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A "Motif-Oriented" Total Synthesis of Nannocystin Ax. Preparation and Biological Assessment of Analogues

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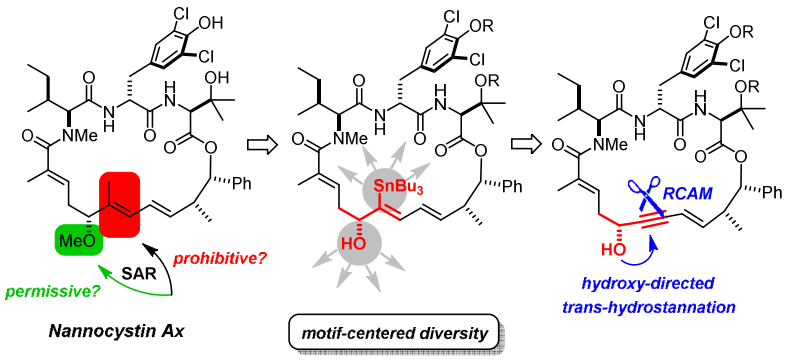
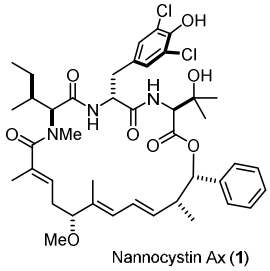


Abstract: The highly cytotoxic cyclodepsipeptides of the nannocystin family are known to bind to the eukaryotic translation elongation factor 1α (EF-1α). Analysis of the docking pose, as proposed by a previous in silico study, suggested that the trisubstituted alkene moiety and the neighboring methyl ether form a domain that might be closely correlated with biological activity. This hypothesis sponsored a synthetic campaign which was designed to be "motif-oriented": specifically, a sequence of ring closing alkyne metathesis (RCAM) followed by hydroxy-directed *trans*-hydrostannation of the resulting cycloalkyne was conceived, which allowed this potentially anchoring substructure to be systematically addressed at a late stage. This inherently flexible approach opened access to nannocystin Ax (**1**) itself as well as to ten non-natural analogues. While the biological data confirmed the remarkable potency of this class of compounds and showed that the domain in question is

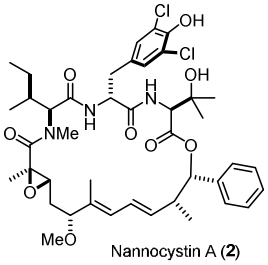
indeed an innate part of the pharmacophore, the specific structure/activity relationships can only partly be reconciled with the original in silico docking study; therefore we conclude that this model needs to be carefully revisited.

Introduction

Myxobacteria are a prolific source of bioactive natural products.[1] In accord with this notion, the hitherto fairly untapped genus *Nannocystis* sp. has recently been shown to produce a small family of cyclodepsipeptides endowed with remarkable antifungal and cytotoxic properties.[2,3] An extensive screening exercise revealed that the naturally occurring nannocystins exhibit desirable differential activity across a comprehensive panel of up to 472 cancer cell lines, including cell lines that are resistant to clinically approved drugs. Importantly, they seem to interfere neither with the actin nor the tubulin cytoskeleton and do not inhibit a number of representative kinases either;[2,3] rather, the eukaryotic translation elongation factor 1α (EF-1α) was identified as the primary biological target.[3] Apart from the potential relevance in a medicinal chemistry context,[4,5] the nannocystins are therefore valuable probe molecules for chemical biology to interrogate translation and protein transport processes in eukaryotic cells.



Nannocystin Ax (**1**)



Nannocystin A (**2**)

As the source organism produces a small compound collection, some preliminary insights into structure/activity relationships (SAR) have been established by the two independent isolation teams (Scheme 1).[2,3] Specifically, nannocystin Ax (**1**) and nannocystin A (**2**) were found almost equipotent

against the HCT-116 colon carcinoma cell line, which suggests that the epoxide ring might not be required for high activity[3] (although one of the isolation teams had originally concluded otherwise).[2] The chlorine substituents on the D-tyrosine unit are not essential either and can be replaced by –H or –Br without much loss in potency.[2,3] In this context it is interesting to note that epoxidation and chlorination occur late in the biosynthesis pathway, only after the macrocyclic framework has been forged by lactonization with concomitant cleavage of the mixed polyketide/peptide chain off the carrier protein.[3] In silico docking studies suggested that nannocystin A (**2**) binds to a rather shallow cavity on the surface of EF-1α,[6] whereby hydrophobic interactions seem to prevail over hydrogen bonding between guest and host.[3] In line with this analysis, derivatization of the phenol –OH group or exchange of L-isoleucine for L-valine did not alter the cytotoxicity by much.[2,3]

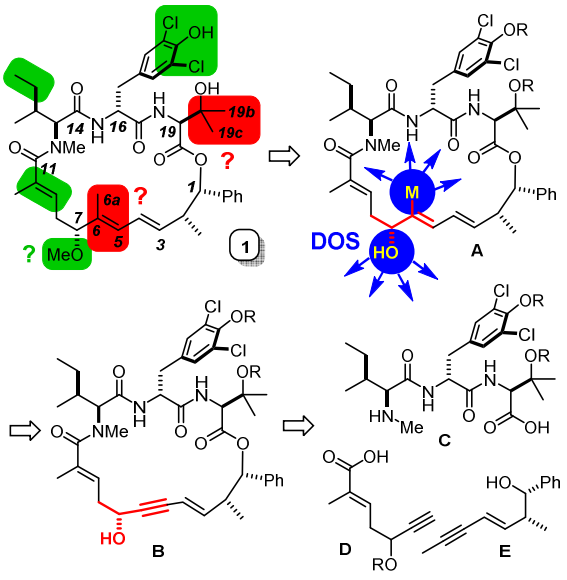
For their potency and relevance, the nannocystins immediately caught the attention of the synthetic community; no less than six different total syntheses have been reported in short order.[7,8,9,10,11,12] While two of them resorted to macrolactamization to form the 21-membered backbone,[10,12] it is chemically telling that all other successful approaches targeted the conspicuous diene unit embedded into the polyketide sector, using either robust cross coupling[7,9,11] or equally well-established alkene metathesis to form the ring (although the latter was not stereoselective).[8,13] The total synthesis outlined below is conceptually different in that it was not designed for the sake of rapid conquest of a single representative of this family but rather meant to open access to structural variants that allow the pharmacophore to be mapped at a potentially critical but as yet uncharted domain. Although certainly in keeping with the general concept of "diverted total synthesis",[14,15] the logic of the approach is more focused in that it is strictly oriented towards a potential key motif within the pharmacophore.

Results and Discussion

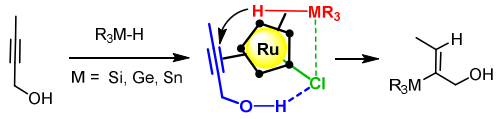
Strategic Considerations. As alluded to above, the computed docking pose of nannocystin A (**2**) seems to result from weak but likely additive hydrophobic interactions with its EF-1α protein host.[3] A closer look reveals only two somewhat deeper sub-pockets within an overall rather shallow binding site: one of them accommodates the *gem*-dimethyl group of the 3-hydroxy-L-valine unit, whereas the other one embraces the C6a-Me substituent on the diene; the neighboring C7–OMe group, in

contrast, was computed to point away from the protein surface, just as the epoxide ring does, which is known not to be mandatory for high activity.[3] One can therefore expect that the allylic methyl ether is also a potentially forgiving site: if so, it might qualify for chemical modification in order to adjust the physico-chemical properties of the compounds or to attach appropriate linkers. On the other hand, excision of the C6a and the C19b,c methyl substituents is forecasted to be detrimental, while their formal replacement by other hydrophobic residues might allow potency and lipophilicity to be fine-tuned.

SCHEME 1. Color-Coded Summary of Confirmed and Anticipated ("?") SAR (green/red = permissive/prohibitive site), see Text; Retrosynthetic Analysis of Nannocystin A Focusing on the Presumably Critical Trisubstituted Alkene Entity; "DOS" Indicates the Envisaged Sites for "Motif-Oriented" Diversity



SCHEME 2. Directing Effect Exerted by a Propargylic –OH Group onto the Regiochemical Course of *trans*-Hydrometalation Catalyzed by [Cp*Ru–Cl]; in the Newman-type Projection of the Putative Loaded Catalyst, • Denotes the Me-Substituents of the Cp* Ring



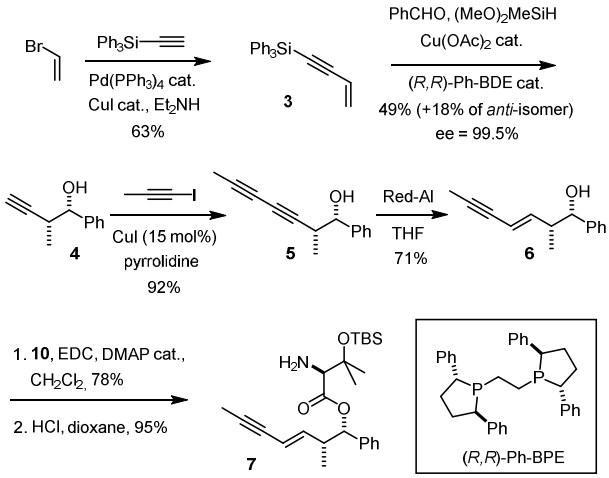
Based on this analysis, we considered the trisubstituted C5-C6 double bond flanked by the –OMe group to be the strategic site for disconnection (Scheme 1): it is this substructure which we wished to address for the purpose of late-stage diversification. The stereoselective and – at the same time – flexible formation of highly substituted alkenes embedded into a macrocyclic scaffold, however, is far from trivial. Ring closing alkyne metathesis (RCAM)[16] followed by regioselective *trans*-hydrometalation[17,18] of the ensuing alkyne might allow this challenge to be met, even though this tactic has not yet been applied within a similarly challenging chemical environment. Although RCAM had previously excelled with complex peptidic substrates,[19,20] it was by no means clear at the outset of this investigation whether *trans*-hydrometalation qualifies in the present context: this transformation gains high regioselectivity only if a protic substituent on the substrate steers the incoming [Cp*Ru–Cl] catalyst via hydrogen bonding to the chloride ligand and, in doing so, imposes directionality on the transition state (Scheme 2).[21,22] While the C7–OMe ether of **1** can obviously be traced back to a propargylic –OH group which then provides the necessary handle, we felt unable to assess with any level of certainty whether or not the protic amide linkages in transannular proximity in a substrate of type **B** interfere with or potentially even disrupt this crucial preorganization.[23] If regioselective *trans*-hydrometalation is successful, however, the –OH substituent in the resulting product **A** provides an additional opportunity for late-stage modification: under the premise that the –OR group truly points away of the protein surface once the compound is bound to EF-1α,[3] it should not matter much whether this group remains unprotected, is converted into the parental methyl ether, or is transformed into another biologically viable substituent.

Preparation of the Building Blocks and Fragment Coupling. Since one of the isolation teams had shown that the epoxide ring is not necessary for high potency,[3] we chose nannocystin Ax (**1**) as our lead target. For the preparation of the required enyne fragment **E** (Scheme 1), we adapted the copper-catalyzed asymmetric carbonyl addition chemistry recently developed by Buchwald and coworkers.[24] This transformation was described only for ketone substrates, most likely because aldehydes are subject to competing reduction by the copper hydride species generated in situ. As the

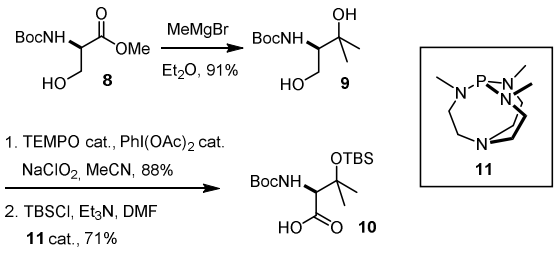
projected application required nothing but benzaldehyde, it was deemed acceptable to drive the conversion by using this cheap substrate in excess. In doing so, optically active **4** (ee = 99.5%) became available in only two steps from vinyl bromide (Scheme 3). The brevity of the approach, the attractive catalyst loading (0.5 mol%, unoptimized), and the excellent optical purity of product **4** clearly outweighed the modest diastereoselectivity (dr = 2.8:1), not least because the *anti*-isomer could be removed by flash chromatography. Alkyne **4** was then cross coupled with iodopropyne,[25] followed by a regio- and stereoselective semireduction of the propargylic triple bond of 1,3-diyne **5** thus formed.[26] The resulting product **6** was esterified with protected 3-hydroxyvalinate **10**, which in turn was readily available from D-serinate **8** by taking advantage of the hidden symmetry (Scheme 4).[27]

Since the asymmetric allylation of propynal derivatives such as **12** tend to be unsatisfactory under a multitude of conditions,[28] the preparation of the acid fragment commenced with enzymatic resolution of *rac*-**13**, which furnished optically pure **14** (ee > 99%) on multigram scale (Scheme 5);[29] the recovered alcohol (*S*)-**13** can also be converted into **14** by a Mitsunobu reaction.[30] The elaboration of **14** into acid **16** involved selective ozonolysis of the double bond in the presence of the alkyne, Wittig olefination,[31] saponification of the two ester units and attachment of a TBS protecting group. Ghosez's chloroenamine reagent proved most adequate for the conversion of the acid **16** into the required acid chloride **17**.[32,33]

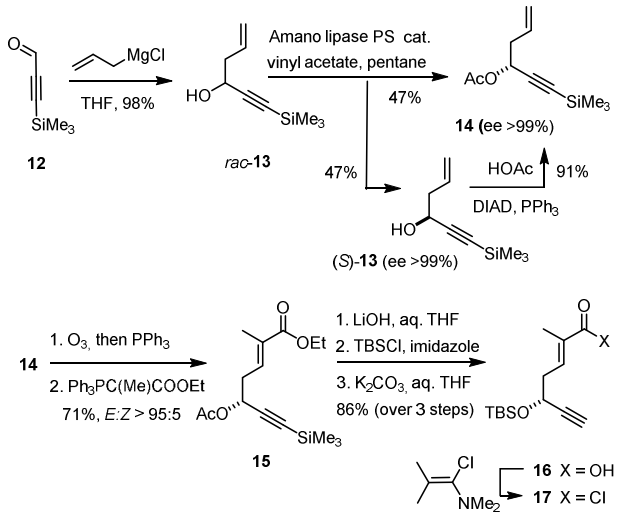
SCHEME 3. **Preparation of the Enyne Building Block**



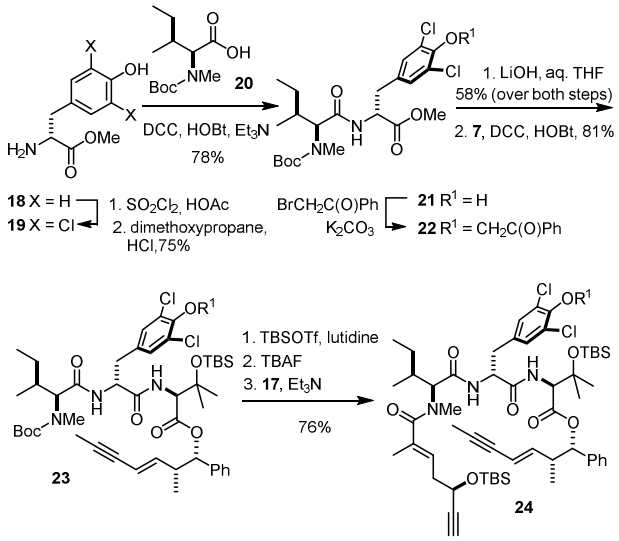
SCHEME 4. Preparation of the 3-Hydroxyvalinate Building Block



SCHEME 5. Preparation of the Acid Segment



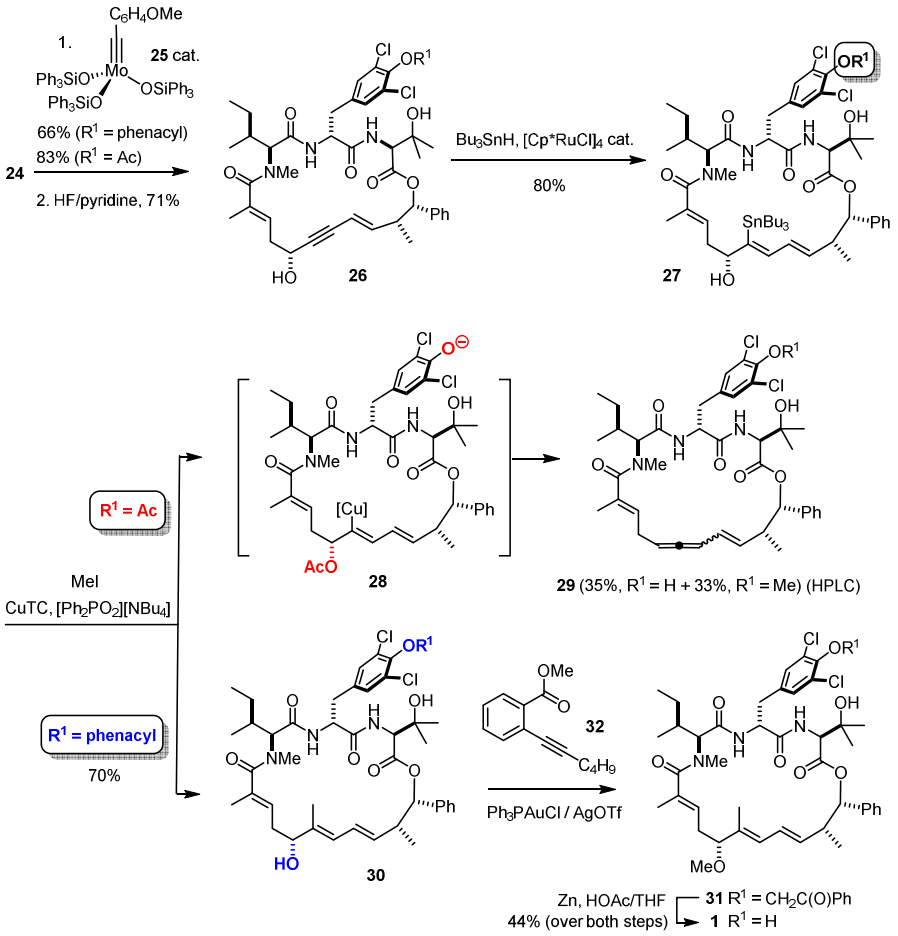
SCHEME 6. Preparation of the Cyclization Precursor



The synthesis of the dipeptide fragment **22** largely followed established routes (Scheme 6). Specifically, selective dichlorination of methyl tyrosinate **18** and condensation with commercially available N-Boc-N-methyl isoleucine **20** furnished **21**.[34,35] An acetyl group was initially considered as the protecting group for the phenol to avoid problems in the subsequent esterification and peptide coupling events; this group, however, later turned out to engage in transannular acyl migration (see below). The phenacyl group proved to be a practical and more stable alternative.[36] Whereas coupling of amine **7** with dipeptide **22** proceeded without incident, the missing amide linkage at the sterically hindered N-methyl-L-isoleucine terminus was more difficult to form (Scheme 6).[37] To this end, **23** was treated with a large excess of TBSOTf/lutidine because (partial) silylation of the amides preceded cleavage of the N-Boc residue; work up of the crude material with TBAF gave the desired free amine; this compound reacted well with acid chloride **17**, which was prepared from **16** on demand as mentioned above.

Macrocyclization and Completion of the Total Synthesis. With compound **24** in hand, the stage was set for ring closure by RCAM and downstream elaboration of the resulting cycloalkyne into nannocystin Ax (**1**) (Scheme 7). While metathesis of two terminal alkynes remains erratic in our hands,[38] previous work from this laboratory has shown that reactions of substrates comprising *one* terminal and *one* internal alkyne are robust and scalable.[39,40] Indeed, the molybdenum alkylidyne catalyst **25**[41] endowed with silanolate ligands converted compound **24** within no more than 15 minutes at ambient temperature into the corresponding macrocyclic enyne which was desilylated to give **26** in readiness for the projected *trans*-hydrostannation. This example highlights the reactivity and functional group tolerance of **25** as the prototype member of the arguably most selective generation of alkyne metathesis catalysts currently available. Since Schrock alkylidynes are inherently nucleophilic at carbon,[42] the compatibility with protic sites as well as different carbonyl groups is by no means obvious.[43] Equally important in the present case is the ability of **25** to distinguish between triple and double bonds: whereas alkynes react smoothly, olefins are inert independent of their electronic nature, degree of substitution and chemical microenvironment.[16,44,45]

SCHEME 7. Completion of the Total Synthesis of Nannocystin Ax (1)



After the propargylic –OH group had been unveiled, which is needed to impose directionality on the projected *trans*-hydrostannation (see Scheme 2) and has to overwrite any detrimental influence of the two other protic sites embedded into the macrocyclic array,[21,22] alkyne **26** was reacted with Bu_3SnH and catalytic amounts of $[Cp^*RuCl]_4$ in CH_2Cl_2. Gratifyingly, this transformation proceeded cleanly, provided that the stannane was slowly added to the reaction mixture. Under these conditions, product **27** was basically formed as a single regio- and stereoisomer,[46] which was isolated in 80% yield. The structure of the enyne substrate **26** in the solid state (Figure 1) might help to explain why this transformation proceeded so selectively: it shows that the directing hydroxy group at C7 as well as the flanking C5-C6 alkyne to be hydrometalated are well exposed to the sterically

demanding [Cp*RuCl] catalyst.[47] In any case, this elaborate example illustrates the robustness of this emerging methodology that has already served total synthesis well on several other occasions.[48]

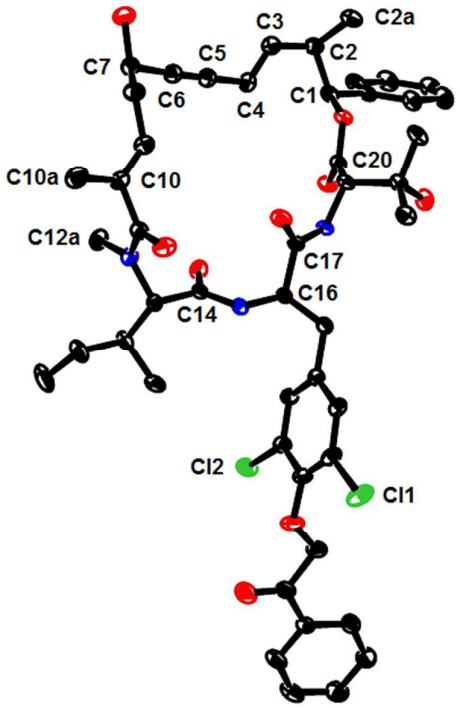
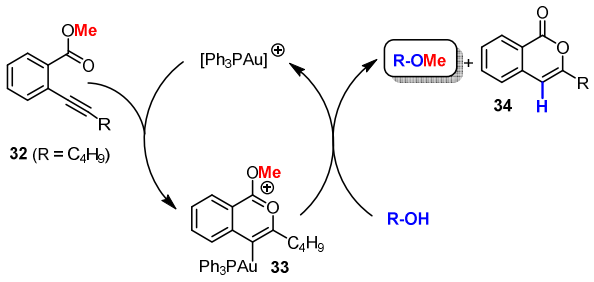


Figure 1. Structure of cycloalkyne **26** in the solid state; the compound crystallized as a mono-hydrate, (not shown for clarity); numbering scheme as introduced by the isolation team and used throughout this paper. Anisotropic displacement parameters are shown at 50% probability level.

The alkenylstannane unit in **27a** (R^1 = phenacyl) was amenable to C-methylation under conditions previously developed in our laboratory:[49] thus, treatment with CuTC, $[Ph_2PO_2][NBu_4]$ and MeI furnished the desired alkene **30** in good yield without scrambling of the double bond geometry. It was at this stage that the phenacyl protecting group proved necessary: compound **27b** (R^1 = Ac) differing only in the presence of an acetyl moiety on the tyrosine's phenolic –OH reacted much less cleanly; actually, allene formation prevailed (with or without concomitant methylation of the liberated phenol). We feel confident to ascribe this outcome to transannular acyl migration prior to/concomitant with tin/copper exchange; the presence of the good leaving group at the allylic position of the putative organocopper intermediate **28** entails rapid elimination that outcompetes

the desired C-methylation. Although allene formation was undesirable in the present context, it provides an opportunity for alternative downstream processing of the products available by hydroxy-directed *trans*-hydrometalation. Studies along these lines are underway and will be reported in due course.

SCHEME 8. Base-free, Gold Catalyzed Formation of Methyl Ethers



With access to **30** secured, the completion of the total synthesis appeared to be straightforward. Yet, the seemingly trivial O-methylation proved to be rather challenging. Although the desired product **31** could be formed under a variety of conditions (e. g. MeI/Ag_2O, $[Me_3O]BF_4$/proton sponge, eOTs/K_2CO_3), the reactions were not overly clean and the yields fairly erratic. After considerable experimentation, we conceived of a somewhat unorthodox yet potentially widely applicable alternative method (Scheme 8): the required $[H_3C^+]$ equivalent was generated in situ by a gold-catalyzed cyclization of **32**;[50] in this case, addition of an external base is not necessary as the proton of the alcohol to be methylated gets trapped upon protodeauration of intermediate **33**, which releases the $[LAu^+]$ fragment and closes the catalytic cycle. When applied to **30**, this method proved indeed more reliable than the classical alternatives; the resulting crude methyl ether **31** was subjected to reductive cleavage of the phenacyl group with zinc dust in acidic medium[36] to furnish nannocystin Ax (**1**). Although the spectra of our synthetic samples were in good accord with the published data, we noticed the presence of a second set of signals which had not been described by the isolation team.[3] Variable-temperature NMR proved that this characteristic spectral signature is caused by a second conformer and not by any isomer that might have gone unrecognized throughout the synthesis. Liu and coworkers have recently described a similar observation.[11]

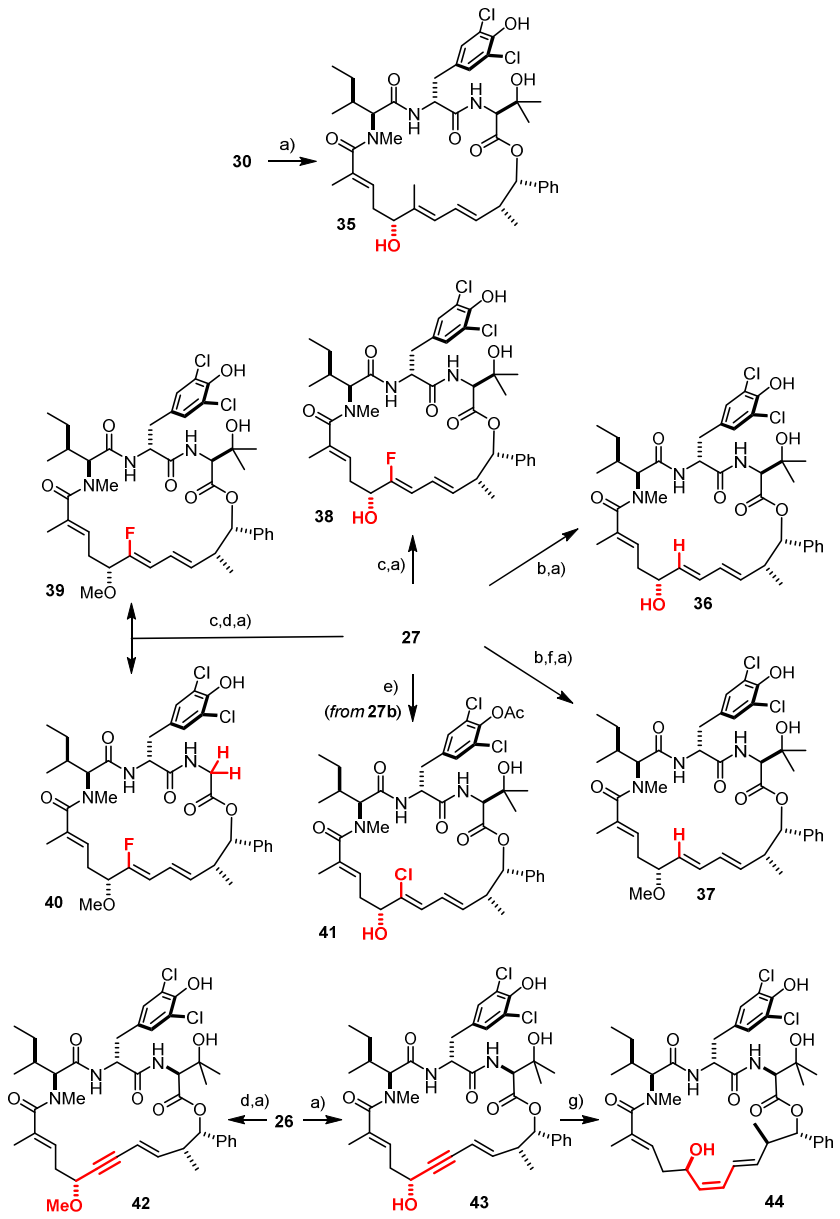
Late-Stage Diversification. For its convergence, the route to nannocystin Ax (**1**) described above provides many opportunities for structural modifications of the skeleton and variation of the stereostructure, if desirable. In a first foray, we intended to alter the trisubstituted alkene and its flanking –OR substituent to probe whether this substructure is critical for the biological activity or not. It is emphasized, however, that none of the transformations leading to the analogues shown in Scheme 9 has been fully optimized at this point.

Deprotection of compound **30** prior to O-methylation afforded product **35** differing from the natural product **1** only by the absence of the methyl ether; the comparison should hence reveal if this substituent, which is supposed to point away from the binding side,[3] exerts any noticeable influence on cytotoxicity. In contrast, the C6a-methyl group branching off the alkene was computed to be immersed into one of only two deeper hydrophobic sub-pockets of the binding site;[3] formal deletion should therefore have a quite pronounced effect. This structural modification was readily attained by protodestannation of **27**, which paved the way to the desired nor-methyl compound in O-unprotected (**36**) as well as O-methylated format (**37**).

Along the same lines, formal replacement of the C6a-methyl group by a fluorine atom was deemed interesting.[51] To this end, fluoro-destannation of **27** according to a procedure recently developed in our laboratory[52] furnished the fluoroalkene analogue in form of the corresponding alcohol **38** and the derived methyl ether **39**. In this particular case, O-methylation had actually been carried out before the new gold-catalyzed procedure was developed, using MeOTs/K_2CO_3 in acetone. Under these basic conditions, partial cleavage of the *tert*-alcohol group of the 3-hydroxyvaline unit took place. This unexpected but certainly not implausible retro-aldol reaction warrants further optimization because it might allow for profound modifications of the skeleton at a late stage. Comparison of the fluorinated analogues **40** and **39** with a truncated and intact backbone, respectively, should show whether this site is critically important for activity as the in silico docking study insinuates.

Additional analogues for testing were the chloroolefin **41**[53] as well as the alkynylogous nannocystins **42** and **43**, differing only in the presence or absence of the methyl ether cap. Finally, a Lindlar-type semi-reduction of **43** furnished the geometrical isomer **44**, which – upon comparison with **35** – should indicate whether the stereochemical integrity of the diene is relevant or not.

SCHEME 9. Preparation of a Focused Library of Analogues; Structural Modifications Relative to the Parent Compound 1 are Indicated in Red[a]



[a] Reagents and Conditions: a) Zn, HOAc, THF, 78% (**35**), 75% (**36**), 37% (**37**) (over steps f,a)), 87% (**38**), [34% (**39**) + 28% (**40**)] (over steps d,a))], 45% (**42**, over steps d,a)), 80% (**43**); b) CuTC, $[Ph_2PO_2][NBu_4]$, DMF, 86%; c) $AgOP(O)Ph_2$, F-TEDA-PF_6, acetone, 54%; d) K_2CO_3, MeOTs, acetone; e) $CuCl_2$, lutidine, THF, 82%; f) **32**, Ph_3PAuCl, AgOTf, benzene; g) Zn(Cu/Ag), aq. MeOH/1,4-dioxane, 62%.

From the conceptual viewpoint, we like to emphasize that all compounds described herein were fairly straightforward to make; yet, they invariably feature deep-seated structural modifications that could not be reached – without undue effort – by chemical derivatization of the natural product. Therefore this set of ten non-natural analogues exemplifies the concept of "diverted total synthesis" as a means to explore chemical space surrounding a prevalidated natural lead.[14,15] Yet, the modifications are not random but "motif-oriented" in that they exclusively address a presumably relevant domain.

Biological Assessment. The first round of screening assessed the cytotoxicity of this panel of compounds using the HCT-116 human colon carcinoma and the HL-60 human promyelocytic leukemia cell lines. Synthetic nannocystin Ax (**1**) allowed for comparison with the literature and hence served as the calibration point. Actually, the IC_{50} for synthetic **1** was lower than that reported for natural **1** in the literature (Table 1),[3] but both data points lie in the low single-digit nanomolar range. Whether this difference is due to different assay conditions or is caused by other reasons cannot be decided; in this context, however, we like to point out that the two different isolation teams reported a similar differential in the IC_{50} for the sister compound **2**.[2,3] Therefore we feel confident that the data are relevant and comparable.

Table 1. Initial Profiling of Nannocystins in Terms of Cytotoxic Activity (Half-Inhibitory Concentrations after 5 d of Incubation, IC_{50} [nM]) on HCT-116 and HL-60 Cells

Compound	HCT-116	HL-60
1	0.8 [5.4][3]	5.9
2	[1.2][2] / [5.1][3]	[12][2]
39	1.5	58.6
37	4.3	46.4
42	22.2	245
35	198	767
41	1190	2964
38	1345	2702
36	1549	2108
43	1761	4254
44	2472	4366
40	3918	10229

The results compiled in Table 1 show several clear-cut trends: nannocystin Ax (**1**) itself proved to be the most potent compound of the series, but the desmethyl derivative **37** as well as the fluoro-analogue **39** are almost as active; even the alkynylogous derivative **42** retains appreciable potency, most notably against the HCT-116 cell line. However, these findings are difficult to reconcile with the forecast from the in silico docking experiments, which had suggested that the C6a-Me group occupies a privileged site within an otherwise rather featureless and shallow binding pocket.[3] Its excision, as manifest in **37**, or its replacement by a strongly polarized C–F unit as in **39** had therefore been expected to entail a stronger biological response.

Equally if not even more surprising was the other remarkable pattern manifest in the data: Nannocystin Ax (**1**) is more than two orders of magnitude more potent than its alcohol sibling **35**, although the –OMe substituent had been computed to point out of the binding pocket.[3] Therefore this dramatic difference was unexpected but is consistently found for all alcohol/ether pairs (**35**/**1**, **36**/**37**, **38**/**39**). None of the other C7-OH derivatives (**41**, **44**) showed appreciable activity either. Within the –OH subseries, however, **35** comprising the *E,E*-configured diene is clearly more potent than is geometrical isomer **44** with an *E,Z*-entity.

Of arguably very high relevance is the fact that the truncated fluoroalkene analogue **40** is > $2.6 \cdot 10^3$ times less active than fluoroalkene **39** featuring the intact backbone. **40** is actually the least cytotoxic compound of the entire series, which advocates the notion that 3-hydroxyvaline is a very critical segment within the pharmacophore, likely because the two methyl groups engage in hydrophobic contacts with the protein host.[3] This conclusion warrants a much more detailed assessment in future studies.

Table 2. Half-Inhibitory Concentrations (IC_{50} [nM]) of the Most Potent Nannocystin Derivatives on a Panel of Six Cancer Cell Lines of Human Origin[a]

Compound	HCT-116	HL-60	KB-3.1	THP-1	U-2 OS	U937
1	0.8	5.9	1.7	1.3	0.2	5.0
39	1.5	58.6	7.8	33.4	11.2	141
37	4.3	46.4	5.9	20.5	3.5	33.5
42	22.2	245	83.6	81.2	20.2	198

[a] The histotypes are as follows: HCT-116: colon carcinoma; HL-60: promyelocytic leukemia; KB-3.1: cervical carcinoma; THP-1: acute monocytic leukemia; U-2 OS: osteosarcoma; U937: histiocytic lymphoma

Nannocystin Ax (**1**) and the three single most potent analogues were then screened more broadly. As can be seen from Table 2, the ranking in terms of potency between the fluoro-analogue **39** and the nor-methyl derivative **37** observed with HCT-116 was inverted in all other cell lines, although the differences are rather small and must not be overinterpreted. Importantly, the sensitivity of the chosen six human cancer cell lines towards the individual compounds provides a consistent picture. Therefore, it seems that the trisubstituted alkene motif of nannocystin Ax is a more permissive site for structural modification than anticipated, whereas changes to the flanking –OMe ether substituent are much more critical than forecasted by the currently only binding model published in the literature.[3] Although our data suggest that this purely computational proposal needs to be revisited and calibrated in more detail, we like to emphaisze that cell toxicity is the total score of various factors. Therefore additional SAR data are necessary before a final conclusion can be drawn.

Conclusions

In contrast to all previous syntheses of members of the nannocystin family,[7-12] the approach described herein is "motif-focused" rather than purely "target-oriented" in conceptual terms.[54] It was deliberately designed to alter and hence interrogate a subsite embedded into the molecular frame that was suggested to play a critical role in the binding of these highly cytotoxic agents to EF-1α as their primary biological target. This goal was accomplished with the aid of a reaction sequence comprised of ring closing alkyne metathesis followed by hydroxy-directed *trans*-hydrostannation of the resulting macrocyclic propargyl alcohol derivative. This tactic opened a selective yet flexible entry into di- as well as trisubstituted alkenes including nannocystin Ax itself and a set of ten non-natural analogues; these derivatives are distinguished by deep-seated structural "point mutations" that would not be accessible by derivatization of the natural lead. Moreover, the chosen strategy is almost certainly of interest in entirely different chemical contexts too. Assessment of the cytotoxicity

of the synthetic compound collection provided important insights into the SAR of the critical motif, which calls for revision reassessment of the only available model meant to describe the binding of the cyclodepsipeptides of the nannocystin family to their protein host.[3]

EXPERIMENTAL SECTION

Cytotoxic activity (IC_{50}). Cell lines were obtained from the German Collection of Microorganisms and Cell Cultures (*Deutsche Sammlung für Mikroorganismen und Zellkulturen*, DSMZ) or the American Type Culture Collection (ATCC). All cell lines were cultured under conditions recommended by the depositor. Cells were seeded at 5 x 10^4 cells per well in 96-well plates in 180 µL medium supplemented with 10% FBS (McCoy´s 5A modified medium for HCT-116, U-2OS, and KB-3.1 cells; RPMI 1640 medium for HL-60 ,THP- 1, and U937 cells) and treated with nannocystins dissolved in DMSO in serial dilution after 2 h of equilibration. Cells were treated for 5 d. For adherent cells, 20 µL of 5 mg/mL MTT (thiazolyl blue tetrazolium bromide) in PBS (phosphate-buffered saline; pH 7.4) were added per well and cells were incubated for additional 2 h at 37 °C and 5 % CO_2. The medium was discarded and 100 µL 2-propanol/ HCl (10 M, 250:1) was added in order to dissolve formazan granules. The absorbance at 570 nm was measured using a microplate reader (Tecan M200Pro). For suspension cell lines, 20 µL of 0.2 mg/mL alamar blue (resazurin sodium salt) in PBS were added per well and cells were incubated for additional 24 h at 37 °C and 5% CO_2. The fluorescence intensity at 570 nm (excitation wavelength: 540 nm) was measured using a microplate reader (Tecan M200Pro). Cell viability correlates with the absorbance and fluorescence intensity values, respectively, and was expressed as percentage relative to the respective solvent control. Half inhibitory concentrations (IC_{50}) were determined by sigmoidal curve fitting.

General Remarks. Unless stated otherwise, all reactions were carried out under argon in flame-dried glassware using anhydrous solvents. The solvents were purified by distillation over the following drying agents and were transferred: THF, Et_2O (Mg/anthracene), CH_2Cl_2, toluene (Na/K), MeOH (Mg, stored over MS 3 Å); DMF, DMSO, Et_3N, 1,4-dioxane and pyridine were dried by an adsorption solvent purification system based on molecular sieves; anhydrous (99.9%) cyclopentyl methyl ether (CPME) purchased from Aldrich was kept in a flame-dried Schlenk flask containing MS 4 Å under argon. Thin layer chromatography (TLC): Macherey-Nagel precoated plates (POLYGRAM®SIL/UV254);

Preparative TLC: Macherey-Nagel precoated plates (SIL G-100 UV 254; silica gel layer: 1.0 mm); Flash chromatography: Merck silica gel 60 (40–63 μm) with predistilled or HPLC grade solvents; Celite® was dried at 170 °C for 48 h under high vacuum (1×10^{-3} mbar) and stored under argon. NMR: Spectra were recorded on Bruker DPX 300, AV 400, AV 500 or AVIII 600 spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_C = 77.16 ppm; residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm; CD_3OD: δC = 49.0 ppm; residual CHD_2OD: δ_H = 3.31 ppm, $(CD_3)_2CO$: δC = 29.8, 206.3 ppm; residual CD_3CHD_2OD: δ_H = 2.05 ppm, $(CD_3)_2SO$: δ_C = 39.5 ppm; residual CD_3CHD_2SO: δ_H = 2.50 ppm). IR: Spectrum One (Perkin-Elmer) spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV, doubly focused sectorfield MS), ESI-MS: ESQ3000 (Bruker, ion trap), accurate mass determinations: Bruker APEX III FTMS (7 T magnet, ion cyclotron resonance MS) or Mat 95 (Finnigan, doubly focused sectorfield MS). Optical rotations ($[\alpha]_D^{20}$) were measured with a Perkin-Elmer Model 343 polarimeter. LC-MS analyses were conducted on a Shimadzu LCMS 2020 instrument (pumps LC-20AD, autosampler SIL-20AC, column oven CTO-20AC, diode array detector SPD-M20A, controller CBM-20A, ESI detector and software Labsolutions) with an ZORBAX Eclipse Plus C18 1.8 μm, 3.0 or 4.6 mm ID × 50 mm (Agilent). A binary gradient of MeCN or MeOH in water or aq. triethylammonium acetate buffer (10 mmol. pH 8) was used at a flow rate of 0.5 (3.0 mm ID) or 0.8 (4.6 mm ID) mL/min. The oven temperature was kept at 35 °C and the detection wave length at 254 nm. Preparative LC was performed with a Shimadzu LC-20A prominence system (pumps LC-20AP, column oven CTO-20AC, diode array detector SPD-M20A, fraction collector FRC-10A, controller CBM-20A and software LC-solution); conditions for each compound are specified below. Determinations of the enantiomeric excess (ee) were performed by HPLC or GC using the chiral stationary phases and conditions specified below. Unless stated otherwise, all commercially available compounds (Alfa Aesar, Aldrich, TCI, Strem Chemicals) were used as received.

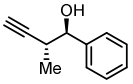
But-3-en-1-yn-1-yltriphenylsilane (3).[55] Ethynyltriphenylsilane (5.00 g, 17.6 mmol) and vinyl bromide (1.0 M in THF, 22.9 mL, 22.9 mmol) were added to a solution of CuI (67.0 mg, 0.352 mmol) and $[Pd(Ph_3P)_4]$ (101 mg, 87.4 μmol) in diethylamine (8.7 mL). The resulting mixture was stirred at ambient temperature for 24 h before the reaction was quenched with water. The aqueous layer was

extracted with pentane/diethyl ether (1:1, 100 mL), the combined extracts were washed with HCl (1 M), dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography on silica gel (hexanes) to afford the title compound as a white solid (3.41 g, 63%). mp = 99.0-99.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.66 (m, 6H), 7.48–7.37 (m, 9H), 5.98 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.87 (dd, *J* = 17.6, 2.4 Hz, 1H), 5.64 (dd, *J* = 11.0, 2.4 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.7, 133.6, 130.1, 129.4, 128.1, 117.3, 108.2, 90.0 ppm; IR (film) ν = 3068, 2152, 1428 cm^{-1}; MS (EI)*: m/z* (%): 105 (94), 129 (50), 155 (41), 181 (100), 203 (20), 232 (83), 310 (29); HRMS (ESI)*: m/z* calcd. for $C_{22}H_{18}Si$ [M^+]: 310.1172, found: 310.1177.

(1*S*,2*R*)-2-Methyl-1-phenylbut-3-yn-1-ol (4). Dimethoxymethylsilane (1.3 mL, 10.5 mmol) was added at 0 °C to a stirred solution of $Cu(OAc)_2$ (1.9 mg, 10.5 μmol), (*R,R*)-Ph-BPE (6.4 mg, 12.6 μmol), **3** (650 mg, 2.09 mmol), benzaldehyde (640 μL, 6.30 mmol) and *t*-BuOH (200 μL, 2.10 mmol) in cyclohexane (4.2 mL). The mixture was stirred at this temperature for 10 h. The reaction was carefully quenched with NaOH solution in MeOH (2 M, ca. 30 mL) (*Caution*: gas evolution) and stirring continued for 10 h before the mixture was diluted with H_2O. The aqueous layer was extracted with EtOAc (3 x 100 mL), the combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated. After a recrystallization from hexane, the crude material was purified by flash chromatography on silica gel (hexanes/*tert*-butyl methyl ether, 10:1 to 8:1) to afford the title compound **4** (165 mg, 49%, 99.5% ee) and the *anti*-isomer (61.4 mg, 18%, 98.7% ee), each as a colorless oil. [The ee was determined by HPLC analysis: Daicel Chiralpak IA (4.6 mm × 250 mm), *n*-heptane/2-propanol = 98/2, *v* = 1.0 mL·min-1, λ = 220 nm, t (minor) = 13.42 min, t (major) = 14.81 min; HPLC analysis of the *anti*-isomer: Daicel Chiralpak IC-3 (4.6 mm × 150 mm), *n*-heptane/2-propanol = 99.5/0.5, *v* = 1.0 mL·min-1, λ = 220 nm, t (minor) = 10.33 min, t (major) = 14.92 min].

Analytical data of **4**: $[\alpha]_D^{20}$ = –47.6 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.28 (m, 5H), 4.75 (dd, *J* = 5.5, 3.6 Hz, 1H), 2.88 (qdd, *J* = 7.0, 5.5, 2.5 Hz, 1H), 2.22 (d, *J* = 3.6 Hz, 1H), 2.12 (d, *J* = 2.4 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.3, 128.3, 128.0, 126.6, 86.0, 76.3, 71.0, 34.2, 15.7 ppm; IR (film) ν = 3292, 2977, 2936 cm^{-1}; MS (ESI) *: m/z*: 178 [$M+NH_4^+$], 183 [$M+Na^+$]; HRMS (ESI)*: m/z* calcd. for $C_{11}H_{12}ONa$ [$M+Na^+$]: 183.0780, found: 183.0782.

Analytical data of the *anti*-isomer: $[\alpha]_D^{20}$ = +68.3 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CHCl_3$): δ = 7.42–

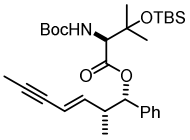


7.28 (m, 5H), 4.52 (dd, *J* = 7.2, 3.6 Hz, 1H), 2.81 (pd, *J* = 7.1, 2.4 Hz, 1H), 2.50 (d, *J* = 3.8

Hz, 1H), 2.22 (d, *J* = 2.4 Hz, 1H), 1.11 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.4, 128.5, 128.2, 126.8, 85.6, 77.6, 71.5, 35.3, 17.5 ppm; IR (film) ν = 3293, 2977, 2936 cm^{-1}; MS (EI)*: m/z* (%):79 (100), 107 (74); HRMS (ESI)*: m/z* calcd. for $C_{11}H_{12}ONa$ [M+Na^+]: 183.0780, found: 183.0781.

(1*S*,2*R*)-2-Methyl-1-phenylhepta-3,5-diyn-1-ol (5).[56] CuI (24.9 mg, 0.131 mmol) was added to a stirred solution of **4** (140 mg, 0.874 mmol) and freshly prepared iodopropyne (excess, ca. 10 equiv.)[25] in degassed pyrrolidine (44 mL), causing an immediate color change to green. After stirring for 10 h, the then yellow mixture was diluted with HCl (2 M, 50 mL). and extracted with *tert*-butyl methyl ether (3 × 100 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether, 10:1) to afford the title compound as a pale yellow oil (159 mg, 92%). $[\alpha]_D^{20}$ = –9.0 (c 2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.33 (m, 4H), 7.32–7.27 (m, 1H), 4.72 (d, *J* = 5.5 Hz, 1H), 2.95–2.86 (m, 1H), 2.17 (d, *J* = 3.2 Hz, 1H), 1.90 (d, *J* = 1.1 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.3, 128.3, 128.0, 126.6, 77.6, 76.4, 74.7, 68.1, 64.3, 35.0, 15.6, 4.4 ppm; IR (film) ν = 3420, 2975, 2932, 2914, 1453 cm^{-1}; MS (ESI): *m/z*: 198 [M+NH_4^+], 221 [M+Na^+]; HRMS (ESI): *m/z:* calcd. for $C_{14}H_{14}ONa$ [M+Na^+]: 221.0937, found: 221.0938.

(1*S*,2*R*,*E*)-2-Methyl-1-phenylhept-3-en-5-yn-1-ol (6). Red-Al® (3.5 M in toluene, 0.57 mL, 2.0 mmol) was added to a stirred solution of **5** (100 mg, 0.504 mmol) in THF (1.0 mL) at room temperature. The mixture was stirred at 65 °C for 2 h before the reaction was carefully quenched with HCl (1 M, 4.0 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined extracts were washed with brine and dried with Na_2SO_4. The solvent was evaporated and the residue purified by chromatography on silica gel (hexanes/EtOAc, 20:1) to afford the title compound as a colorless oil (71.3 mg, 71%). $[\alpha]_D^{20}$ = +8.5 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.24 (m, 5H), 5.97 (ddd, *J* = 16.0, 7.6, 0.8 Hz, 1H), 5.44 (dqd, *J* = 16.0, 2.3, 1.3 Hz, 1H), 4.60 (dd, *J* = 5.6, 3.6 Hz, 1H), 2.69–2.54 (m, 1H), 1.91 (d, *J* = 2.3 Hz, 3H), 1.87 (d, *J* = 3.6 Hz, 1H), 1.01 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.2, 142.4, 128.3, 127.7, 126.6, 111.1, 85.4, 78.2, 44.4, 14.5, 4.4 ppm; IR (film) ν = 3428, 3029, 2964, 2916, 1494, 1453, 1376 cm^{-1}; MS (EI): *m/z* (%):79 (100), 94 (38), 105 (20), 107 (37); HRMS (ESI): *m/z:* calcd. for $C_{14}H_{16}ONa$ [M+Na^+]: 223.1093, found: 223.1095.

(1*S*,2*R*,*E*)-2-Methyl-1-phenylhept-3-en-5-yn-1-yl (S)-2-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylbutanoate (S1): 

N-Ethyl-*N*'-(dimethylamino-propyl)-carbodiimide hydrochloride (143.6 mg, 0.750 mmol) was added to a stirred solution of **6** (100 mg, 0.500 mmol), **10** (208 mg, 0.600 mmol) and DMAP (12.2 mg, 0.100 mmol) in CH_2Cl_2 (0.66 mL) at 0 °C. After stirring for 15 min at 0 °C and for 5 h at ambient temperature, the mixture was partitioned between EtOAc and sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc (3 x 10 mL) before it was acidified to pH 2 with HCl (2 M) and extracted again with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (hexanes/EtOAc, 10:1) to afford the title compound as a colorless oil (206 mg, 78%). $[\alpha]_D^{20}$ = –17 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 5H), 5.79 (dd, *J* = 16.0, 7.7 Hz, 1H), 5.62 (d, *J* = 7.7 Hz, 1H), 5.33 (ddd, *J* = 16.0, 2.4, 1.3 Hz, 1H), 5.26 (d, *J* = 9.5 Hz, 1H), 4.10 (d, *J* = 9.5 Hz, 1H), 2.84–2.75 (m, 1H), 1.87 (d, *J* = 2.4 Hz, 3H), 1.44 (s, 9H), 1.25 (s, 3H), 1.17 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.77 (s, 9H), 0.01 (s, 3H), –0.12 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2, 155.9, 142.4, 137.9, 128.2, 128.2, 127.9, 111.5, 85.4, 79.9, 79.8, 78.2, 75.0, 62.9, 42.2, 28.5, 28.4, 27.6, 25.8, 18.1, 16.2, 4.4, –2.2, –2.4 ppm; IR (film) ν = 3453, 2930, 2956, 2857, 1802, 1720, 1495 cm^{-1}; MS (ESI)*: m/z*: 530 [M+H$^+$], 547 [M+NH$_4^+$], 552 [M+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{30}H_{47}NO_5SiNa$ [M+Na$^+$]: 552.3116, found: 552.3118.

(1*S*,2*R*,*E*)-2-Methyl-1-phenylhept-3-en-5-yn-1-yl (*S*)-2-amino-3-((*tert*-butyldimethylsilyl)oxy)-3-methylbutanoate (7). HCl (4 M in 1,4-dioxane, 7.5 mL, 30.0 mmol) was added to a solution of compound **S1** (200 mg, 0.370 mmol) in 1,4-dioxane (3.8 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and then at room temperature for 5 h. The reaction was quenched with sat. aq. Na_2CO_3 and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 4:1) to afford the title compound as a colorless oil (154 mg, 95%). $[\alpha]_D^{20}$ = –2.0 (c 2.2 , $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 5H), 5.81 (ddd, *J* = 16.0, 7.7, 0.8 Hz, 1H), 5.63 (d, *J* = 7.4 Hz, 1H), 5.33 (ddd, *J* = 16.0, 2.3, 1.2 Hz, 1H), 3.36 (s, 1H), 2.84–2.76 (m, 1H), 1.94–1.83 (m, 3H), 1.64 (s, 2H), 1.25 (s, 3H), 1.09–1.04 (m, 6H), 0.81 (s, 9H), 0.06 (s, 3H), –0.01 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.6, 142.4, 137.9, 128.3, 128.2, 127.8, 111.5,

85.6, 79.5, 78.1, 75.3, 65.1, 42.1, 28.2, 25.9, 25.5, 18.2, 16.2, 4.4, –2.1, –2.1 ppm; IR (film) ν = 3394, 2929, 2955, 2856, 1738, 1687, 1461 cm^{-1}; MS (ESI): *m/z*: 430 [M+H^+]; HRMS (ESI): *m/z:* calcd. for $C_{25}H_{40}NO_3Si$ [M+H^+]: 430.2772, found: 430.2772.

***tert*-Butyl (*R*)-(1,3-dihydroxy-3-methylbutan-2-yl)carbamate (9).**[27] A solution of MeMgBr in Et_2O (3.0 M in Et_2O, 29.0 mL, 86.7 mmol) was added dropwise to a solution of *N*-Boc-L-Ser-OMe (**8**) (4.80 g, 21.7 mmol) in Et_2O (108 mL) at –78 °C. The mixture was allowed to reach room temperature and was stirred for 1 h. After cooling to 0 °C, the reaction was quenched with sat. aq. NH_4Cl. The aqueous phase was extracted with diethyl ether (3 x 25 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 1:3) to afford the title compound as a white solid (4.33 g, 91%). $[\alpha]_D^{20}$ = –23 (c 1.1, $CHCl_3$); mp = 63-64 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.45 (d, *J* = 9.0 Hz, 1H), 3.98 (dt, *J* = 11.3, 3.6 Hz, 1H), 3.84–3.71 (m, 1H), 3.52–3.38 (m, 1H), 3.27–3.18 (m, 1H), 3.16 (s, 1H), 1.43 (s, 9H), 1.33 (s, 3H), 1.22 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6, 79.7, 73.9, 63.5, 57.8, 28.5, 27.7, 27.4 ppm; IR (film) ν = 3350, 2977, 2934, 1684, 1505 cm^{-1}; MS (EI): *m/z*: 242 [M+Na^+]; HRMS (ESI)*: m/z:* calcd. for $C_{10}H_{21}NO_4Na$ [M+Na^+]: 242.1363, found: 242.1362.

***N*-Boc-L-Val-OH (S2).**[27] Phosphate buffer (pH 6.7, 30 mL), $PhI(OAc)_2$ (290 mg, 0.900 mmol) and TEMPO (142 mg, 0.909 mmol) were added to a solution of alcohol **9** (2.80 g, 12.6 mmol) in MeCN (36 mL). The mixture was cooled to 0 °C before sodium chlorite (1.3 g, 15 mmol) was added. Stirring was continued at 0 °C for 2 h and at room temperature for 16 h. The reaction was quenched with sat. aq. NH_4Cl, the aqueous layer was acidified to pH 2 and extracted with EtOAc (3 x 25 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was recrystallized from EtOAc/hexanes to afford the title compound in the form of white crystals (2.58 g, 88%). $[\alpha]_D^{20}$ = –3.0 (c 0.9, $CHCl_3$); mp = 123-124 °C ; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.44 (s, 1H), 4.25 (d, *J* = 8.5 Hz, 1H), 1.46 (s, 9H), 1.38 (s, 3H), 1.29 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.9, 156.4, 80.9, 72.6, 61.2, 28.4, 27.3, 25.9 ppm; IR (film) ν = 3337, 2979, 2936, 2583, 1694, 1508 cm^{-1}; MS (ESI)*: m/z*: 256 [M+Na^+]; HRMS (ESI): *m/z:* calcd. for $C_{10}H_{19}NO_5Na$ [M+Na^+]: 256.1155, found: 256.1155.

***N*-Boc-L-Val-OTBS (10).** Et_3N (1.40 mL, 10.0 mmol), TBSCl (1.10 g, 7.30 mmol) and Verkade's base **11** (146 mg, 0.675 mmol) were added to a stirred solution of **S2** (785 mg, 3.37 mmol) in DMF (3.0 mL)

and the resulting mixture was stirred at 80 °C for 48 h. The reaction was quenched with HCl (2 M, 10 mL), the aqueous layer was extracted with EtOAc (3 x 5 mL), the combined extracts were washed with brine (1 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 5:1 to 3:1) to afford the title compound as a white solid (830 mg, 71%). $[\alpha]_D^{20}$ = +31 (c 1.5, $CHCl_3$); mp = 93.6-94.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.26 (d, *J* = 9.0 Hz, 1H), 4.18 (d, *J* = 9.0 Hz, 1H), 1.44 (s, 9H), 1.41 (s, 3H), 1.28 (s, 3H), 0.86 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.8, 156.0, 80.2, 76.2, 62.5, 28.4, 27.7, 26.8, 25.8, 18.1, –2.1, –2.2 ppm; IR (film) ν = 3453, 3091, 2928, 2856, 1717, 1501, 1473, 1463 cm^{-1}; MS (EI): *m/z* (%): 173 (100), 190 (28), 234 (26); HRMS (ESI): *m/z*: calcd. for $C_{16}H_{33}NO_5SiNa$ [M+Na^+]: 370.2020, found: 370.2023.

1-(Trimethylsilyl)hex-5-en-1-yn-3-ol (13).[29] A solution of allylmagnesium chloride (2 M in THF, 27.4 mL, 54.8 mmol) was added over 30 min to a solution of **12** (6.02 g, 47.7 mmol) in THF (95 mL) at 0 °C. After the addition was complete, the mixture was allowed to reach ambient temperature. After stirring for another 2 h, the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with *tert*-butyl methyl ether (3 x 50 mL), the combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/*tert*-butyl methyl ether, 5:1) to afford the title compound as a colorless oil (7.9 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96–5.80 (m, 1H), 5.24–5.17 (m, 1H), 5.17 (t, *J* = 1.2 Hz, 1H), 4.41 (q, *J* = 6.1 Hz, 1H), 2.47 (ddq, *J* = 7.1, 5.9, 1.2 Hz, 2H), 1.91 (dd, *J* = 6.1, 1.2 Hz, 1H), 0.17 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 133.1, 119.2, 106.0, 90.0, 62.1, 42.2, 0.0 ppm; IR (film) ν = 3330, 3080, 2960, 2175, 1643 cm^{-1}; MS (EI): *m/z* (%):75 (32), 83 (9), 99 (100), 127 (64); HRMS (ESI)*: m/z:* calcd. for $C_9H_{16}OSiNa$ [M+Na^+]: 191.0863, found: 191.0863.

(*R*)-1-(Trimethylsilyl)hex-5-en-1-yn-3-yl acetate (14).[29] **Method A**: Molecular sieves (4 Å, 500 mg), Amano lipase PS (395 mg) and vinyl acetate (15.0 mL, 164 mmol) were added to a solution of compound **13** (7.90 g, 47.0 mmol) in pentane (313 mL). The suspension was gently stirred for 56 h before it was filtered through a pad of Celite®. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel (hexanes/Et_2O, 10: 1) to afford the title compound as a colorless oil (4.65 g, 47%, 99% ee). [Conditions for GC analysis: column 30.0 m, BGB-17/BGB-15, G/698; 0.50 bar H_2; 230/50min iso, 80 4/min 220, 5/min iso 350, t (minor) = 30.75 min, t (major) =

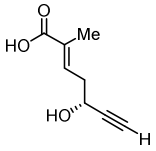
32.67 min]. **Method B**: Acetic acid (1.9 mL, 32.6 mmol) and triphenylphosphine (8.54 g, 32.6 mmol) were added to a solution of (*S*)-**13** (3.73 g, 21.7 mmol) in Et_2O (109 mL) at 0 °C. After stirring for 5 min at 0 °C, diisopropylazodicarboxylate (6.4 mL, 32.6 mmol) was added dropwise and stirring was continued for 1.5 h at this temperature. The reaction was quenched with sat. aq. $NaHCO_3$, the aqueous layer was extracted with *tert*-butyl methyl ether, the combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography on silica gel (hexanes/*tert*-butyl methyl ether, 20:1) to give the title compound as colorless oil (4.13 g, 91%). $[\alpha]_D^{20}$ = +100 (c 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (ddt, *J* = 17.3, 10.3, 7.0 Hz, 1H), 5.43 (t, *J* = 6.5 Hz, 1H), 5.18–5.14 (m, 1H), 5.14–5.11 (m, 1H), 2.51 (td, *J* = 6.5, 1.2 Hz, 2H), 2.08 (s, 3H), 0.17 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.0, 132.3, 118.9, 102.1, 91.0, 63.7, 39.5, 21.2, –0.1 ppm; IR (film) ν = 2961, 1746 cm^{-1}; MS (EI)*: m/z* (%): 43 (100), 75 (45), 99 (20), 117 (17), 127 (11), 135 (16), 169 (35); HRMS (ESI)*: m/z:* calcd. for $C_{11}H_{18}O_2SiNa$ [M+Na^+]: 233.0968, found: 233.0970.

(*S*)-1-(Trimethylsilyl)hex-5-en-1-yn-3-ol ((*S*)-13)).[29] Obtained as the second fraction from the enzymatic resolution described above; colorless oil (3.73 g, 47%, 99% ee) [Conditions for GC analysis: column 24.5 m, Hydrodex-beta-TBDAC; G/589; 0.80 bar H_2; 220/10 min iso, 105 6/min 220, 5 min iso/350, t (minor) = 3.57 min, t (major) = 3.73 min]. $[\alpha]_D^{20}$ = –29 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96–5.80 (m, 1H), 5.24–5.17 (m, 1H), 5.17 (t, *J* = 1.2 Hz, 1H), 4.41 (q, *J* = 6.1 Hz, 1H), 2.47 (ddq, *J* = 7.1, 5.9, 1.2 Hz, 2H), 1.91 (dd, *J* = 6.1, 1.2 Hz, 1H), 0.17 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 133.1, 119.2, 106.0, 90.0, 62.1, 42.2, 0.0 ppm; IR (film) ν = 3330, 3080, 2960, 2175, 1643, cm^{-1}; MS (EI): *m/z* (%): 75 (32), 99 (100), 127 (64); HRMS (ESI)*: m/z:* calcd. for $C_9H_{16}OSiNa$ [M+Na^+]: 191.0863, found: 191.0863.

Ethyl (*R*,*E*)-5-acetoxy-2-methyl-7-(trimethylsilyl)hept-2-en-6-ynoate (15): A solution of **14** (2.0 g, 9.5 mmol) and Sudan red III (5.0 mg, 14 μmol) in CH_2Cl_2 (38 mL) was cooled to –78 °C. Ozone gas was bubbled through the red solution at –78 °C until the color faded away. At this point, excess ozone was removed by bubbling argon through the solution for 15 min. Triphenylphosphine (2.90 g, 11.4 mmol) was then added. After stirring at –78 °C for 5 min, the mixture was warmed to room temperature and stirring was continued for 3 h. The mixture was then cooled to 0 °C before a solution of (1-ethoxycarbonylethylidene)triphenylphosphorane (4.82 g, 13.3 mmol) in CH_2Cl_2 (19 mL) was added over 30 min. After stirring for 3 h at ambient temperature, the solvent was evaporated

and the residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 10: 1) to afford the title compound as a colorless oil (2.01 g, *E*:*Z* > 95:5, 71%). $[\alpha]_D^{20}$ = +53 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (tq, *J* = 7.3, 1.4 Hz, 1H), 5.47 (t, *J* = 6.3 Hz, 1H), 4.20 (q, *J* = 7.3 Hz, 2H), 2.65 (ddt, *J* = 7.3, 6.3, 0.9 Hz, 2H), 2.09 (s, 3H), 1.87 (dq, *J* = 1.6, 0.9 Hz, 3H), 1.30 (t, *J* = 7.3 Hz, 3H), 0.17 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.9, 167.8, 134.9, 131.3, 101.7, 91.6, 63.1, 60.8, 34.3, 21.2, 14.4, 12.9, –0.2 ppm; IR (film) ν = 2962, 1748, 1713 cm^{-1}; MS (EI): *m/z* (%): 43 (100), 73 (61), 75 (59), 100 (26), 117 (12); HRMS (ESI): *m/z:* calcd. for $C_{15}H_{24}O_4SiNa$ [M+Na$^+$]: 319.1336 , found: 319.1335.

(*R*,*E*)-5-Hydroxy-2-methylhept-2-en-6-ynoic acid (S3): Lithium hydroxide (477 mg, 19.9 mmol) was added in portions to a solution of compound **15** (1.97 g, 6.6 mmol) in THF/H_2O (66 mL, 1:1). The mixture was stirred for 16 h before it was acidified to pH 2 by addition of HCl (2 M). The aqueous layers were extracted with EtOAc (3 x 25 mL), the combined extracts were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (hexanes/EtOAc, 1:1) to afford the title compound as a colorless oil (1.01 g, 99%). $[\alpha]_D^{20}$ = + 19 (c 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.18 (br, 1H), 7.00 (td, *J* = 7.3, 1.5 Hz, 1H), 4.54 (td, *J* = 6.3, 2.1 Hz, 1H), 2.66 (ddt, *J* = 7.3, 6.3, 1.0 Hz, 2H), 2.52 (d, *J* = 2.1 Hz, 1H), 1.88 (q, *J* = 1.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.1, 138.6, 130.3, 83.8, 74.0, 61.1, 37.1, 12.6 ppm; IR (film) ν = 3293, 1688, 1646, 1421 cm^{-1}; MS (ESI): *m/z*: 153 [M-H$^+$]; HRMS (ESI neg) *m/z* calcd. for $C_8H_9O_3$ [M-H$^-$]: 153.0557, found: 153.0558.



(*R*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-methylhept-2-en-6-ynoic acid (16): Imidazole (1.47 g, 21.6 mmol) and *tert*-butyldimethylsilyl chloride (3.12 g, 20.7 mmol) were added to a solution of **S3** (1.45 g, 9.4 mmol) in DMF (38 mL). The mixture was stirred for 8 h before it was partitioned between water (50 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), the combined organic phases were washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated.

The residue was dissolved in THF/MeOH/H_2O (117 mL, 2:2:1) and the solution cooled to 0 °C. Potassium carbonate (1.95 g, 14.1 mmol) was added and the mixture stirred at 0 °C for 10 min and for 20 min at room temperature. The mixture was partitioned between water (50 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude

material was purified by flash chromatography on silica gel (hexanes/EtOAc, 5:1) to afford the title compound as a colorless oil (2.18 g, 87%). $[\alpha]_D^{20}$ = +36 (c 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.92 (br, 1H), 6.97 (td, *J* = 7.4, 1.5 Hz, 1H), 4.47 (td, *J* = 6.3, 2.1 Hz, 1H), 2.60 (dddd, *J* = 7.4, 6.3, 2.4, 1.1 Hz, 2H), 2.42 (d, *J* = 2.1 Hz, 1H), 1.87 (q, *J* = 1.1 Hz, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.5, 139.7, 129.5, 84.7, 72.9, 61.7, 38.3, 25.8, 18.3, 12.5, –4.5, –5.0 ppm; IR (film) ν = 3309, 2930, 2956, 2858, 2887, 2663, 1690, 1648 cm^{-1}; MS (EI)*: m/z* (%): 75 (100), 83 (13), 91 (11), 129 (47); HRMS (ESI neg): *m/z:* calcd. for $C_{14}H_{23}O_3Si$ [M-H$^-$]: 267.1422, found: 267.1424.

3,5-Dichloro-L-tyrosine methyl ester hydrochloride (19·HCl).[34,35] Sulfuryl chloride (38.0 mL, 380 mmol) was added to a suspension of D-tyrosine (2.75 g, 15.2 mmol) in glacial acetic acid (15.2 mL, 15.2 mmol) at room temperature. The resulting suspension was stirred for 24 h before the mixture was concentrated to afford 3,5-dichloro-D-Tyr-OH hydrochloride salt as a white solid.

Hydrochloric acid (36% *w*/*w*, 3.8 mL, 45.5 mmol) was added dropwise to a suspension of this salt in 2,2-dimethoxypropane (43.0 mL, 104 mmol) at room temperature. The resulting dark brown solution was stirred for 3 d. The mixture was then concentrated to dryness, the residue was dissolved in a minimum amount of MeOH, and crystallized from diethyl ether to afford the title compound as a light pink solid (3.40 g, 75%). $[\alpha]_D^{20}$ = –9.0 (c 1.25, MeOH); mp = 137-138 °C; ^{1}H NMR (300 MHz, [D_4]-MeOH): δ = 7.21 (s, 2H), 4.30 (dd, *J* = 7.6, 6.0 Hz, 2H), 3.83 (s, 3H), 3.18 (dd, *J* = 14.6, 6.0 Hz, 1H), 3.04 (dd, *J* = 14.6, 7.6 Hz, 1H) ppm; ^{13}C NMR (126 MHz, [D_4]-MeOH): δ = 170.2, 150.5, 130.5, 127.8, 123.8, 54.9, 53.7, 35.9 ppm; IR (film) ν = 3190, 2956, 1744, 1570, 1489, 1444, 1417 cm^{-1}; MS (ESI): *m/z*: 264 [M+H$^+$]; HRMS (ESI)*: m/z* calcd. for $C_{10}H_{12}NO_3Cl_2$ [M]$^+$: 264.0189, found: 264.0189.

***N*-Boc-Ile-3,5-dichloro-Tyr-OMe (21):** Et_3N (1.3 mL, 9.8 mmol) and *N*-hydroxybenzotriazole (1.40 g, 10.6 mmol) were added to a solution of **20** (2.0 g, 8.2 mmol) and **19**·HCl (2.7 g, 9.0 mmol) in THF (45 mL) at 0 °C. After stirring for 5 min at 0 °C, *N*,*N*′-dicyclohexylcarbodiimide (2.20 g, 10.6 mmol) was introduced and the resulting mixture stirred for 1 h at 0 °C and for 3 h at room temperature. The mixture was diluted with ethyl acetate and the precipitated dicyclohexylurea was filtered off. The filtrate was washed with sat. aq. $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL) before it was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 3:1) to afford the title compound as a white solid (3.14 g, 78%). $[\alpha]_D^{20}$ = –84 (c 1.03, $CHCl_3$); mp = 120-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (s, 2H), 6.81 (d, *J* = 8.2 Hz, 1H),

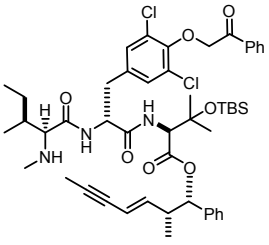
6.25 (s, 1H), 4.74 (q, *J* = 7.0 Hz, 1H), 4.11 (d, *J* = 11.3 Hz, 1H), 3.69 (s, 3H), 3.04 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.90 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.72 (s, 3H), 2.11–1.95 (m, 1H), 1.42 (s, 9H), 1.44–1.33 (m, 1H), 1.08–0.94 (m, 1H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.81 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2, 170.7, 157.3, 147.2, 129.7, 129.1, 121.3, 80.6, 63.0, 53.0, 52.5, 36.8, 31.5, 30.4, 28.4, 28.4, 24.6, 15.8, 10.6 ppm; IR (film) ν = 3342, 2966, 2933, 2877, 1743, 1666 cm^{-1}; MS (EI): *m/z*: 491 [M+H$^+$]; 513 [M+Na$^+$]; HRMS (ESI)*: m/z:* calcd. for $C_{22}H_{32}N_2O_6Cl_2Na$ [M+Na$^+$]: 513.1530, found: 513.1536.

(*R*)-2-((2*S*,3*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)-3-methylpentanamido)-3-(3,5-dichloro-4-(2-oxo-2-phenylethoxy)phenyl)propanoic acid (S4): To a stirred solution of compound **21** (4.02 g, 8.19 mmol) and α-bromoacetophenone (3.26 g, 16.4 mmol) in acetone (16.4 mL) were added KI (2.72 g, 16.4 mmol) and K_2CO_3 (2.26 g, 16.4 mmol). The mixture was stirred at 40 °C for 12 h. After reaching ambient temperature, the mixture was diluted with water, the aqueous layer was extracted with EtOAc (3 x 50 mL), the combined organic phases were washed with brine (5 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 3:1 to 1:1) to provide the desired compound **22** as a yellow solid.

The product was dissolved in THF (40 mL) and H_2O (40 mL). LiOH (391 mg, 16.4 mmol) was added at 0 °C and the solution was stirred at ambient temperature for 24 h. The mixture was acidified to pH 2 by addition of HCl (2 M). The aqueous layer was extracted with EtOAc (3 x 100 mL), the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 2:1 to 1:1) to afford the title compound as a yellow oil (2.82 g, 58%). $[\alpha]_D^{20}$ = –25.8 (c 1.0, MeOH); ^{1}H NMR (400 MHz, [D_4]-MeOH): δ = 8.04–7.98 (m, 2H), 7.69–7.63 (m, 1H), 7.56–7.50 (m, 2H), 7.32 (s, 2H), 5.32 (d, *J* = 2.9 Hz, 2H), 4.69 (s, 1H), 4.19–4.04 (m, 1H), 3.24 (dd, *J* = 14.0, 4.6 Hz, 1H), 3.02–2.88 (m, 1H), 2.77 (s, 3H), 1.99–1.88 (m, 1H), 1.46 (s, 9H), 1.40–1.30 (m, 2H), 1.08–0.95 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.69 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (101 MHz, [D_4]-MeOH): δ = 195.2, 172.2, 150.7, 137.6, 135.7, 135.1, 131.2, 130.0, 130.0, 129.2, 81.6, 75.9, 63.6, 37.1, 33.2, 30.5, 28.6, 25.6, 15.9, 10.7 ppm; IR (film) ν = 3066, 2968, 2932, 2878, 1449, 1446 cm^{-1}; MS (ESI): *m/z*: 593 [M-H$^-$]; HRMS (ESI)*: m/z* calcd. for $C_{29}H_{35}N_2O_7Cl_2Na$ [M-H$^-$]: 593.1827, found: 593.1828.

Compound 23. *N*-Hydroxybenzotriazole (236 mg, 1.75 mmol) was added to a solution of amine **7** (500 mg, 1.16 mmol) and acid **S4** (830 mg, 1.40 mmol) in CH_2Cl_2 (5.8 mL) at 0 °C. After stirring for 5 min at 0 °C, *N*,*N*′-dicyclohexylcarbodiimide (360 mg, 1.75 mmol) was introduced. The mixture was stirred for 1 h at 0 °C and for 2 h at ambient temperature before ethyl acetate (100 mL) was added. The precipitate was filtered off, and the filtrate was washed with sat. aq. $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 5:1) to afford the title compound as a white solid (945 mg, 81%). $[\alpha]_D^{20}$ = –50.8 (c 0.8, $CHCl_3$); mp = 60.9-61.5 °C; ^{1}H NMR (400 MHz, [D_4]-MeOH): δ = 8.03–7.99 (m, 2H), 7.68–7.63 (m, 1H), 7.55–7.50 (m, 2H), 7.36 (s, 2H), 7.34–7.25 (m, 5H), 5.69 (dd, *J* = 15.9, 7.9 Hz, 1H), 5.56 (d, *J* = 8.0 Hz, 1H), 5.35–5.26 (m, 3H), 4.81–4.74 (m, 1H), 4.44 (s, 1H), 4.24–4.09 (m, 1H), 3.14 (dd, *J* = 13.9, 5.9 Hz, 1H), 2.92–2.79 (m, 2H), 2.81 (s, 3H), 2.02–1.90 (m, 1H), 1.82 (d, *J* = 2.2 Hz, 3H), 1.48 (s, 9H), 1.37–1.28 (m, 1H), 1.18 (s, 6H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.92–0.82 (m, 4H), 0.74 (s, 9H), 0.70–0.61 (m, 3H), 0.01 (s, 3H), –0.07 (s, 3H) ppm; ^{13}C NMR (101 MHz, [D_4]-MeOH): δ = 195.0, 172.5, 172.3, 170.2, 158.1, 150.8, 143.1, 139.2, 137.5, 135.7, 135.1, 131.3, 130.1, 130.0, 129.3, 129.2, 129.2, 129.1, 113.0, 86.0, 81.5, 78.8, 75.9, 63.4, 62.9, 55.2, 43.3, 37.3, 33.7, 30.7, 28.8, 28.2, 28.1, 27.2, 26.4, 25.5, 18.8, 16.8, 15.9, 10.8, 3.8, –1.9, –2.0 ppm; IR (film) ν = 2965, 2931, 2857, 1745, 1680 cm^{-1}; MS (ESI): *m/z*: 1006 [M+H$^+$], 1023 [M+Na$^+$]; HRMS (ESI): *m/z*: calcd. for $C_{54}H_{73}N_3O_9Cl_2SiNa$ [M+Na$^+$]: 1028.4385, found: 1028.4392.

Compound S5. TBSOTf (1.3 mL, 5.69 mmol) was added dropwise to a stirred solution of **23** (603 mg, 0.599 mmol) and 2,6-lutidine (700 μL, 6.00 mmol) in CH_2Cl_2 (6.0 mL) at 0 °C. The resulting mixture was stirred for 5 h at room temperature before the reaction was quenched with sat. aq. NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL), the combined extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated.



A solution of tetrabutylammonium fluoride (1 M in THF, 1.1 mL, 1.1 mmol) was added to a solution of the residue in THF (28 mL) at 0 °C. The mixture was stirred for 5 min before sat. aq. $NaHCO_3$ (5 mL) was introduced. The aqueous layer was extracted with EtOAc (3 x 50 mL), the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (CH_2Cl_2/*tert*-

butyl methyl ether, 10:1 to 4:1) to afford the title compound as a colorless oil (543 mg, quant.). $[\alpha]_D^{20}$ = –3.4 (c 1.2, MeOH); ^{1}H NMR (400 MHz, [D$_4$]-MeOH): δ = 8.03–7.98 (m, 2H), 7.69–7.63 (m, 1H), 7.57–7.50 (m, 2H), 7.39 (s, 2H), 7.35–7.23 (m, 5H), 5.73–5.65 (m, 1H), 5.58 (d, *J* = 7.7 Hz, 1H), 5.35–5.27 (m, 3H), 4.86–4.83 (m, 1H), 4.45 (s, 1H), 3.14 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.91 (dd, *J* = 14.0, 9.5 Hz, 1H), 2.84–2.76 (m, 2H), 2.23 (s, 3H), 1.83(d, *J* = 2.3 Hz, 3H), 1.60–1.53 (m, 1H), 1.48–1.40 (m, 1H), 1.19 (s, 6H), 1.07–1.01 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 1.02–0.96 (m, 1H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.78–0.76 (m, 3H), 0.75 (s, 9H), 0.01 (s, 3H), –0.06 (s, 3H) ppm; ^{13}C NMR (126 MHz, [D$_4$]-MeOH): δ = 195.1, 176.2, 172.6, 170.4, 150.8, 143.1, 139.1, 137.4, 137.4, 135.7, 135.1, 131.3, 130.1, 130.0, 129.3, 129.2, 129.2, 129.2, 129.1, 112.9, 85.9, 81.5, 78.8, 76.0, 76.0, 70.1, 63.1, 55.0, 43.4, 39.3, 37.5, 35.5, 28.2, 28.1, 26.5, 26.3, 18.9, 16.8, 15.8, 12.0, 3.7, –2.0, –2.0 ppm; IR (film) ν = 3322, 2961, 2931, 2856, 1737, 1683 cm^{-1}; MS (ESI): *m/z*: 908 [M+H$^+$], 930 [M+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{49}H_{66}N_3O_9Cl_2Si$ [M+H$^+$]: 906 :4042, found: 906.4051.

Compound 24: Ghosez's reagent (199 mg, 197 μL, 1.49 mmol) was added to a solution of the carboxylic acid **16** (333 mg, 1.24 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. After stirring for 10 min at 0 °C, the mixture was stirred at ambient temperature for another 2 h.

A solution of the crude acid chloride **17** thus formed was added dropwise to a solution of amine **S5** (750 mg, 0.827 mmol) and Et_3N (230 μL, 1.65 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. The mixture was stirred for 1 h at this temperature. The reaction was quenched with water (5 mL), the aqueous layer was extracted with EtOAc (3 x 10 mL), the combined extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 4:1) to afford the title compound as a colorless solid (730 mg, 76%). $[\alpha]_D^{20}$ = –8 .5 (c 1.0, $CHCl_3$); mp = 74.2-75.7 °C; ^{1}H NMR (500 MHz, [D$_4$]-MeOH): δ = 8.05–7.99 (m, 2H), 7.66 (td, *J* = 7.3, 1.3 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 2H), 7.38 (s, 2H), 7.34-7.26 (m, 5H), 5.75–5.65 (m, 2H), 5.56 (d, *J* = 7.9 Hz, 1H), 5.38–5.26 (m, 3H), 4.86–4.78 (m, 1H), 4.61 (d, *J* = 19.1 Hz, 2H), 4.43 (s, 1H), 3.16 (d, *J* = 12.1 Hz, 1H), 3.00 (s, 3H), 2.97–2.79 (m, 3H), 2.61–2.46 (m, 2H), 2.05–2.01 (m, 1H), 1.88 (s, 3H), 1.84–1.82 (m, 4H), 1.20 (s, 3H), 1.19 (s, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.91–0.87 (m, 6H), 0.74 (s, 9H), 0.66 (d, *J* = 6.5 Hz, 3H), 0.16 (s, 3H), 0.14 (s, 3H), 0.01 (s, 3H), –0.07 (s, 3H) ppm; ^{13}C NMR (126 MHz, [D$_4$]-MeOH): δ = 195.1, 176.6, 172.2, 171.9, 170.3, 150.8, 143.1, 139.1, 137.6, 135.7, 135.2, 135.1, 131.3, 130.1, 130.0, 129.3, 129.3, 129.2, 129.1, 128.0, 113.0, 86.0, 85.8, 81.5, 78.8, 76.0, 74.6,

63.2, 63.0, 61.7, 55.1, 43.4, 37.8, 37.2, 33.9, 33.2, 28.2, 26.4, 26.3, 25.6, 19.0, 18.9, 16.9, 15.8, 14.9, 10.7, 3.8, –2.0, –4.3, –4.8 ppm; IR (film) ν = 3300, 3271, 2958, 2929, 1744, 1607, 1471 cm^{-1}; MS (ESI): *m/z*: 1156 [M+H^+], 1173 [M+NH_4^+], 1178 [M+Na^+], 1194 [M+K^+]; HRMS (ESI): *m/z:* calcd. for $C_{63}H_{87}N_3O_9Cl_2Si_2Na$ [M+Na^+]: 1178.5250, found: 1178.5261.

Compound S6a (R^1 = phenacyl). A flame-dried Schlenk flask was charged with powdered 4 Å molecular sieves (1.8 g) and 5 Å molecular sieves (3.5 g). The flask was evacuated and the molecular sieves were flame-dried. After reaching ambient temperature, a solution of diyne **24** (132 mg, 0.114 mmol) in dry toluene (56 mL) was added and the resulting suspension was stirred for 45 min. In a separate flame-dried Schlenk flask, a solution of complex **25** (35.6 mg, 34.2 μmol) in toluene (0.6 mL) was prepared. This solution was added to the flask containing the diyne and the resulting mixture was stirred at room temperature for 15 min. The suspension was filtered through a short pad of Celite®. The filtrate was evaporated and the crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 9:1 to 4:1) to afford the title compound as a white solid (84.5 mg, 66%). $[\alpha]_D^{20}$ = –93.2 (c 1.0, $CHCl_3$); mp = 103-103.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.97 (m, 2H), 7.63–7.56 (m, 1H), 7.50–7.43 (m, 2H), 7.32–7.23 (m, 5H), 7.22 (s, 2H), 6.93 (d, *J* = 8.9 Hz, 1H), 6.68 (d, *J* = 9.3 Hz, 1H), 5.99 (dd, *J* = 15.9, 8.0 Hz, 1H), 5.72 (d, *J* = 2.6 Hz, 1H), 5.51–5.40 (m, 2H), 5.19 (s, 2H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.60–4.49 (m, 2H), 4.43 (d, *J* = 9.1 Hz, 1H), 3.09 (dd, *J* = 13.5, 9.0 Hz, 1H), 2.84–2.78 (m, 1H), 2.77 (s, 3H), 2.74–2.61 (m, 2H), 2.45–2.36 (m, 1H), 2.20–2.12 (m, 1H), 1.96 (s, 3H), 1.41–1.34 (m, 1H), 1.32 (s, 3H), 1.12–1.03 (m, 1H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 1.2 Hz, 6H), 0.91 (s, 9H), 0.88 (d, *J* = 7.9 Hz, 3H), 0.67 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), –0.10 (s, 3H), –0.17 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.9, 175.9, 170.2, 169.5, 169.2, 149.8, 144.8, 137.5, 135.0, 135.0, 134.6, 133.9, 130.1, 129.3, 128.9, 128.3, 128.2, 128.2, 128.1, 128.1, 127.3, 125.2, 110.4, 90.5, 83.0, 80.3, 75.3, 74.8, 74.8, 63.0, 60.9, 59.9, 54.4, 42.6, 37.5, 36.6, 32.1, 30.3, 28.1, 28.0, 25.9, 25.8, 25.8, 25.7, 24.5, 18.4, 18.0, 16.1, 14.7, 13.2, 10.5, –2.1, –2.4, –4.4, –4.8 ppm; IR (film) ν = 3552, 3287, 2957, 2929, 1683, 1511 cm^{-1}; MS (ESI): *m/z*: 1133 [M+NH_4^+], 1138 [M+Na^+]; HRMS (ESI): *m/z*: calcd. for $C_{60}H_{83}N_3O_9Cl_2Si_2Na$ [M+Na^+]: 1138.4937, found: 1138.4954.

Compound S6b. (R^1 = Ac). Prepared analogously as colorless oil (9.8 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 (dd, *J* = 7.2, 1.7 Hz, 2H), 7.26 (s, 3H), 7.25 (d, *J* = 5.5 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 1H), 6.66 (d, *J* = 9.2 Hz, 1H), 5.99 (dd, *J* = 15.9, 8.0 Hz, 1H), 5.72 (d, *J* = 2.5 Hz, 1H), 5.49 (dt, *J* = 15.9, 1.5 Hz, 1H), 5.43 (ddd, *J* = 10.6, 5.1, 1.7 Hz, 1H), 4.69 (d, *J* = 11.5 Hz, 1H), 4.56 (td, *J* = 9.5, 6.3 Hz, 1H), 4.55–4.50 (m, 1H), 4.41 (d, *J* = 9.2 Hz, 1H), 3.10 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.84 (dd, *J* = 13.4, 6.0 Hz, 1H), 2.77 (s, 3H), 2.72 (dt, *J* = 13.0, 10.7 Hz, 1H), 2.68–2.60 (m, 1H), 2.44–2.37 (m, 1H), 2.36 (s, 3H), 2.17 (td, *J* = 11.3, 9.2, 4.6 Hz, 1H), 1.97 (s, 3H), 1.38 (ddd, *J* = 13.6, 7.8, 2.7 Hz, 1H), 1.32 (s, 3H), 1.09–1.00 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 9H), 0.90 (t, *J* = 7.1 Hz, 3H), 0.87 (s, 3H), 0.66 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), –0.12 (s, 3H), –0.17 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.8, 170.1, 169.3, 169.1, 167.0, 144.9, 143.0, 137.6, 136.3, 135.0, 129.6, 128.8, 128.1, 127.9, 127.2, 124.9, 110.2, 90.4, 82.8, 80.1, 75.2, 62.9, 60.8, 59.7, 54.5, 42.6, 37.4, 36.5, 32.0, 30.1, 28.0, 27.7, 25.8, 25.6, 24.4, 20.2, 18.3, 17.9, 15.9, 14.6, 13.0, 10.4, –2.4, –2.6, –4.5, –4.9 ppm; MS (ESI) *m/z* (%): 1057 (23), 1062 (100), 1078 (17); HRMS (ESI) *m/z* calcd. for $C_{54}H_{79}N_3O_9Cl_2Si_2Na$ $[M+Na]^+$: 1062.4624, found: 1062.4624.

Compound 26a (R^1 = phenacyl). HF•py (600 μL) was added at 0 °C to a stirred solution of **S6a** (R^1 = phenacyl, 94.5 mg, 95.8 μmol) in THF (600 μL). The mixture was stirred for 15 min at 0 °C and for 1 h at ambient temperature before aq. $NaHCO_3$ was introduced at 0 °C. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined extracts were washed with brine (2 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated and the residue purified by flash chromatography on silica gel (CH_2Cl_2/*tert*-butyl methyl ether, 6:1 to 5:2) to afford the title compound as a white solid (60.8 mg, 71%). $[\alpha]_D^{20}$ = –63.4 (c 0.8, MeOH); mp = 128-130.3 °C ; ^{1}H NMR (400 MHz, [D_4]-MeOH, mixture of rotamers ca. 2.3:1): δ = 8.05–7.95 (m, 2H), 7.69–7.64 (m, 1H), 7.55–7.52 (m, 2H), 7.41 (s, 2H), 7.39–7.37 (m, 2H), 7.35–7.31 (m, 2H), 7.29–7.25 (m, 1H), 6.35 (dd, *J* = 16.2, 5.8 Hz, 0.3H, minor), 6.18–6.08 (m, 1H), 5.91–5.84 (m, 0.3H, minor), 5.75 (d, *J* = 3.0 Hz, 0.7H, major), 5.67–5.63 (m, 0.7H, major), 5.58–5.49 (m, 1H), 5.35–5.27 (m, 2H), 4.85–4.77 (m, 1.3H), 4.68–4.65 (m, 1.4H), 4.55–4.47 (m, 1H), 4.14 (d, *J* = 10.9 Hz, 0.3H, mionr), 3.40–3.33 (m, 0.3H, minor), 3.12 (dd, *J* = 13.9, 5.7 Hz, 0.7H, major), 3.07 (d, *J* = 11.9 Hz, 0.3H, minor), 3.02 (s, 0.9H, minor), 2.88 (s, 2.1H, major), 2.86–2.83 (m, 1H), 2.80–2.70 (m, 1H), 2.60–2.50 (m, 1.4H), 2.43 (d, *J* = 15.0 Hz, 0.3H, minor), 2.07–1.98 (m, 0.7H, major),

1.96–1.92 (m, 0.3H, minor), 1.94 (s, 2.1H, major), 1.84 (s, 0.9H, minor), 1.43–1.28 (m, 1H), 1.25 (s, 0.9H, minor), 1.22 (s, 0.9H, minor), 1.18 (s, 2.1H, major), 1.12 (s, 2.1H, major), 1.08–1.01 (m, 1H), 0.94–0.87 (m, 6H), 0.73 (d, *J* = 6.5 Hz, 2.1H, major), 0.45 (d, *J* = 6.5 Hz, 0.9H, minor) ppm; ^{13}C NMR (151 MHz, [D$_4$]-MeOH): δ = 195.2, 177.1, 176.9, 172.6, 172.4, 171.4, 171.4, 171.2, 150.8, 148.6, 145.8, 139.7, 138.9, 137.3, 135.7, 135.7, 135.1, 131.3, 131.0, 130.1, 130.0, 130.0, 129.3, 129.2, 129.0, 128.8, 128.6, 128.4, 128.1, 127.1, 111.5, 110.3, 90.8, 89.4, 85.4, 84.1, 81.2, 77.8, 75.9, 72.8, 72.1, 68.4, 62.5, 62.1, 61.9, 61.6, 61.5, 55.9, 54.7, 43.9, 43.3, 38.2, 37.3, 37.2, 35.4, 35.1, 33.1, 32.4, 29.2, 28.0, 27.3, 26.5, 26.4, 25.9, 25.4, 16.0, 15.5, 15.4, 14.7, 13.8, 11.7, 10.7, 10.0 ppm; IR (film) ν = 3340, 2971, 2928, 2857, 1678, 1602, 1469 cm^{-1}; MS (ESI): *m/z*: 888 [M+H$^+$], 905 [M+NH$_4^+$], 910 [M+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{48}H_{56}N_3O_9Cl_2$ [M+H$^+$]: 888.3388, found: 888.3404.

Compound 26b (R^1 = Ac). A solution of TBAF (1 M in THF, 94 µL, 94 µmol) was added to a solution of compound **S6b** (46.5 mg, 45 µmol) in THF (0.45 mL) at 0 °C. After stirring for 10 min at 0 °C, stirring was continued at ambient temperature for 2 h. The reaction was quenched with sat. aq. NH_4Cl, the aqueous layer was extracted with EtOAc (3 x 10 mL), the combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (hexanes/EtOAc, 1:1) to afford title compound as colorless oil (24 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32-7.29 (dd, *J* = 5.1, 1.9 Hz, 3H), 7.25–7.23 (m, 2H), 7.10 (s, 2H), 7.08 (d, *J* = 9.1 Hz, 1H), 6.64 (d, *J* = 8.6 Hz, 1H), 6.19 (dd, *J* = 16.0, 7.3 Hz, 1H), 5.76 (d, *J* = 3.1 Hz, 1H), 5.58 (td, *J* = 6.8, 3.3 Hz, 1H), 5.52 (ddd, *J* = 9.4, 4.4, 1.4 Hz, 1H), 5.44 (dt, *J* = 16.1, 1.5 Hz, 1H), 4.65 (q, *J* = 7.7 Hz, 1H), 4.58 (d, *J* = 9.0 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 2.99 (dd, *J* = 14.0, 7.7 Hz, 1H), 2.89 (s, 3H), 2.88–2.83 (m, 1H), 2.78–2.71 (m, 1H), 2.71–2.63 (m, 1H), 2.55 (dt, *J* = 12.9, 5.6 Hz, 1H), 2.16–2.10 (m, 1H), 2.10 (s, 3H), 2.00–1.94 (m, 3H), 1.75–1.54 (m, 2H), 1.48–1.36 (m, 1H), 1.14 (s, 3H), 1.12–1.06 (m, 1H), 1.04 (s, 3H), 0.99–0.87 (m, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.0, 170.6, 170.5, 170.0, 169.9, 147.0, 145.9, 136.9, 135.8, 129.7, 129.1, 128.3, 128.2, 127.2, 125.0, 121.2, 110.1, 85.7, 84.7, 80.2, 72.4, 63.5, 61.2, 60.4, 53.9, 42.1, 36.5, 33.2, 32.8, 31.0, 27.1, 26.5, 25.2, 21.2, 16.1, 14.7, 13.5, 10.7 ppm; MS (ESI) *m/z* (%): 834 (100), 1645 (10); HRMS (ESI) *m/z* calcd. for $C_{42}H_{51}N_3O_9Cl_2Na$ [M+Na]$^+$: 834.2895, found: 834.2895.

Compound 27a (R^1 = phenacyl). A solution of tributyltin hydride (21.8 µL, 81.0 µmol) in CH_2Cl_2 (1.1 mL) was added dropwise over 20 min to a stirred solution of [Cp*RuCl]$_4$ (8.1 mg, 7.5 µmol) and

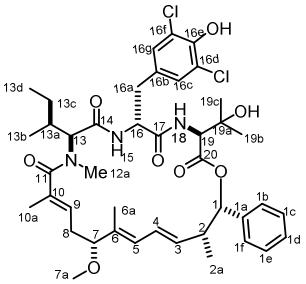
substrate **26** (60.0 mg, 67.5 μmol) in CH_2Cl_2 (0.5 mL). After the addition was complete, all volatile materials were evaporated. The residue was quickly purified by flash chromatography on silica gel (CH_2Cl_2/*tert*-butyl methyl ether, 4:1 to 5:2) to afford the title compound as a yellow oil (64.0 mg, 80%). $[\alpha]_D^{20}$ = –34.8 (c 0.88, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.96 (m, 2H), 7.64–7.58 (m, 1H), 7.49 (dd, *J* = 8.4, 7.1 Hz, 2H), 7.36–7.27 (m, 5H), 7.18 (s, 2H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.65 (d, *J* = 10.4 Hz, 1H), 6.07 (ddd, *J* = 15.0, 10.5, 1.4 Hz, 1H), 5.86 (d, *J* = 2.5 Hz, 1H), 5.76 (dd, *J* = 15.0, 6.5 Hz, 1H), 5.54–5.48 (m, 1H), 5.20 (s, 2H), 4.60 (dd, *J* = 8.6, 6.4 Hz, 1H), 4.50 (dd, *J* = 19.7, 9.9 Hz, 2H), 4.42 (d, *J* = 8.9 Hz, 1H), 3.08 (dd, *J* = 13.8, 8.5 Hz, 1H), 2.80 (dd, *J* = 13.8, 6.3 Hz, 1H), 2.72 (s, 3H), 2.67 (t, *J* = 6.9 Hz, 1H), 2.56 (dt, *J* = 14.3, 9.0 Hz, 1H), 2.45–2.42 (m, 2H), 2.17–2.09 (m, 1H), 1.85 (m, 3H), 1.55–1.46 (m, 6H), 1.34 (h, *J* = 7.3 Hz, 6H), 1.13 (s, 3H), 1.11–1.00 (m, 10H), 1.00 (d, *J* = 2.6 Hz, 3H), 0.92–0.88 (m, 15H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.9, 175.9, 170.7, 170.3, 169.8, 151.2, 149.7, 139.3, 137.9, 137.2, 134.9, 134.5, 133.9, 132.9, 131.2, 129.9, 129.2, 128.8, 128.2, 128.0, 128.0, 126.9, 80.6, 74.7, 72.4, 60.7, 60.4, 54.1, 41.9, 36.1, 35.4, 32.7, 30.9, 29.4, 29.3, 27.9, 27.5, 27.0, 26.9, 26.5, 24.8, 17.6, 16.0, 14.8, 13.7, 13.7, 12.2, 11.2, 10.5 ppm; ^{119}Sn NMR (149 MHz, $CDCl_3$): δ = –51.9 ppm; IR (film) ν = 3349, 2957, 2926, 2854, 1677, 1600, 1468 cm^{-1}; MS (ESI): *m/z*: 1202 [M+Na$^+$]; HRMS (ESI): *m/z*: calcd. for $C_{60}H_{83}N_3O_9Cl_2SnNa$ [M+Na$^+$]: 1202.4420, found: 1202.4435.

Compound 27b (R^1 = Ac). Prepared analogously in the form of a white solid (13.8 mg, 56%); $[\alpha]_D^{20}$ = –72.5 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5H), 7.11 (s, 2H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.73 (d, *J* = 8.9 Hz, 1H), 6.64 (d, *J* = 10.5 Hz, 1H), 6.06 (ddd, *J* = 15.0, 10.6, 1.6 Hz, 1H), 5.88 (d, *J* = 2.4 Hz, 1H), 5.87 (d, *J* = 3.2 Hz, 1H), 5.78 (dd, *J* = 15.0, 6.1 Hz, 1H), 5.50 (ddd, *J* = 8.6, 6.6, 1.7 Hz, 1H), 5.41 (dd, *J* = 9.4, 3.0 Hz, 1H), 4.55 (td, *J* = 8.8, 6.2 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.47 (d, *J* = 8.5 Hz, 1H), 3.01 (dd, *J* = 13.9, 8.8 Hz, 1H), 2.80 (dd, *J* = 13.8, 6.1, 1H), 2.73 (s, 3H), 2.71–2.63 (m, 1H), 2.56–2.50 (m, 1H), 2.50–2.43 (m, 1H), 2.14 (tq, *J* = 9.2, 2.8 Hz, 1H), 2.06 (s, 3H), 1.84 (s, 3H), 1.51 (ddt, *J* = 10.5, 8.0, 6.1 Hz, 6H), 1.43–1.39 (m, 1H), 1.38–1.30 (m, 6H), 1.10 (s, 3H), 1.08–1.05 (m, 1H), 1.04–1.02 (m, 9H), 1.01 (s, 3H), 0.93–0.88 (m, 15H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 175.8, 170.8, 170.4, 170.1, 169.8, 146.9, 146.4, 141.5, 138.1, 138.0, 133.9, 130.9, 129.9, 129.2, 128.3, 128.1, 127.1, 126.9, 121.2, 80.5, 79.9, 72.7, 60.8, 60.4, 54.4, 41.9, 35.8, 33.2, 32.7, 30.9, 29.3, 29.2, 27.5, 27.0, 26.4, 24.9, 21.6, 16.1, 14.9, 13.8, 11.8, 11.3, 10.6 ppm; ^{119}Sn NMR (300 MHz, $CDCl_3$): δ = –50.4 ppm;

IR (film) ν = 3351, 2957, 2926, 2855, 1605, 1489 cm^{-1}; MS (ESI) *m/z*: 1126 (100) [M+Na^+]; HRMS (ESI) *m/z* calcd. for $C_{54}H_{79}N_3O_9Cl_2SnNa$ 1126.4107, found: 1126.4111.

Compound 30. MeI (13 μL, 0.209 mmol) was added to a solution stannane **27a** (41.1 mg, 34.8 μmol) and flame-dried $[Ph_2PO_2][NBu_4]$ (32.0 mg, 69.7 μmol) in DMSO (230 μL). The mixture was stirred for 1 min before CuTC (13.2 mg, 69.2 μmol) was introduced. Stirring was continued for 2 h at room temperature. EtOAc before water was added. The aqueous layer was extracted with EtOAc (3 x 3 mL), the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/*tert*-butyl methyl ether, 5:1 to 3:1) to afford the title compound (22.1 mg, 70%); a second fraction contained recovered starting material (3.6 mg, 9%). $[\alpha]_D^{20}$ = –11.8 (c 1.0, MeOH); ^{1}H NMR (600 MHz, [D_4]-MeOH): δ = 8.01 (d, *J* = 7.8 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 7.3 Hz, 2H), 7.38 (s, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 6.39 (dd, *J* = 15.4, 10.6 Hz, 1H), 6.03 (d, *J* = 10.9 Hz, 1H), 5.88 (dd, *J* = 15.3, 6.4 Hz, 1H), 5.81 (s, 1H), 5.48 (t, *J* = 7.5 Hz, 1H), 5.32 (d, *J* = 3.5 Hz, 2H), 4.77 (t, *J* = 7.8 Hz, 1H), 4.63 (d, *J* = 11.1 Hz, 1H), 4.59 (s, 1H), 4.12 (d, *J* = 8.8 Hz, 1H), 3.05 (dd, *J* = 13.8, 6.5 Hz, 1H), 2.84 (dd, *J* = 13.8, 8.9 Hz, 1H), 2.77 (s, 3H), 2.71–2.65 (m, 1H), 2.54 (dt, *J* = 16.2, 8.3 Hz, 1H), 2.49 (d, *J* = 7.5 Hz, 1H), 2.06–1.97 (m, 1H), 1.86 (s, 3H), 1.79 (s, 3H), 1.36 (p, *J* = 7.2 Hz, 1H), 1.18 (s, 3H), 1.08 (s, 3H), 1.07–1.01 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.73 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (151 MHz, [D_4]-MeOH): δ = 195.2, 177.0, 172.3, 171.6, 171.5, 150.8, 140.4, 138.2, 137.3, 137.1, 135.7, 135.2, 134.2, 131.3, 130.0, 130.0, 129.2, 129.2, 129.0, 128.6, 128.5, 127.7, 127.4, 127.2, 81.8, 76.4, 75.9, 72.9, 61.5, 61.4, 55.1, 43.4, 37.8, 33.8, 33.1, 32.6, 28.3, 25.7, 25.4, 16.0, 14.6, 13.1, 12.2, 10.6 ppm; IR (film) ν = 3316, 2958, 2924, 1599, 1494 cm^{-1}; MS (ESI): *m/z*: 904 [M+H^+], 921 [M+NH_4^+], 926 [M+Na^+]; HRMS (ESI)*: m/z:* calcd. for $C_{49}H_{59}N_3O_9Cl_2Na$ [M+ Na^+]: 926.3521, found: 926.3525.

Nannocystin Ax (1). Ph_3PAuCl (8.7 mg, 17.6 μmol) and AgOTf (4.5 mg, 17.5 μmol) were successively added to a solution of **30** (4.0 mg, 4.4 μmol) and **32** (9.6 mg, 44.4 μmol)[57] in benzene (0.4 mL) at ambient temperature. After the mixture had been stirred for 15 min, the suspension was filtered through a short pad of silica. The filtrate was evaporated and the residue purified by preparative TLC (*tert*-butyl methyl ether/CH_2Cl_2, 3:1).

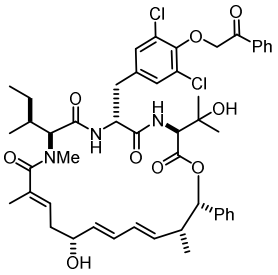


Zn powder (11.5 mg, 0.176 mmol) was added to a stirred solution of the

resulting product **31** in HOAc (90 μL) and THF (90 μL). The resulting mixture was stirred for 7 h before the suspension was filtered through a short pad of Celite®. The filtrate was neutralized with sat. aq. $NaHCO_3$ (1 mL), the aqueous layer was extracted with EtOAc (3 x 3 mL), the combined organic phases were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative LC (150 mm Kromasil 5-C18, 5 µm, ∅ 30 mm, MeOH/H_2O = 75:25, 35 mL/min, 6.4 MPa, 308 K, UV, 240 nm) to afford the title compound (1.5 mg, 44%) as a white solid. $[\alpha]_D^{20}$ = −55.4 (c 0.26, MeOH); for a tabular comparison of the ^{1}H NMR and ^{13}C NMR data with those of the natural product published in the literature, see the Supporting Information; IR (film) ν = 2853, 1456, 1379 cm^{-1}; MS (ESI): *m/z*: 798 [M-H$^-$]; HRMS (ESI): *m/z:* calcd. for $C_{42}H_{54}N_3O_8Cl_2$ [M-H$^-$]: 798.3294, found: 798.3296.

Analogues.

Compound S7. CuTC (4.7 mg, 24.6 μmol) was added at room temperature to a stirred solution of **27**



(26.7 mg, 22.6 μmol) and $[Ph_2PO_2][NBu_4]$ (12.5 mg, 27.2 μmol) in DMF (230 μL). The mixture was stirred for 1 h before it was diluted with EtOAc and water. The aqueous layer was extracted with EtOAc (3 x 3 mL), the combined organic phases were dried over $MgSO_4$, the drying agent was filtered off, and the filtrate was concentrated. The residue was purified by flash chromatography (CH_2Cl_2/*tert*-butyl methyl ether, 5:1 to 2:1) to afford the title compound as a white solid (17.3 mg, 86%). $[\alpha]_D^{20}$ = –74.7 (c 0.15, MeOH); ^{1}H NMR (600 MHz, [D_4]-MeOH, mixture of rotamers, ca. 3.5:1): δ = 8.01–8.00 (m, 2H), 7.68–7.65 (m, 1H), 7.55–7.53 (m, 2H), 7.43–7.37 (m, 2H), 7.40 (s, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.30–7.25 (m, 1H), 6.25–6.11 (m, 2H), 5.99 (s, 0.22H, minor), 5.95 (dd, *J* = 15.3, 7.3 Hz, 0.22H, minor), 5.84–5.81 (m, 1.56H, major), 5.75 (dd, *J* = 15.3, 5.4 Hz, 0.22H, minor), 5.65 (dd, *J* = 14.9, 6.6 Hz, 0.78H, major), 5.57–5.54 (m, 1H), 4.90–4.87 (m, 0.44 H, minor), 4.86–4.82 (m, 1.56H, major), 4.64 (d, *J* = 11.2 Hz, 0.78H, major), 4.63 (s, 0.78H, major), 4.57 (s, 0.22H, minor), 4.40–4.38 (m, 0.22H, minor), 4.19–4.16 (m, 0.78H, major), 4.08 (d, *J* = 10.8 Hz, 0.22H, minor), 3.23 (dd, *J* = 14.3, 4.4 Hz, 0.22H, minor), 3.09 (dd, *J* = 13.8, 5.8 Hz, 0.78H, major), 2.97 (s, 0.66H, minor), 2.83–2.77 (m, 0.78H, major), 2.80 (s, 2.34H, major), 2.69–2.64 (m, 1.22H), 2.59–2.52 (m, 1H), 2.42–2.35 (m, 1H), 2.03–1.99 (m, 1H), 1.91–1.87 (m, 2.34H, major), 1.85 (s, 0.66H, minor), 1.67–1.61 (m, 1H), 1.41–1.36 (m, 1H), 1.37–1.34 (m, 1H), 1.26

(s, 0.66H, minor), 1.22 (s, 0.66H, minor), 1.19 (s, 2.34H, major), 1.10 (s, 2.34H, major), 1.06–1.01 (m, 1H), 0.98–0.95 (m, 3H), 0.95–0.93 (m, 3H), 0.90–0.86 (m, *J* = 7.3 Hz, 3H), 0.70 (d, *J* = 6.5 Hz, 2.34H, major), 0.46 (d, *J* = 6.6 Hz, 0.66H, minor) ppm; ^{13}C NMR (151 MHz, [D$_4$]-MeOH): δ = 195.2, 195.2, 177.3, 176.8, 172.2, 172.1, 171.4, 171.3, 150.8, 140.3, 140.2, 137.9, 137.3, 137.0, 135.7, 135.7, 135.1, 134.5, 134.1, 133.5, 132.1, 131.4, 131.4, 131.3, 131.1, 130.1, 130.0, 130.0, 129.5, 129.2, 129.2, 129.0, 128.5, 128.4, 127.7, 127.3, 81.4, 79.3, 73.1, 72.3, 72.2, 71.3, 68.4, 62.2, 61.5, 61.4, 55.2, 54.7, 43.0, 42.9, 38.3, 36.7, 36.2, 35.1, 34.7, 33.1, 32.5, 29.4, 29.2, 28.3, 28.2, 27.5, 26.7, 26.4, 25.9, 25.4, 16.0, 15.5, 15.1, 14.5, 14.0, 12.2, 12.0, 11.6, 10.7 ppm; IR (film) ν = 3350, 2964, 2929, 2874, 1662, 1598, 1465 cm^{-1}; MS (ESI): *m/z*: 890 [M+H$^+$], 907 [M+NH$_4^+$], 912 [M+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{48}H_{57}N_3O_9Cl_2Na$ [M+Na$^+$]: 912.3364, found: 912.3372.

Compound S8. In a flame-dried Schlenk-tube under argon, solid AgOP(O)Ph$_2$ (13.6 mg, 41.7 μmol) and F-TEDA-PF$_6$ (32.7 mg, 69.5 μmol) were stirred for ca. 10 min until a homogenous grey powder was obtained. Dry acetone (500 μL) was added and the resulting grey suspension was stirred vigorously. Meanwhile, in a separate flask, the vinyl stannane **27** (16.3 mg, 13.8 μmol) was dissolved in acetone (200 μL) and the obtained solution was slowly added to the suspension over 60 min *via* syringe pump. Once the addition was complete, the mixture was diluted with EtOAc/*tert*-butyl methyl ether (1:1, 10 mL) and poured into sat. aq. NH$_4$Cl (10 mL). The aqueous phase was extracted with a EtOAc/*tert*-butyl methyl ether (1:1, 2 x 30 mL), the combined extracts were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH$_2$Cl$_2$/*tert*-butyl methyl ether, 6:1 to 2:1) to afford the title compound as a white solid (6.8 mg, 54%). [α]$_D^{20}$ = –72.2 (c 0.4, CHCl$_3$); ^{1}H NMR (400 MHz, [D$_4$]-MeOH): δ = 8.05–7.99 (m, 2H), 7.69–7.64 (m, 1H), 7.54 (dd, *J* = 8.4, 7.1 Hz, 2H), 7.43 (dd, *J* = 7.1, 1.8 Hz, 2H), 7.39 (s, 2H), 7.36–7.29 (m, 2H), 7.29–7.22 (m, 1H), 6.36 (ddd, *J* = 15.6, 10.7, 1.5 Hz, 1H), 5.92 (dd, *J* = 15.6, 6.7 Hz, 1H), 5.80 (d, *J* = 2.5 Hz, 1H), 5.63–5.54 (m, 1H), 5.59–5.52 (m, 1H), 5.32 (d, *J* = 2.2 Hz, 2H), 4.83–4.76 (m, 1H), 4.65 (d, *J* = 11.2 Hz, 1H), 4.61 (s, 1H), 4.21 (ddd, *J* = 14.0, 9.4, 3.8 Hz, 1H), 3.07 (dd, *J* = 13.8, 6.2 Hz, 1H), 2.83 (dd, *J* = 13.8, 9.2 Hz, 1H), 2.77 (s, 3H), 2.71–2.64 (m, 1H), 2.61–2.56 (m, 1H), 2.52–2.48 (m, 1H), 2.05–1.98 (m, 1H), 1.87 (s, 3H), 1.39–1.33 (m, 1H), 1.19 (s, 3H), 1.09 (s, 3H), 1.07–1.02 (m, 1H), 0.98 (d, *J* = 6.9

Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.72 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (126 MHz, [D_4]-MeOH): δ = 195.2, 176.7, 172.3, 171.5, 171.4, 160.9, 158.8, 150.8, 140.3, 137.5, 137.2, 135.7, 135.2, 135.1, 131.3, 130.0, 129.1, 129.0, 128.5, 127.6, 127.3, 122.4, 122.3, 109.0, 108.9, 81.6, 75.9, 72.9, 70.2, 69.9, 61.4, 61.4, 54.9, 43.6, 38.0, 33.1, 32.6, 28.3, 25.7, 25.4, 16.0, 14.5, 12.2, 10.7 ppm; ^{19}F NMR (282 MHz, [D_4]-MeOH): δ = –120.5, –121.9 ppm; IR (film) ν = 2958, 2924, 2855, 1684, 1601, 1469 cm^{-1}; MS (ESI): *m/z*: 907 [M+Na^+]; HRMS (ESI): *m/z:* calcd. for $C_{48}H_{56}Cl_2FN_3O_9Na$ [M+Na^+]: 930.3270, found: 930.3272.

Compound 37. Ph_3PAuCl (12.9 mg, 26.1 μmol) and AgOTf (6.7 mg, 26.1 μmol) were successively added to a stirred solution of **S7** (5.8 mg, 6.5 μmol) and **32** (14.0 mg, 67.4 μmol) in benzene (650 μL). After the reaction mixture had been stirred for 15 min, sat. aq. $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc (3 x 3 mL), the combined organic phases were washed with brine (1 mL), dried over Na_2SO_4, and evaporated. The crude product was purified by preparative TLC (*tert*-butyl methyl ether/CH_2Cl_2, 3:1).

The resulting product was dissolved in HOAc (130 μL) and THF (130 μL). Zn powder (17.1 mg, 0.262 mmol) was added and the resulting mixture was stirred for 7 h. The suspension was filtered and the filtrate neutralized with sat. aq. $NaHCO_3$ (1 mL). The aqueous layer was extracted with EtOAc (3 x 3 mL), the combined extracts were washed with brine (1 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative HPLC (150 mm Kromasil 5-C18, 5 µm, ∅ 30 mm, MeOH/H_2O = 75:25, 35 mL/min, 6.4 MPa, 308 K, UV, 230 nm) to afford the title compound as a white solid (1.9 mg, 37%). $[\alpha]_D^{20}$ = –71.8 (c 0.11, acetone); ^{1}H NMR (600 MHz, [D_6]-acetone, mixture of rotamers, ca. 4:1): δ = 7.72 (d, *J* = 8.9 Hz, 0.2H, minor), 7.68 (d, *J* = 9.5 Hz, 0.8H, major), 7.55–7.50 (m, 1.6H, major), 7.46 (d, *J* = 7.0 Hz, 0.4H, minor), 7.37–7.29 (m, 4H), 7.28–7.23 (m, 1.2H), 7.12 (d, *J* = 9.3 Hz, 0.8H), 6.27 (dd, *J* = 15.7, 10.1 Hz, 0.2H, minor), 6.23–6.13 (m, 2H), 6.01 (dd, *J* = 15.7, 6.9 Hz, 0.2H, minor), 5.96 (s, 0.2H, minor), 5.91–5.85 (m, 1.6H, major), 5.78 (dd, *J* = 15.6, 5.3 Hz, 0.2H, minor), 5.56–5.48 (m, 1.8H), 5.00–4.96 (m, 0.2H, minor), 4.87–4.83 (m, 0.8H, major), 4.72–4.65 (m, 1H), 4.57 (d, *J* = 11.3 Hz, 0.8H, major), 4.20 (s, 0.6H, major), 4.11–4.04 (m, 0.4H, minor), 3.86–3.84 (m, 0.2H, minor), 3.73–3.69 (m, 0.8H, major), 3.31 (s, 0.6H, minor), 3.23 (s, 2.4H, major), 3.08 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.81–2.75 (m, 1H), 2.70 (s, 2.4H, major), 2.71–2.66 (m, 1.6H), 2.50–2.46 (m, 1H), 2.36 (dt, *J* = 13.8, 9.5 Hz, 1H), 2.02–1.97(m, 1H), 1.84 (s, 2.4H, major), 1.81 (d, *J* = 6.2 Hz, 0.6H, minor), 1.40–1.34 (m, 1H), 1.29 (s, 0.6H, minor), 1.23 (s, 0.6H, minor), 1.22 (s, 2.4H, major), 1.08 (s, 2.4H,

major), 1.03–0.99 (m, 1H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H), 0.73 (d, *J* = 6.5 Hz, 2.4H, major), 0.47 (d, *J* = 6.5 Hz, 0.6H, minor) ppm; ^{13}C NMR (151 MHz, [D_6]-acetone): δ = 175.3, 171.4, 171.1, 170.5, 148.6, 140.5, 137.1, 134.7, 133.9, 133.4, 133.1, 132.3, 131.6, 130.7, 130.4, 130.4, 130.3, 128.9, 128.7, 128.0, 127.3, 127.2, 126.9, 122.4, 122.3, 86.2, 81.7, 81.1, 80.1, 78.3, 72.9, 67.4, 61.5, 60.7, 60.5, 56.1, 56.0, 54.2, 42.5, 42.0, 37.8, 37.3, 34.4, 34.1, 32.6, 31.6, 31.5, 28.5, 28.5, 25.6, 25.6, 25.0, 16.0, 15.0, 14.6, 12.1, 11.5, 11.2, 10.6 ppm; IR (film) ν = 3338, 2972, 2932, 1665, 1606, 1490 cm^{-1}; MS (ESI): *m/z*: 808 [M+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{41}H_{53}N_3O_8Cl_2Na$ [M+ Na$^+$]: 808.3102, found: 808.3112.

Compounds 39 and 40. K_2CO_3 (13.7 mg, 99.1 μmol) and methyl-*p*-toluenesulfonate (36.9 mg, 0.198 mmol) were added to a solution of **S8** (3.0 mg, 3.3 μmol) in acetone (10 μL). After stirring at 50 °C for 24 h, TLC analysis indicated that the starting material had been fully consumed. The material obtained after preparative TLC (*tert*-butyl methyl ether/CH_2Cl_2, 3 :1) was used in the next step without further characterization.

Zn powder (8.7 mg, 0.113 mmol) was added to a stirred solution of the compound in HOAc (70 μL) and THF (70 μL). The resulting mixture was stirred for 7 h before the suspension was filtered and the filtrate neutralized with sat. aq. $NaHCO_3$. The aqueous layers were extracted with EtOAc (3 x 3 mL), the combined organic layers phases were washed with brine (1 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative HPLC (150 mm Kromasil 5-C18, 5 µm, ∅ 30 mm, CH_3CN/H_2O = 65:35, 35 mL/min, 4.2 MPa, 308 K, UV, 227 nm) to afford compound **39** (0.9 mg, 34%) and compound **40** (0.7 mg, 28%) as a white solid each.

Analytical data of compound **39**: $[\alpha]_D^{20}$ = –75.0 (c 0.08, acetone); ^{1}H NMR (600 MHz, [D_6]-acetone): δ = 7.63 (d, *J* = 9.5 Hz, 1H), 7.58–7.50 (m, 2H), 7.34-7.31 (d, *J* = 8.6 Hz, 4H), 7.27–7.22 (m, 1H), 7.04 (d, *J* = 9.4 Hz, 1H), 6.37 (ddd, *J* = 15.6, 10.7, 1.7 Hz, 1H), 5.98 (dd, *J* = 15.6, 5.9 Hz, 1H), 5.85 (d, *J* = 2.2 Hz, 1H), 5.64 (dd, *J* = 36.1, 10.7 Hz, 1H), 5.50 (ddd, *J* = 8.8, 6.9, 1.7 Hz, 1H), 4.83 (td, *J* = 9.2, 5.8 Hz, 1H), 4.72–4.68 (m, 1H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.16 (s, 1H), 3.84 (ddd, *J* = 20.7, 10.5, 3.4 Hz, 1H), 3.30 (s, 3H), 3.06 (dd, *J* = 13.9, 5.8 Hz, 1H), 2.72–2.61 (m, 2H), 2.68 (s, 3H), 2.44 (ddd, *J* = 13.8, 7.2, 3.4 Hz, 1H), 2.01–1.96 (dtt, *J* = 9.3, 6.7, 3.3 Hz, 1H), 1.87(s, 3H), 1.41–1.35 (m, 1H), 1.22 (s, 3H), 1.07 (s, 3H), 1.05–1.00 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H), 0.75 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (151 MHz, [D_6]-acetone): δ = 175.2, 171.4, 171.1, 170.6, 157.3, 155.5, 148.6, 140.6, 137.9,

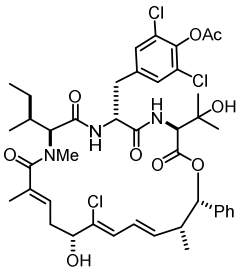
135.7, 131.6, 130.4, 128.7, 128.0, 127.3, 126.0, 122.2, 121.5, 121.5, 111.4, 111.4, 80.1, 79.5, 79.3, 72.9, 72.8, 60.7, 60.5, 56.4, 54.2, 54.2, 43.0, 37.7, 32.6, 31.5, 30.9, 28.6, 25.5, 25.1, 16.0, 14.4, 11.2, 10.5 ppm; ^{19}F NMR (470 MHz, [D_6]-acetone): δ = –119.9, –123.7 ppm; IR (film) ν = 2967, 2932, 1735, 1665, 1606, 1490 cm^{-1}; MS (ESI): *m/z*: 804 [M+H$^+$], 821 [M+NH$_4^+$] ; HRMS (ESI): *m/z:* calcd. for $C_{41}H_{52}N_3O_8Cl_2FNa$ [M+Na$^+$]: 826.3008, found: 826.3012.

Analytical data of compound **40**: $[\alpha]_D^{20}$ = –26.7 (c 0.06, acetone); ^{1}H NMR (600 MHz, [D_6]-acetone): δ = 8.65 (s, 1H), 7.46 (s, 1H), 7.42–7.36 (m, 4H), 7.34 (d, *J* = 9.4 Hz, 1H), 7.29 (s, 3H), 6.37 (ddd, *J* = 15.7, 10.7, 1.8 Hz, 1H), 6.23 (d, *J* = 2.2 Hz, 1H), 6.01 (dd, *J* = 15.7, 5.3 Hz, 1H), 5.67 (dd, *J* = 35.7, 10.7 Hz, 1H), 5.56 (t, *J* = 7.4 Hz, 1H), 4.73 (td, *J* = 9.4, 5.2 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.04 (t, *J* = 5.3 Hz, 2H), 3.81 (ddd, *J* = 23.7, 11.0, 3.5 Hz, 1H), 3.29 (s, 3H), 3.11 (dd, *J* = 14.3, 5.3 Hz, 1H), 2.81-2.79 (m, 5H), 2.62 (ddd, *J* = 14.2, 10.9, 8.2 Hz, 1H), 2.50–2.40 (m, 1H), 2.10–2.06 (m, 1H), 1.81 (s, 3H), 1.45–1.40 (m, 1H), 1.06–0.99 (m, 1H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.75 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (151 MHz, [D_6]-acetone): δ = 175.7, 171.9, 171.4, 169.4, 156.8, 155.0, 148.5, 140.2, 138.1, 135.6, 132.0, 130.2, 129.1, 128.2, 126.9, 126.5, 122.3, 121.1, 121.1, 112.1, 112.0, 79.6, 79.4, 77.1, 61.5, 56.3, 54.2, 54.1, 54.1, 42.7, 41.6, 41.5, 36.1, 33.0, 31.9, 31.0, 25.5, 15.9, 14.5, 10.6, 10.2 ppm; ^{19}F NMR (470 MHz, [D_6]-acetone): δ = –125.5 ppm; IR (film) ν = 2967, 2932, 1751, 1677, 1605, 1490 cm^{-1}; MS (ESI): *m/z*: 746 [M+H$^+$], 763 [M+NH$_4^+$], 768 [M+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{38}H_{46}N_3O_7Cl_2FNa$ [M+Na$^+$]: 768.2589, found: 768.2594.

Compound 42. Prepared analogously as a white solid (1.8 mg, 45%). $[\alpha]_D^{20}$ = –91.2 (c 0.16, acetone); ^{1}H NMR (600 MHz, [D_4]-MeOH, mixture of rotamers, ca. 4:1): δ = 7.40–7.37 (m, 2H), 7.36–7.30 (m, 2H), 7.29–7.25 (m, 1H), 7.23 (s, 2H), 6.34 (dd, *J* = 16.1, 6.3 Hz, 0.2H, minor), 6.17 (dd, *J* = 16.0, 7.6 Hz, 0.8H, major), 6.04 (s, 0.2H, minor), 5.75–5.72 (m, 1H), 5.63 (td, *J* = 7.2, 4.0 Hz, 0.8H, minor), 5.61–5.55 (m, 1H), 4.77 (dd, *J* = 9.4, 6.1 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 0.8H, major), 4.64 (s, 0.8H, major), 4.50 (s, 0.2H, minor), 4.33 (d, *J* = 7.4 Hz, 0.2H, minor), 4.19 (ddd, *J* = 9.2, 5.1, 1.6 Hz, 0.8H, major), 4.03 (d, *J* = 10.9 Hz, 0.2H, minor), 3.39 (s, 2.4H, major), 3.33 (s, 0.6H, minor), 3.23–3.20 (m, 0.2H, minor), 3.02 (dd, *J* = 13.9, 6.1 Hz, 0.8H, major), 2.98 (s, 0.6H, minor), 2.96–2.91 (m, 0.4H, minor),2.87 (s, 2.4H, major), 2.80–2.71 (m, 1.8H), 2.59–2.51 (m, 1.6H, major), 2.49–2.47 (m, 0.2H, minor), 2.06–1.98 (m, 1H), 1.93 (d, *J* = 1.6 Hz, 2.4H, major), 1.86 (s, 0.6H, minor), 1.40–1.33 (m, 1H), 1.29 (s, 1H), 1.23 (s, 0.6H, minor), 1.18 (s, 0.6H, minor), 1.15 (s, 2.4H, major), 1.08 (s, 2.4H, major), 1.06–1.00 (m,

1H), 0.94 (d, *J* = 7.0 Hz, 2.4H, major), 0.93–0.90 (m, 1.2H, minor), 0.88 (t, *J* = 7.4 Hz, 2.4H, major), 0.72 (d, *J* = 6.5 Hz, 2.4H, major), 0.55 (d, *J* = 6.5 Hz, 0.6H, minor) ppm; ^{13}C NMR (151 MHz, [D$_4$]-MeOH): δ = 176.8, 172.7, 171.4, 171.4, 150.0, 148.7, 146.4, 139.0, 135.8, 130.5, 130.4, 130.2, 129.2, 129.0, 128.8, 128.6, 128.0, 127.4, 127.2, 126.8, 123.3, 111.1, 110.3, 88.2, 85.9, 81.2, 78.7, 72.9, 72.3, 71.7, 68.3, 61.8, 61.5, 56.7, 55.4, 55.1, 43.7, 43.5, 37.8, 36.4, 35.1, 34.7, 33.7, 33.1, 32.4, 29.4, 28.0, 27.6, 26.5, 26.3, 25.7, 25.4, 15.8, 15.6, 15.3, 14.6, 13.6, 11.7, 11.1, 10.7 ppm; IR (film) ν = 2853, 1732, 1675, 1608, 1450 cm^{-1}; MS (ESI): *m/z*: 784 [M+H$^+$], 784 [M+NH$_4^+$], 806 [M+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{41}H_{51}N_3O_8Cl_2Na$ [M+Na$^+$]: 806.2945, found: 806.2948.

Compound 41. 2,6-Lutidine (1.0 M in THF, 65 μL, 65 μmol) and anhydrous $CuCl_2$ (17.2 mg, 128 μmol) were consecutively added to a solution of stannane **27b** (7.0 mg, 6.3 μmol) in THF (600 μL). The resulting green mixture was stirred at ambient temperature for 72 h. The then orange suspension was diluted with EtOAc (30 mL) and poured into aq. sat. NH_4OH/NH_4Cl solution (1:9, 10 mL). The phases were separated and the aqueous phase extracted with EtOAc (2 x 30 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silical gel (EtOAc/hexanes, 1:1) to afford the title compound as a white solid (4.4 mg, 82%). $[\alpha]_D^{20}$ = –74.5 (c 0.4, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 5H), 7.06 (s, 3H), 6.54 (d, *J* = 8.4 Hz, 1H), 6.41 (ddd, *J* = 15.3, 10.2, 1.3 Hz, 1H), 6.25 (d, *J* = 10.2 Hz, 1H), 5.92–5.87 (m, 1H), 5.86 (d, *J* = 2.7 Hz, 1H), 5.79 (s, 1H), 5.55 (td, *J* = 7.7, 1.7 Hz, 1H), 5.41 (dd, *J* = 7.9, 3.5 Hz, 1H), 4.62–4.55 (m, 1H), 4.51 (d, *J* = 8.8 Hz, 1H), 4.47 (d, *J* = 11.3 Hz, 2H), 3.64–3.59 (m, 1H), 2.99 (dd, *J* = 14.0, 7.7 Hz, 1H), 2.77 (s, 3H), 2.74–2.64 (m, 2H), 2.61–2.57 (m, 1H), 2.12 (s, 3H), 2.11–2.05 (m, 1H), 1.88 (d, *J* = 1.5 Hz, 3H), 1.45–1.32 (m, 2H), 1.18 (s, 3H), 1.05 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.5, 170.7, 170.4, 169.8, 169.5, 146.9, 140.0, 137.5, 135.6, 129.9, 129.7, 129.1, 128.3, 127.3, 127.2, 125.8, 125.4, 121.2, 80.2, 74.8, 72.2, 61.1, 60.6, 54.2, 42.2, 36.1, 32.4, 31.3, 30.2, 27.1, 26.6, 25.0, 21.3, 15.9, 14.7, 13.1, 10.6 ppm; IR (film) ν = 3361, 2964, 2929, 1735, 1663, 1606, 1489 cm^{-1}; MS (ESI): *m/z*: 870 [M+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{42}H_{52}Cl_3N_3O_9Na$ [M+Na$^+$]: 870.2261, found: 870.2269.



Representative Procedure for Phenacyl Cleavage. Compound 35. Zn powder (11.6 mg, 0.177 mmol) was added to a stirred solution of **30** (4.0 mg, 4.4 μmol) in HOAc (90 μL) and THF (90 μL) at room temperature. The resulting mixture was stirred for 7 h before the suspension was filtered. The filtrate was neutralized with sat. aq. $NaHCO_3$, the aqueous layer was extracted with EtOAc (3 x 3 mL), the combined organic layers were washed with brine (1 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative HPLC (150 mm Kromasil 5-C18, 5 µm, ∅ 30 mm, MeOH/H_2O = 70:30, 35 mL/min, 7.0 MPa, 308 K, UV, 230 nm) to afford the title compound as a white solid (2.7 mg, 78%). $[\alpha]_D^{20}$ = –21.1 (c 0.19, acetone); ^{1}H NMR (600 MHz, [D_4]-MeOH, mixture of rotamers, ca. 4:1): δ = 7.43–7.42 (m, 1.6H, major), 7.40–7.38 (m, 0.4H, minor), 7.34–7.30 (m, 2H), 7.26–7.22 (m, 1.4H), 7.21 (s, 1.6H), 6.46–6.41 (m, 0.2H, minor), 6.38 (ddd, *J* = 15.2, 10.7, 1.5 Hz, 0.8H, major), 6.06–6.01 (m, 1H), 5.97–5.92 (m, 0.4H, minor), 5.87 (dd, *J* = 15.3, 6.4 Hz, 0.8H, major), 5.80 (d, *J* = 2.5 Hz, 0.8H, major), 5.48 (dd, *J* = 8.5, 6.9 Hz, 1H), 4.70 (dd, *J* = 8.6, 6.9 Hz, 0.8H, major), 4.62 (d, *J* = 11.1 Hz, 0.8H, major), 4.58–4.57 (m, 2.6H), 4.12 (dd, *J* = 9.2, 3.4 Hz, 0.8H, major), 2.98–2.93 (m, 1.4H), 2.77–2.73 (m, 1H), 2.76 (s, 2.4H, major), 2.67 (t, *J* = 7.2 Hz, 1H), 2.56–2.51 (m, 1.4H), 2.50–2.44 (m, 0.8H, major), 2.05–1.97 (m, 1H), 1.85 (s, 2.4H, major), 1.82 (s, 0.6H, minor), 1.81 (s, 0.6H, minor), 1.79 (s, 2.4H, major), 1.37–1.33 (m, 2H), 1.25 (s, 0.6H, minor), 1.20 (s, 0.6H, minor), 1.14 (s, 2.4H, major), 1.04 (s, 2.4H, major), 0.99 (d, *J* = 6.9 Hz, 3H), 0.95–0.90 (m, 1H), 0.88 (d, *J* = 7.4 Hz, 3H), 0.72 (d, *J* = 6.5 Hz, 2.4H), 0.50 (d, *J* = 6.5 Hz, 0.6H) ppm; ^{13}C NMR (151 MHz, [D_4]-MeOH): δ = 176.9, 172.6, 171.6, 171.5, 140.4, 138.1, 137.3, 134.2, 130.4, 129.0, 128.5, 128.4, 127.7, 127.4, 127.1, 81.7, 76.4, 72.9, 61.4, 55.4, 43.5, 37.5, 33.8, 33.1, 32.6, 28.3, 25.5, 25.5, 15.9, 14.6, 13.1, 12.2, 10.6 ppm; IR (film) ν = 3349, 2966, 2929, 1603, 1490 cm^{-1}; MS (ESI) *m/z*: 786 [M+H$^+$], 803 [M+NH_4^+], 808 [M+Na^+]; HRMS (ESI): *m/z:* calcd. for $C_{41}H_{53}N_3O_8Cl_2Na$ [M+Na^+]: 808.3102, found: 808.3107.

Compound 38. Prepared analogously from **S8** (4.9 mg, 5.4 μmol) as a white solid (3.7 mg, 87%); preparative HPLC: 150 mm YMC ODS-A 5 µm, ∅ 20 mm, MeOH/H_2O = 75:25, 15 mL/min, 8.8 MPa, 298 K, UV, 220 nm. $[\alpha]_D^{20}$ = –35.2 (c 0.23, acetone); ^{1}H NMR (600 MHz, [D_4]-MeOH, mixture of rotamers, ca. 5.7:1): δ = 7.44–7.40 (m, 1.7H, major), 7.39–7.38 (m, 0.3H, minor), 7.35–7.31 (m, 2H), 7.28–7.23 (m, 1.3H), 7.21 (s, 1.7H, major), 6.36 (ddd, *J* = 15.6, 10.7, 1.4 Hz, 1H), 6.05–6.01 (m, 0.3H, minor), 5.91 (dd, *J* = 15.5, 6.8 Hz, 0.85H, major), 5.79 (d, *J* = 2.5 Hz, 0.85H, major), 5.68–5.54 (m, 2H), 4.72 (dd, *J* = 8.9, 6.6 Hz, 1H), 4.65 (d, *J* = 11.1 Hz, 0.85H, major), 4.59 (s, 0.85H, major), 4.49 (s, 0.15H,

minor), 4.39–4.36 (m, 0.15H, minor), 4.26–4.19 (m, 0.85H, major), 4.09 (d, *J* = 7.2 Hz, 0.15H, minor), 3.13 (dd, *J* = 14.4, 4.8 Hz, 0.15H, minor), 3.00–2.92 (m, 1.3H), 2.840 (dd, *J* = 14.3, 10.6 Hz, 0.15H), 2.76 (s, 2.55H, major), 2.75–2.72 (m, 0.85H, major), 2.69–2.63 (m, 1H), 2.63–2.56 (m, 1H), 2.54–2.47 (m, 1H), 2.05–1.96 (m, 0.85H, major), 1.88–1.83 (m, 3.15H), 1.39–1.32 (m, 1H), 1.26 (s, 0.45H, minor), 1.23 (s, 0.45H, minor), 1.16 (s, 2.55H, major), 1.05 (s, 2.55H, major), 1.04–0.99 (m, 1H), 0.97 (d, *J* = 6.9 Hz, 2.55H, major), 0.93 (d, *J* = 6.9 Hz, 0.45H, minor), 0.87 (t, *J* = 7.4 Hz, 3H), 0.72 (d, *J* = 6.5 Hz, 2.55H, major), 0.47 (d, *J* = 6.5 Hz, 0.45H, minor) ppm; ^{13}C NMR (151 MHz, [D_4]-MeOH): δ = 176.8, 172.8, 171.6, 171.5, 160.9, 159.1, 150.2, 140.4, 137.7, 135.4, 130.6, 129.2, 128.6, 127.8, 127.4, 123.5, 122.5, 122.5, 109.1, 109.0, 81.7, 73.1, 70.3, 70.1, 61.6, 55.4, 43.8, 37.9, 33.2, 33.2, 32.8, 28.4, 25.7, 25.6, 16.0, 14.6, 12.4, 10.8 ppm; ^{19}F NMR (282 MHz, [D_4]-MeOH): δ = –120.4, –121.7 ppm; IR (film) ν = 3331, 2970, 2931, 2877, 1664, 1604, 1522, 1490 cm^{-1}; MS (ESI): *m/z*: 812 [M+Na$^+$]; HRMS (ESI): *m/z:* calcd. for $C_{40}H_{50}N_3O_8Cl_2FNa$ [M+Na$^+$]: 812.2851, found: 812.2856.

Compound 43. Prepared analogously from **26** (6.6 mg, 7.4 μmol) as a white solid (4.6 mg, 80%); purification by preparative HPLC (150 mm YMC Pack Pro C18, 5 μm, ∅ 10 mm, MeOH/H_2O = 80:20, 4.7 mL/min, 9.6 MPa, 308 K, UV, 220 nm); $[\alpha]_D^{20}$ = –106 (c 0.1, acetone); ^{1}H NMR (600 MHz, [D_6]-acetone, mixture of rotamers, ca. 2.3:1): δ = 8.65 (s, 0.6H), 7.79– 7.70 (m, 0.9H), 7.51 (d, *J* = 8.8 Hz, 0.2H), 7.48–7.44 (m, 2.2H), 7.38–7.27 (m, 4.5H), 7.14 (d, *J* = 9.2 Hz, 0.6H), 6.38 (dd, *J* = 16.2, 5.9 Hz, 0.3H, minor), 6.21–6.09 (m, 1H), 5.87 (d, *J* = 9.2 Hz, 0.3H, minor), 5.76 (d, *J* = 2.9 Hz, 0.7H, major), 5.63–5.56 (m, 1H), 5.56–5.48 (m, 0.7H, major), 4.92 (s, 0.3H, minor), 4.89–4.83 (m, 0.7H, major), 4.78 (s, 0.3H, minor), 4.72 (d, *J* = 9.5 Hz, 0.7H, major), 4.59–4.57 (m, 1.3H), 4.56–4.51 (m, 0.7H, major), 4.20 (d, *J* = 10.9 Hz, 0.3H, minor), 4.14 (s, 0.5H, major), 3.82 (s, 0.2H, minor), 3.40–3.34 (m, 0.3H, minor), 3.12 (dd, *J* = 14.0, 5.5 Hz, 0.7H, major), 2.98 (d, *J* = 14.0 Hz, 0.3H, minor), 2.95 (s, 0.9H, major), 2.81 (s, 4.4H, major), 2.77–2.75 (m, 0.7H, major), 2.58 (dt, *J* = 13.0, 9.6 Hz, 0.7H, major), 2.49 (dt, *J* = 12.5, 5.3 Hz, 0.7H, major), 2.42–2.37 (m, 0.3H, minor), 2.01–1.97 (m, 0.7H, major), 1.94 (s, 2.1H, major), 1.90–1.88 (s, 0.3H, minor), 1.78 (s, 0.9H, minor), 1.42–1.37 (m, 0.7H, major), 1.33–1.25 (m, 2.4H), 1.22 (s, 3.1H), 1.12 (s, 2.1H, major), 1.05–0.99 (m, 0.7H, major), 0.92–0.88 (m, 3H), 0.88–0.83 (m, 3H), 0.76 (d, *J* = 6.5 Hz, 2.1H, major), 0.42 (d, *J* = 6.5 Hz, 0.9H, minor) ppm; ^{13}C NMR (151 MHz, [D_6]-acetone): δ = 175.6, 174.7, 171.8, 171.7, 171.2, 171.1, 171.0, 170.6, 148.6, 148.0, 145.4, 139.8, 139.1, 135.6, 135.3, 132.7, 131.7, 130.3, 130.0, 129.0, 128.7, 128.3, 128.2, 127.7, 126.8, 126.5, 126.1,

122.4, 122.3, 111.2, 110.1, 91.7, 85.1, 83.2, 80.2, 76.6, 72.6, 71.7, 67.5, 62.2, 61.9, 61.3, 61.1, 60.7, 55.5, 54.2, 43.2, 43.0, 37.8, 37.4, 36.8, 35.2, 34.6, 32.7, 31.6, 28.4, 28.3, 27.8, 26.3, 26.0, 25.7, 25.2, 16.1, 15.5, 15.2, 14.8, 14.4, 13.5, 11.7, 10.6, 10.1 ppm; IR (film) ν = 3342, 2970, 2931, 2877, 1738, 1605, 1521 cm^{-1}; MS (ESI): *m/z*: 770 [$M+H^+$], 787 [$M+Na^+$], 792[$M+Na^+$]; HRMS (ESI): *m/z:* calcd. for $C_{40}H_{49}N_3O_8Cl_2Na$ [$M+Na^+$]: 792.2789, found: 792.2795.

Compound 36. Prepared analogously from **S7** (4.0 mg, 4.5 μmol) as a white solid (2.6 mg, 75%); preparative HPLC: 150 mm YMC Pack Pro C18, 5 µm, ∅ 10 mm, MeOH/H_2O = 80:20, 4.7 mL/min, 9.6 MPa, 308 K, UV, 220 nm); $[\alpha]_D^{20}$ = –91.0 (c 0.2, acetone); ^{1}H NMR (600 MHz, [D_4]-MeOH, mixture of rotamers, ca. 3.5:1): δ = 7.42 (d, *J* = 7.4 Hz, 1.56H, major), 7.39 (d, *J* = 7.9 Hz, 0.44H, minor), 7.35–7.30 (m, 2H), 7.27–7.24 (m, 1.44H), 7.22 (s, 1.56H), 6.24–6.09 (m, 2H), 5.99 (s, 0.22H, minor), 5.94 (dd, *J* = 15.3, 7.3 Hz, 0.22H, minor), 5.85–5.79 (m, 1.56H, major), 5.75 (dd, *J* = 15.3, 5.4 Hz, 0.22H, minor), 5.65 (dd, *J* = 14.8, 6.6 Hz, 0.78H, major), 5.55 (td, *J* = 6.8, 6.1, 3.4 Hz, 1H), 4.76 (dd, *J* = 9.3, 6.2 Hz, 1H), 4.63 (d, *J* = 11.2 Hz, 0.78H, major), 4.60 (s, 0.78H, major), 4.56 (s, 0.22H, minor), 4.41–4.32 (m, 0.22H, minor), 4.2–4.13 (m, 0.78H, major), 4.07 (d, *J* = 10.8 Hz, 0.22H, minor), 3.14 (dd, *J* = 14.3, 4.6 Hz, 0.22H, minor), 3.00 (dd, *J* = 13.8, 6.2 Hz, 0.78H, major), 2.96 (s, 0.66H, minor), 2.92–2.84 (m, 0.22H, minor), 2.78 (s, 2.34H, major), 2.73 (dd, *J* = 13.8, 9.4 Hz, 0.78H, major), 2.69–2.62 (m, 1.22H), 2.55–2.50 (m, 1H), 2.41–2.35 (m, 0.78H, major), 2.04–1.95 (m, 0.78H, major), 1.87 (d, *J* = 1.5 Hz, 2.34H, major), 1.83 (s, 0.88H), 1.39–1.31 (m, 1H), 1.29 (s, 1H), 1.24 (s, 0.66H, minor), 1.20 (s, 0.66H, minor), 1.16 (s, 2.34H, major), 1.06 (s, 2.34H, major), 1.06–1.00 (m, 1H), 0.97 (d, *J* = 6.9 Hz, 2.34H, major), 0.95 (d, *J* = 7.1 Hz, 0.66H, minor), 0.87 (t, *J* = 7.4 Hz, 3H), 0.69 (d, *J* = 6.5 Hz, 2.34H, major), 0.44 (d, *J* = 6.5 Hz, 0.66H, minor) ppm; ^{13}C NMR (151 MHz, [D_4]-MeOH): δ = 177.3, 176.8, 172.4, 172.4, 172.1, 171.4, 171.3, 171.3, 149.7, 140.3, 140.2, 137.2, 137.0, 135.1, 134.5, 134.2, 133.4, 132.1, 132.1, 131.4, 131.3, 131.1, 130.8, 130.5, 130.4, 129.5, 129.2, 129.0, 128.5, 128.4, 128.4, 127.7, 127.3, 123.4, 123.3, 81.4, 79.3, 73.1, 72.3, 72.2, 71.3, 68.4, 62.1, 61.5, 61.3, 55.5, 55.0, 43.0, 42.8, 38.0, 36.5, 36.2, 35.1, 34.8, 33.1, 32.5, 29.4, 28.2, 27.5, 26.6, 26.4, 25.7, 25.4, 15.9, 15.3, 15.1, 14.5, 12.2, 12.0, 11.6, 10.7 ppm; IR (film) ν = 3369, 2969, 2929, 2875, 1735, 1663, 1604, 1490 cm^{-1}; MS (ESI): *m/z*: 772 [$M+H^+$], 789 [$M+NH_4^+$], 794 [$M+Na^+$]; HRMS (ESI): *m/z:* calcd. for $C_{40}H_{51}N_3O_8Cl_2Na$ [$M+ Na^+$]: 794.2945, found: 794.2952.

Compound 44. Zn(Cu/Ag) alloy (20 mg) was added to a solution of **43** (3.7 mg, 4.8 μmol) in MeOH/dioxane/H_2O (300 μL, 1:1:1) and the resulting suspension was stirred at 60 ^{o}C for 12 h. All insoluble materials were filtered off through a pad of Celite®. The filtrate was evaporated and the crude product purified by preparative HPLC (150 mm YMC ODS-A 5 µm, ∅ 20 mm, MeOH/H_2O = 75:25, 15 mL/min, 10.8 MPa, 298 K, UV, 220 nm) to afford the title compound as a white solid (2.3 mg, 62%) . $[\alpha]_D^{20}$ = –113.5 (c 0.23, acetone); ^{1}H NMR (600 MHz, [D_4]-MeOH), mixture of rotamers, ca. 2.6:1): δ = 7.41–7.36 (m, 2H), 7.35–7.31 (q, *J* = 8.8, 7.7 Hz, 2H), 7.29–7.25 (m, 1H), 7.24 (s, 2H), 6.34 (dd, *J* = 16.2, 5.8 Hz, 0.28H, minor), 6.17–6.09 (m, 1H), 5.91–5.85 (m, 0.28H, minor), 5.74 (s, 0.72H, major), 5.64 (dt, *J* = 8.0, 4.4 Hz, 0.72H, major), 5.56 (d, *J* = 16.0 Hz, 0.72H, major), 5.51 (d, *J* = 16.2 Hz, 0.28H, minor), 4.85–4.81 (m, 1H), 4.77 (dd, *J* = 9.3, 6.1 Hz, 1H), 4.72 (dd, *J* = 11.2, 3.8 Hz, 1H), 4.66 (d, *J* = 11.3 Hz, 0.72H, major), 4.63 (s, 0.72H, major), 4.53 (s, 0.28H, minor), 4.52–4.48 (m, 0.72H, major), 4.14 (d, *J* = 10.8 Hz, 0.28H, minor), 3.26 (d, *J* = 15.7 Hz, 0.28H, minor), 3.04–3.01 (m, 0.72H, major), 3.01 (s, 0.84H, minor), 2.96 (dd, *J* = 14.6, 11.4 Hz, 0.28H, minor), 2.87 (s, 2.16H, major), 2.79–2.72 (m, 2H), 2.59–2.49 (m, 1.44H, major), 2.43 (d, *J* = 15.0 Hz, 0.28H, minor), 2.06–1.97 (m, 0.72H, major), 1.94 (s, 2.16H, major), 1.87 (d, *J* = 27.2 Hz, 0.28H, minor), 1.84 (s, 0.84H, major), 1.40–1.33 (m, 1H), 1.24 (s, 0.84H, minor), 1.20 (s, 0.84H, minor), 1.15 (s, 2.16H, major), 1.08 (s, 2.16H, major), 1.07–0.97 (m, 1H), 0.93 (d, *J* = 6.9 Hz, 2.16H, major), 0.91–0.86 (m, 3.84H), 0.72 (d, *J* = 6.5 Hz, 2.16H, major), 0.44 (d, *J* = 6.5 Hz, 0.84H, minor) ppm; ^{13}C NMR (151 MHz, [D_4]-MeOH): δ = 177.1, 176.9, 172.6, 172.6, 172.2, 171.4, 171.3, 171.2, 149.9, 148.5, 145.9, 139.7, 139.0, 135.7, 134.8, 130.7, 130.4, 130.1, 129.3, 129.0, 128.8, 128.5, 128.4, 128.0, 127.1, 127.0, 111.4, 110.3, 90.8, 89.4, 85.3, 84.1, 81.2, 77.8, 72.9, 72.2, 68.3, 62.5, 62.0, 61.8, 61.5, 61.5, 56.2, 55.1, 43.8, 43.4, 37.9, 37.2, 37.2, 35.2, 35.2, 33.1, 32.4, 29.2, 28.0, 27.4, 26.4, 26.4, 25.7, 25.4, 15.8, 15.4, 15.4, 14.6, 13.7, 11.7, 10.7, 10.1 ppm; IR (film) ν = 2923, 2853, 1659, 1604, 1455 cm^{-1}; MS (ESI): *m/z*: 772 [M+H$^+$], 794 [M+Na$^+$] ; HRMS (ESI): *m/z:* calcd. for $C_{40}H_{51}N_3O_8Cl_2Na$ [M+Na$^+$]: 794.2945, found: 794.2945.

Supporting Information

Crystallographic abstract, tabular comparision of the NMR data of synthetic nannocystin Ax with those of the natural product, copies of HPLC traces, and copies of spectra of new compounds

CCDC-1584397 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via the Internet at: www.ccdc.ca.ac.uk/data_request/cif

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