6 Hz, 1 H), 5.75 (bs, 1 H), 6.17 (d, *J* = 8.5 Hz, 1 H), 6.92 (d, *J* = 8.2 Hz, 1 H), 7.04 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.30 (d, *J* = 2.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 17.7, 18.0, 18.3, 18.9, 27.0, 30.2, 30.6, 32.4, 33.0, 34.2, 39.2, 39.7, 43.1, 45.0, 58.0, 65.6, 77.4, 110.3, 116.3, 128.8, 130.0, 131.6, 151.4, 171.7, 171.7, 177.7 ppm. HRMS (CI) calcd. for $C_{27}H_{43}{}^{79}BrN_2O_6{}^+$ $[M+H]^+$: 569.2221 found 569.2198.

(3*R*,9*S*,11*S*,13*R*,14*S*,16*S*)-3-(3-Chloro-4-hydroxy-5-iodobenzyl)-14-hydroxy-16-isopropyl-4,9,11,13-tetramethyl-1-oxa-4,7-diazacyclohexadecane-2,5,8-trione (17d): Doliculide **17a** (2,4 mg, 3.9 μmol) was dissolved in non-stabilized $CDCl_3$ at room temperature. After three days the solvent was removed in vacuo and the chlorinated derivative **17d** (2.5 mg, 3.9 μmol) obtained as colorless powder without further purification. $[\alpha]_D^{20} = -53$ (c = 0.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.9 Hz, 3 H), 0.93–0.99 (m, 9 H), 1.06 (m, 2 H), 1.13 (d, *J* = 6.6 Hz, 3 H), 1.19 (m, 1 H), 1.27–1.34 (m, 2 H), 1.44 (m, 1 H), 1.52 (m, 1 H), 1.86 (m, 1 H), 2.02 (m, 1 H), 2.42 (m, 1 H), 2.86 (dd, *J* = 15.5, 12.0 Hz, 1 H), 2.95 (s, 3 H), 3.32 (d, *J* = 15.8 Hz, 1 H), 3.42 (dd, *J* = 15.8, 4.4 Hz, 1 H), 3.56 (m, 1 H), 4.82 (d, *J* = 15.8 Hz, 1 H), 5.42 (dd, *J* = 12.0, 4.4 Hz, 1 H), 5.88 (bs, 1 H), 6.16 (bs, 1 H), 7.17 (d, *J* = 1.9 Hz, 1 H), 7.46 (d, *J* = 1.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4, 17.7, 18.0, 18.3, 18.8, 27.0, 30.1, 30.8, 32.3, 32.7, 34.3, 39.2, 39.8, 43.0, 45.0, 58.0, 65.7, 77.5, 83.8, 119.3, 129.3, 131.4, 137.4, 150.0, 171.4, 171.8, 177.7 ppm. HRMS (ESI-ToF) calcd. for $C_{27}H_{40}{}^{127}ICIN_2O_6$ $[M+H]^+$: 651.1692 found 651.1699.

(3*S*,5*S*,6*R*,8*R*,10*S*)-5-[(4-Methoxybenzyl)oxy]-2,6,8,10-tetramethyl-11-(trityloxy)un-decan-3-yl (*R*)-3-[4-(allyloxy)-3-iodophenyl]-2-[(*tert*-butoxycarbonyl)(methyl)amino]-propanoate (19a): According to GP 4 the alcohol **11a** (326 mg, 523 μmol), tyrosine derivative **18a** (724 mg, 1.57 mmol), DMAP (22.0 mg, 183 μmol), EDC·HCl (301 mg, 1.57 mmol) and collidine (209 μl, 1.57 mmol) were reacted to give the ester **19a** in 85% yield (490 mg, 436 μmol) as a colorless resin after reversed phase chromatography (H_2O:MeCN 9:1–0:10). R_f (**19a**) = 0.37 (silica, petroleum ether:ethyl acetate 8:2). $[\alpha]_D^{20} = -6.0$ (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, 373 K, DMSO-D_6): δ = 0.78 (d, *J* = 6.6 Hz, 3 H), 0.82 (d, *J* = 6.6 Hz, 3 H), 0.84–0.88 (m, 6 H), 0.88–0.91 (m, 2 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 1.18 (m, 1 H), 1.33–1.37 (m, 10 H), 1.42 (m, 1 H), 1.52 (m, 2 H), 1.74 (m, 1 H), 1.85 (m, 1 H), 1.91 (m, 1 H), 2.67 (s, 3 H), 2.85 (dd, *J* = 8.8, 6.3 Hz, 1 H), 2.93 (m, 1 H), 2.97 (dd, *J* = 8.8, 5.0 Hz, 1 H), 3.09 (dd, *J* = 14.4, 5.3 Hz, 1 H), 3.21 (m, 1 H), 3.75 (s, 3 H), 4.25 (d, *J* = 11.0 Hz, 1 H), 4.38 (d, *J* = 11.0 Hz, 1 H), 4.57 (ddd, *J* = 5.0, 1.6, 1.6 Hz, 2 H), 4.69 (m, 1 H), 4.99 (m, 1 H), 5.25 (ddt, *J* = 10.7, 1.6 Hz, 1.6 Hz, 1 H), 5.45 (ddt, *J* = 17.3, 1.6, 1.6 Hz, 1 H), 6.02 (ddt, *J* = 17.3, 10.7, 5.0 Hz, 1 H), 6.86 (m, 3 H), 7.15 (dd, *J* = 8.5, 2.2 Hz, 1 H), 7.19–7.26 (m, 5 H), 7.30 (m, 6 H), 7.39 (m, 6 H), 7.61 (d, *J* = 2.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, 373 K, DMSO-D_6): δ = 13.9, 16.7, 17.4, 17.9, 20.5, 27.5, 30.4, 30.9, 31.0, 31.3, 32.6, 40.0, 40.8, 54.7, 59.6, 67.8, 69.1, 70.1, 75.8, 78.0, 78.7, 85.5, 86.0, 112.7, 113.3, 116.5, 126.3, 127.1, 127.8, 128.4, 129.5, 130.6, 131.8, 132.7, 138.6, 143.7, 154.1, 155.2, 158.3, 169.5 ppm. HRMS (ESI-ToF) calcd. for $C_{41}H_{63}{}^{127}INO_8$ $[M\text{-}Trt+H]^+$: 824.3593 found 824.3587.

(2*R*,4*S*,5*R*,7*R*,9*S*)-4-[(4-Methoxybenzyl)oxy]-5,7,9-trimethyl-10-(trityloxy)decan-2-yl (*R*)-3-[4-(allyloxy)-3-iodophenyl]-2-[(tert-butoxycarbonyl)(methyl)amino]propanoate (19b): According to GP 4 the alcohol **11b** (137 mg, 231 μmol), tyrosine derivative **18a** (319 mg, 69.2 μmol), DMAP (9.9 mg, 81 μmol), EDC·HCl (133 mg, 692 μmol) and collidine (92.0 μl, 692 μmol) were reacted to give the ester **19b** in 75% yield (181 mg, 174 μmol) as a colorless resin after chromatography (petroleum ether:ethyl acetate 9:1–8:2). R_f (**19b**) = 0.52 (petroleum ether:ethyl acetate 7:3). $[\alpha]_D^{20} = -6.9$ (c = 0.5, $CHCl_3$). *Major rotamer:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77–0.85 (m, 6 H), 0.86–0.93 (m, 2 H), 0.99 (m, 3 H), 1.13 (m, 1 H), 1.25 (m, 3 H), 1.31–1.44 (m, 11 H), 1.54 (m, 2 H), 1.81 (m, 1 H), 1.99 (m, 1 H), 2.70 (s, 3 H), 2.76–2.89 (m, 2 H), 2.98 (m, 1 H), 3.07 (m, 1 H), 3.25 (m, 1 H), 3.80 (s, 3 H), 4.18 (d, *J* = 10.9 Hz, 1 H), 4.40–4.59 (m, 4 H), 5.17 (m, 1 H), 5.29 (d, *J* = 10.5 Hz, 1 H), 5.48 (dd, *J* = 17.2, 1.6 Hz, 1 H), 6.02 (ddt, *J* = 17.2, 10.5, 5.0 Hz, 1 H), 6.67 (d, *J* = 8.3 Hz, 1 H), 6.87 (m, 2 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 7.19–7.25 (m, 5 H), 7.45 (m, 6 H), 7.61 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 18.6, 20.8, 27.7, 28.2, 30.7, 31.4, 31.4, 33.5, 35.9, 40.9, 41.3, 55.3, 60.2, 68.3, 69.7, 70.5, 77.2, 79.9, 80.2, 86.1, 86.7, 112.3, 113.8, 117.6, 126.8, 127.6, 128.7,

129.7, 129.9, 130.6, 132.1, 132.5, 139.5, 144.4, 154.9, 155.5, 159.1, 170.2 ppm. *Minor rotamer (selected signals):* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.64 (s, 3 H), 7.02 (d, 1 H, *J* = 8.2 Hz), 7.59 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 18.7, 20.8, 21.3, 27.7, 30.9, 32.7, 33.7, 35.9, 40.7, 41.3, 68.5, 68.4, 70.8, 77.5, 86.4, 117.5, 129.7, 130.8, 132.0, 132.6, 139.8, 155.8, 155.9, 170.4 ppm. HRMS (ESI-ToF) calcd. for $C_{39}H_{59}{}^{127}INO_8$ $[M\text{-}Trt+H]^+$: 796.3280 found 796.3257.

(3*S*,5*S*,6*R*,8*R*,10*S*)-5-[(4-Methoxybenzyl)oxy]-2,6,8,10-tetramethyl-11-(trityloxy)undecan-3-yl (*R*)-3-[4-(allyloxy)-3-bromophenyl]-2-[(*tert*-butoxycarbonyl)(methyl)amino]propanoate (19c): According to GP 4 the alcohol **11c** (197 mg, 316 μmol), tyrosine derivative **18b** (393 mg, 949 μmol), DMAP (14.0 mg, 111 μmol), EDC·HCl (182 mg, 949 μmol) and collidine (126 μl, 949 μmol) were reacted to give the ester **19c** in 90% yield (291 mg, 286 μmol) as a colorless resin after chromatography (petroleum ether:ethyl acetate 9:1–8:2). R_f (**19c**) = 0.35 (petroleum ether:ethyl acetate 8:2). $[\alpha]_D^{20}$ = −7.1 (c = 0.5, $CHCl_3$). *Major rotamer:* ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80 (m, 3 H), 0.85 (d, *J* = 6.3 Hz, 3 H), 0.88–0.94 (m, 8 H), 1.00 (d, *J* = 6.6 Hz, 3 H), 1.13 (m, 1 H), 1.36–1.46 (m, 11 H), 1.53 (m, 2 H), 1.80–1.94 (m, 2 H), 2.01 (m, 1 H), 2.71 (s, 3 H), 2.83–3.03 (m, 3 H), 3.10–3.23 (m, 2 H), 3.80 (s, 3 H), 4.20 (m, 1 H), 4.41 (d, *J* = 10.7 Hz, 1 H), 4.53 (m, 2 H), 4.73 (m, 1 H), 5.16 (m, 1 H), 5.29 (d, *J* = 10.7 Hz, 1 H), 5.46 (d, *J* = 17.3 Hz, 1 H), 6.03 (ddt, *J* = 17.3, 10.7, 5.0 Hz, 1 H), 6.75 (d, *J* = 8.2 Hz, 1 H), 6.88 (m, 2 H), 7.09 (d, *J* = 8.2 Hz, 1 H), 7.23 (m, 3 H), 7.26–7.33 (m, 8 H), 7.40 (m, 1 H), 7.46 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 17.4, 18.2, 18.6, 21.3, 27.7, 28.3, 30.6, 31.2, 31.4, 32.0, 32.0, 33.8, 41.3, 41.3, 55.2, 60.1, 68.3, 69.7, 71.0, 76.4, 78.3, 79.9, 86.2, 112.0, 113.5, 113.7, 117.6, 126.8, 127.6, 128.7, 129.6, 131.0, 131.5, 132.6, 133.8, 144.5, 153.6, 155.4, 159.1, 170.6 ppm. *Minor rotamer (selected signals):* ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.80 (s, 3 H), 7.02 (d, 1 H, *J* = 8.2 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 17.5, 18.1, 27.6, 30.4, 32.5, 34.0, 40.7, 40.9, 68.3, 71.0, 80.2, 112.3, 117.7, 129.7, 130.8, 131.2, 133.4, 153.7, 155.0, 159.0, 170.4 ppm. HRMS (ESI-ToF) calcd. for $C_{41}H_{63}{}^{79}BrNO_8{}^+$ $[M\text{-}Trt+H]^+$: 776.3732 found 776.3730.

(2*S*,4*S*,6*R*,7*S*,9*S*)-9-{[(*R*)-3-(4-{Allyloxy}-3-iodophenyl)-2-({*tert*-butoxycarbonyl}{methyl}amino)propanoyl]oxy}-7-[(4-methoxybenzyl)oxy]-2,4,6,10-tetramethylundecanoic acid (20a): According to GP 5 the trityl ether **19a** (410 mg, 358 μmol) and Amberlyst 15 (510 mg) were reacted to give the alcohol **19a-1** in 93% yield (295 mg, 358 μmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 8:2). R_f = 0.19 (silica, petroleum ether:ethyl acetate 8:2). $[\alpha]_D^{20}$ = −7.0 (c = 1.0, $CHCl_3$) ppm. HRMS (ESI) calcd. for $C_{41}H_{63}{}^{127}INO_8$ $[M+H]^+$: 824.3593 found 824.3599.

According to GP 6 the obtained alcohol **19a-1** (261 mg, 317 μmol) and Jones reagent (264 μl, 792 μmol, 3 M) were reacted to give the acid **20a** in 85% yield (225 mg, 269 μmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 8:2–7:3). R_f (**20a**) = 0.34 (silica, petroleum ether:ethyl acetate 7:3). $[\alpha]_D^{20}$ = + 6.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, 373 K, DMSO-D_6): δ = 0.84 (d, *J* = 6.9 Hz, 3 H), 0.85–0.89 (m, 6 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 0.93–1.04 (m, 2 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 1.20 (m, 1 H), 1.36 (s, 9 H), 1.48–1.58 (m, 3 H), 1.68 (m, 1 H), 1.85 (m, 1 H), 1.96 (m, 1 H), 2.42 (m, 1 H), 2.69 (s, 3 H), 2.98 (m, 1 H), 3.12 (dd, *J* = 14.4, 5.7 Hz, 1 H), 3.21 (m, 1 H), 3.77 (s, 3 H), 4.27 (d, *J* = 11.0 Hz, 1 H), 4.42 (d, *J* = 11.0 Hz, 1 H), 4.58 (ddd, *J* = 5.0, 1.6, 1.6 Hz, 2 H), 4.72 (m, 1 H), 5.00 (m, 1 H), 5.27 (ddt, *J* = 10.7, 1.9, 1.6 Hz, 1 H z), 5.45 (ddt, *J* = 17.3, 1.9, 1.6 Hz, 1 H), 6.03 (ddt, *J* = 17.3, 10.7, 5.0 Hz, 1 H), 6.88–6.92 (m, 3 H), 7.19 (dd, *J* = 8.5, 2.2 Hz, 1 H), 7.24 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, 373 K, DMSO-D_6): δ = 13.7, 16.6, 17.4, 17.4, 20.0, 27.5, 27.9, 30.6, 31.0, 31.0, 31.3, 32.6, 36.4, 40.0, 40.3, 54.7, 59.6, 69.1, 70.2, 75.8, 78.3, 78.8, 86.0, 112.7, 113.3, 116.6, 128.5, 129.5, 130.7, 131.9, 132.8, 138.7, 154.1, 155.2, 158.4, 169.6, 176.7 ppm. HRMS (ESI-ToF) calcd. for $C_{41}H_{61}{}^{127}INO_9$ $[M+H]^+$: 838.3386 found 838.3372.

(2*S*,4*S*,6*R*,7*S*,9*R*)-9-{[(*R*)-3-(4-{Allyloxy}-3-iodophenyl)-2-({*tert*-butoxycarbonyl}{methyl}amino)propanoyl]oxy}-7-[(4-methoxybenzyl)oxy]-2,4,6-trimethyldecanoic acid (20b): According to GP 5 the trityl ether **19b** (170 mg, 164 μmol) and Amberlyst 15 (170 mg) were reacted to give the alcohol **19b-1** in 92% yield (119 mg, 150 μmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 8:2). R_f = 0.16 (silica, petroleum ether:ethyl acetate 8:2). $[\alpha]_D^{20}$ = −4.5 (c = 0.5, $CHCl_3$) ppm. HRMS (ESI-ToF) calcd. for $C_{39}H_{59}{}^{127}INO_8$ $[M+H]^+$: 796.3280 found 796.3299.

According to GP 6 the obtained alcohol **19b-1** (112 mg, 141 μmol) and Jones reagent (117 μl, 352 μmol, 3 M) were reacted to give the acid **20b** in 60% yield (68.0 mg, 84.0 μmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 8:2–7:3). R_f (**20b**) = 0.28 (silica, petroleum ether:ethyl acetate 7:3). $[\alpha]_D^{20}$ = + 6.0 (c = 0.5, $CHCl_3$). *Major rotamer:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80–0.94 (m, 9 H), 1.02–1.11 (m, 2 H), 1.19 (m, 3 H), 1.42 (s, 9 H), 1.45–1.66 (m, 4 H), 2.08 (m, 1 H), 2.60 (m, 1 H), 2.74 (s, 3 H), 2.81 (dd, *J* = 14.0, 8.1 Hz, 1 H), 3.09 (dd, *J* = 14.0, 8.1 Hz, 1 H), 3.18 (m, 1 H), 3.79 (s, 3 H), 3.90 (d, *J* = 10.3 Hz, 1 H), 4.27 (m, *J* = 10.3 Hz, 1 H), 4.42 (m, 2 H), 4.96 (m, 1 H), 5.23–5.32 (m, 2 H), 5.44 (m, 1 H), 5.98 (m, 1 H), 6.62 (d, *J* = 8.4 Hz, 1 H), 6.87 (d, *J* = 8.6 Hz, 1 H), 7.19–7.30 (m, 3 H), 7.69 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl3): δ = 14.6, 18.5, 18.5, 28.3, 29.9, 33.5, 33.8, 34.7, 37.7, 40.8, 42.0, 43.2, 69.0, 69.6, 71.2, 76.2, 81.2, 86.3, 112.2, 113.8, 117.4, 129.7, 129.8, 130.4, 130.8, 132.6, 140.2, 155.8, 156.0, 159.1, 170.0, 178.9 ppm. *Minor rotamer (selected signals):* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.60 (s, 3 H), 3.33 (m, 1 H), 4.18 (d, 1 H, *J* = 11.1 Hz), 4.48 (d, 1 H, *J* = 11.1 Hz), 4.55 (m, 2 H), 5.13 (m, 1 H), 6.70 (d, 1 H, *J* = 8.3 Hz), 7.02 (d, 1 H, *J* = 8.3 Hz), 7.63 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 30.6, 34.0, 37.2, 69.8, 69.9, 70.0, 82.9, 86.7, 117.6, 130.0, 131.3, 132.5, 139.7, 170.2 ppm. HRMS (ESI-ToF) calcd. for $C_{39}H_{57}{}^{127}INO_9$ $[M+H]^+$: 810.3073 found 810.3064.

(2*S*,4*S*,6*R*,7*S*,9*S*)-9-{[(*R*)-3-(4-{Allyloxy}-3-bromophenyl)-2-({*tert*-butoxycarbonyl}{methyl}amino)propanoyl]oxy}-7-[(4-methoxybenzyl)oxy]-2,4,6,10-tetramethylundecanoic acid (20c): According to GP 5 the trityl ether **19c** (282 mg, 277 μmol) and Amberlyst 15 (282 mg) were reacted to give the alcohol **19c-1** in 41% yield (87.0 mg, 112 μmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 8:2). R_f = 0.17 (silica, petroleum ether:ethyl acetate 8:2). $[\alpha]_D^{20}$ = −5.4 (c = 0.5, $CHCl_3$) ppm. HRMS (ESI-ToF) calcd. for $C_{41}H_{63}{}^{79}BrNO_8{}^+$ $[M+H]^+$: 776.3732 found 776.3702.

According to GP 6 the obtained alcohol **19c-1** (82.0 mg, 106 μmol) and Jones reagent (88.0 μl, 264 μmol, 3 M) were reacted to give the acid **20c** in 75% yield (62.8 mg, 79.0 μmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 8:2–7:3). R_f (**20c**) = 0.38 (silica, petroleum ether:ethyl acetate 7:3). $[\alpha]_D^{20}$ = + 2.2 (c = 0.5, $CHCl_3$). *Major rotamer:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78–0.91 (m, 12 H), 1.00–1.15 (m, 3 H), 1.20 (d, *J* = 6.9 Hz, 3 H), 1.29 (m, 1 H), 1.41 (m, 2 H), 1.45 (s, 9 H), 1.57 (m, 1 H), 1.74 (m, 1 H), 2.06 (m, 1 H), 2.60 (m, 1 H), 2.77 (s, 3 H), 2.82 (dd, *J* = 13.8, 6.7 Hz, 1 H), 3.02 (m, 1 H), 3.17 (dd, *J* = 13.8, 9.2 Hz, 1 H), 3.75–6.86 (m, 4 H), 4.20 (d, *J* = 10.0 Hz, 1 H), 4.46 (m, 2 H), 5.12 (m, 1 H), 5.21 (m, 1 H), 5.25 (m, 1 H), 5.41 (m, 1 H), 5.99 (ddt, *J* = 17.2, 10.6, 4.9 Hz, 1 H), 6.71 (d, *J* = 8.4 Hz, 1 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 7.24–7.32 (m, 3 H), 7.51 (d, *J* = 2.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 17.0, 18.1, 18.3, 18.4, 27.6, 28.3, 29.2, 29.8, 30.3, 32.3, 33.7, 38.0, 42.3, 43.3, 55.2, 58.2, 69.6, 71.1, 75.6, 76.1, 81.3, 111.9, 113.4, 113.7, 117.5, 129.5, 129.8, 130.6, 131.1, 132.7, 134.4, 153.6, 155.8, 159.0, 170.0, 178.6 ppm. *Minor rotamer (selected signals):* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 9 H), 4.54 (m, 2 H), 6.77 (d, *J* = 8.3 Hz, 1 H), 7.02 (d, *J* = 8.3 Hz, 1 H), 7.40 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 28.2, 31.2, 31.9, 34.1, 37.1, 69.7, 71.0, 80.5, 112.2, 113.5,

113.8, 117.7, 128.8, 132.6, 133.4, 178.6 ppm. HRMS (ESI-ToF) calcd. for $C_{41}H_{61}{}^{79}BrNO_9{}^+$ $[M+H]^+$: 790.3524 found 790.3556.

(3*S*,5*S*,6*R*,8*S*,10*S*)-11-[(*tert*-Butoxycarbonyl)amino]-5-[(4-methoxybenzyl)oxy]-2,6,8,10-tetramethyl-11-oxoundecan-3-yl (*R*)-3-[4-(allyloxy)-3-iodophenyl]-2-[(*tert*-butoxycarbonyl)(methyl)amino]propanoate (21 a): According to GP 7 the acid **20 a** (192 mg, 230 μmol), glycine *tert*-butylester hydrochloride (51.0 mg, 306 μmol), triethylamine (80.0 μl, 575 μmol) and diethyl cyanophosphonate (89.0 μl, 529 μmol) were reacted to give the amide **21 a** in 75% yield (164 mg, 172 μmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 8:2–7:3). R_f (**21 a**) = 0.22 (petroleum ether:ethyl acetate 7:3). $[\alpha]_D^{20} = -28.2$ (c = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-D_6, 373 K): δ = 0.82 (d, 3 H, *J* = 6.9 Hz), 0.85–0.88 (m, 6 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.92–0.97 (m, 2 H), 1.04 (d, *J* = 6.9 Hz, 3 H), 1.17 (m, 1 H), 1.36 (s, 9 H), 1.41 (s, 9 H), 1.48 (m, 1 H), 1.54 (m, 2 H), 1.71 (m, 1 H), 1.86 (m, 1 H), 1.96 (m, 1 H), 2.42 (m, 1 H), 2.69 (s, 3 H), 2.97 (m, 1 H), 3.12 (dd, *J* = 14.4 Hz, *J* = 5.3 Hz, 1 H), 3.20 (m, 1 H), 3.69 (m, 2 H), 3.77 (s, 3 H), 4.27 (d, *J* = 11.0 Hz, 1 H), 4.42 (d, *J* = 11.0 Hz, 1 H), 4.59 (m, 2 H), 4.73 (m, 1 H), 4.99 (m, 1 H), 5.26 (m, 1 H), 5.46 (m, 1 H), 6.03 (m, 1 H), 6.88–6.91 (m, 3 H), 7.19 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.24 (m, 2 H), 7.64 (d, *J* = 2.2 Hz, 1 H), 7.71 (bs, 1 H) ppm. ^{13}C NMR (125 MHz, DMSO-D_6, 373 K): δ = 13.7, 16.6, 17.4, 18.1, 20.2, 27.3, 27.5, 27.6, 30.7, 31.0 (d, C-4), 31.3, 32.6, 32.6, 37.0, 40.4, 41.1, 54.7, 59.6, 69.1, 70.1, 75.9, 78.5, 78.8, 79.8, 86.0, 112.7, 113.3, 116.6, 128.5, 129.5, 130.7, 131.9, 132.8, 138.7, 154.1, 155.2, 158.3, 168.4, 169.6, 175.4 ppm. HRMS (ESI-ToF) calcd. for $C_{47}H_{72}{}^{127}IN_2O_{10}$ $[M+H]^+$: 951.4226 found 951.4225.

(2*R*,4*S*,5*R*,7*S*,9*S*)-10-[(*tert*-Butoxycarbonyl)amino]-4-[(4-methoxybenzyl)oxy]-5,7,9-trimethyl-10-oxodecan-2-yl (*R*)-3-[4-(allyloxy)-3-iodophenyl]-2-[(*tert*-butoxycarbonyl)(methyl)amino]propanoate (21 b): According to GP 7 the acid **20 b** (51.2 mg, 63.0 μmol), glycine *tert*-butylester hydrochloride (14.0 mg, 84.0 μmol), triethylamine (22.0 μl, 158 μmol) and diethyl cyanophosphonate (25.0 μl, 145 μmol) were reacted to give the amide **21 b** in 90% yield (52.5 mg, 57.0 μmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 8:2–7:3). R_f (**21 b**) = 0.11 (petroleum ether:ethyl acetate 7:3). $[\alpha]_D^{20} = -0.2$ (c = 0.5, $CHCl_3$). *Major rotamer:* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (m, 3 H), 0.86–0.93 (m, 6 H), 0.95–1.05 (m, 2 H), 1.15 (d, *J* = 6.7 Hz, 3 H), 1.34 (s, 9 H), 1.43–1.50 (m, 10 H), 1.51–1.58 (m, 3 H), 1.75 (m, 1 H), 2.02 (m, 1 H), 2.37 (m, 1 H), 2.65 (s, 3 H), 2.86 (dd, *J* = 14.0, 10.5 Hz, 1 H), 3.12 (m, 1 H), 3.21 (m, 1 H), 3.80 (s, 3 H), 3.91 (m, 2 H), 4.22 (d, *J* = 10.6 Hz, 1 H), 4.42–4.68 (m, 4 H), 5.16 (m, 1 H), 5.28 (m, 1 H), 5.48 (m, 1 H), 5.97–6.10 (m, 2 H), 6.68 (d, *J* = 8.2 Hz, 1 H), 6.87 (m, 2 H), 7.04 (d, *J* = 8.2 Hz, 1 H), 7.27 (m, 2 H), 7.60 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 19.1, 20.7, 21.1, 28.0, 28.3, 28.4, 31.0, 32.4, 33.4, 36.3, 39.0, 40.9, 41.0, 41.9, 55.3, 60.0, 69.7, 69.7, 70.6, 78.0, 80.3, 82.1, 86.4, 112.2, 113.8, 117.6, 129.7, 129.9, 130.6, 132.0, 132.5, 139.6, 155.0, 155.8, 159.0, 169.2, 170.4, 176.4 ppm. *Minor rotamer (selected signals):* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 2.69 (s, 3 H), 2.80 (dd, *J* = 14.2, 11.5 Hz, 1 H), 7.12 (d, *J* = 7.1 Hz, 1 H), 7.62 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 19.0, 20.8, 31.2, 31.7, 33.4, 36.2, 40.8, 41.0, 60.9, 69.6, 69.9, 71.0, 79.9, 82.0, 86.7, 112.2, 117.5, 130.6, 139.8, 154.6, 155.8, 170.3, 176.5 ppm. HRMS (ESI-ToF) calcd. for $C_{45}H_{68}{}^{127}IN_2O_9$ $[M+H]^+$: 923.3913 found 923.3908.

(3*S*,5*S*,6*R*,8*S*,10*S*)-11-[(*tert*-Butoxycarbonyl)amino]-5-[(4-methoxybenzyl)oxy]-2,6,8,10-tetramethyl-11-oxoundecan-3-yl (*R*)-3-[4-(allyloxy)-3-bromophenyl]-2-[(*tert*-butoxycarbonyl)(methyl)amino]propanoate (21 c): According to GP 7 the acid **20 c** (55.8 mg, 71.0 μmol), glycine *tert*-butylester hydrochloride (16.0 mg, 94.0 μmol), triethylamine (25.0 μl, 176 μmol) and diethyl cyanophosphonate (27.0 μl, 162 μmol) were reacted to give the amide **21 c** in 90% yield (57.2 mg, 63.0 μmol) as a colorless resin after column chromatography (petroleum ether:ethyl acetate 8:2–7:3). R_f (**21 c**) = 0.29 (petroleum ether:ethyl acetate 7:3). $[\alpha]_D^{20} = -25.5$ (c = 1.0, $CHCl_3$). *Major rotamer:* ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.9 Hz, 3 H), 0.86–0.92 (m, 9 H), 0.98–1.10 (m, 3 H), 1.15 (d, *J* = 6.6 Hz, 3 H), 1.40 (s, 9 H), 1.45 (s, 9 H), 1.51 (m, 2 H), 1.75–1.86 (m, 2 H), 2.01 (m, 1 H), 2.37 (m, 1 H), 2.70 (s, 3 H), 2.90 (dd, *J* = 14.2, 9.5 Hz, 1 H), 3.08 (m, 1 H), 3.19 (dd, *J* = 14.2, 6.6 Hz, 1 H), 3.79 (s, 3 H), 3.90 (m, 2 H), 4.18 (d, *J* = 10.4 Hz, 1 H), 4.39 (d, *J* = 10.4 Hz, 1 H), 4.53 (m, 2 H), 4.77 (m, 1 H), 5.12 (m, 1 H), 5.27 (m, 1 H), 5.44 (m, 1 H), 6.01 (m, 1 H), 6.16 (m, 1 H), 6.76 (d, *J* = 8.1 Hz, 1 H), 6.88 (m, 2 H), 7.09 (d, *J* = 8.1 Hz, 1 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.40 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 17.2, 18.2, 19.0, 21.0, 28.0, 28.3, 31.4, 31.9, 32.0, 32.1, 33.6, 33.9, 39.0, 40.6, 40.8, 41.9, 55.2, 59.7, 69.7, 71.2, 76.5, 78.8, 80.0, 81.9, 112.0, 113.5, 113.7, 117.6, 128.9, 129.6, 131.0, 131.4, 132.6, 133.8, 153.6, 155.5, 159.0, 169.2, 170.5, 176.6 ppm. *Minor rotamer (selected signals):* ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.9 Hz, 3 H), 1.36 (s, 9 H), 2.76 (s, 3 H), 2.84 (dd, *J* = 13.9, 11.4 Hz, 1 H), 4.22 (d, *J* = 10.4 Hz, 1 H), 4.45 (d, *J* = 10.4 Hz, 1 H), 7.02 (d, *J* = 8.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 17.4, 18.3, 19.0, 31.6, 33.9, 33.9, 40.8, 41.0, 60.1, 71.1, 79.0, 80.3, 82.1, 112.2, 128.8, 129.7, 130.8, 133.4, 176.3 ppm. HRMS (ESI-ToF) calcd. for $C_{47}H_{72}{}^{79}BrN_2O_{10}{}^+$ $[M+H]^+$: 903.4365 found 903.4359.

Supporting Information

(see footnote on the first page of this article): Copies of NMR spectra of all compounds, synthesis of modified amino acids and peptides.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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