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Total Synthesis of Myxovirescin A_1

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Abstract: A convergent total synthesis of the antibiotic macrolide myxovirescin A_1 (**1**) is described that is largely based on reagent- and catalyst-controlled transformations. This includes a highly regioselective Negishi reaction of dibromo-alkene **48** with an alkynylzinc reagent, and a palladium catalyzed alkyl-Suzuki coupling of the resulting enyne derivative **12** with the 9-BBN-adduct derived from alkene **61**. The latter was obtained via an asymmetric hydrogenation of the chlorinated β-ketoester **49** and an *anti*-selective oxyallylation of the functionalized aldehyde **53** as the key steps. The preparation of the bis-borylated allyl-donor **57** used in the oxyallylation step, however, required careful optimization and led to important insights into the nature of the classical hydroborating agent "di(isopinocampheyl)borane (Ipc_2BH)". It was unambiguously shown by X-ray crystallography that in the solid state this compound is dimeric, but it is prone to undergo an essentially quantitative mono-deborylation when dissolved in CH_2Cl_2 or benzene; its composition in ethereal solvents is even more complex as evident from ^{11}B NMR data. Product **71** derived from **12** and **61** was elaborated into the enyne–yne derivative **75**, which served as the substrate for an exquisitely selective ring closing alkyne metathesis reaction (RCAM) catalyzed by the molybdenum tris-amido complex **20** activated in situ with CH_2Cl_2. The resulting cyclic enyne **76** was subjected to a ruthenium catalyzed *trans*-hydrosilylation/proto-desilylation tandem. Although $[Cp^*Ru(MeCN)_3]PF_6$ had previously been recommended as catalyst of choice for *trans*-hydrosilylation reactions of internal alkynes, this complex failed to afford the desired product, whereas its sterically less hindered congener $[CpRu(MeCN)_3]PF_6$ permitted the reaction to be performed in appreciable yield, but at the expense of a lower stereoselectivity. AgF-mediated proto-desilylation of the isomeric silanes **79** and **80** followed by cleavage of the remaining acetal protecting groups afforded myxovirescin A_1 and its hitherto unknown 14*Z*-isomer **81**, respectively.

Keywords: alkynes · antibiotics · macrocyclization · metathesis · natural products

Introduction

Antibacterial chemotherapy has benefited enormously from natural products, which have found either direct use as therapeutic agents, serve as elaborate building blocks for the preparation of semisynthetic drugs, or play an important role as leads for further optimization. Although challenged by alternative paradigms of contemporary medicinal chemistry, the (re)evaluation of naturally occurring antimicrobial agents of various origins remains a valid strategy in the quest for ever more effective drugs to combat bacterial infections.[1]

In this context, the myxovirescins represent an interesting class of compounds. Isolated as early as 1982 from *Myxococcus virescens* (strain v 48), more than 30 members of this family of macrocyclic lactone/lactam derivatives are known to date.[2–5] Although a few ring-expanded as well as ring-contracted representatives are on this list,[3] most myxovirescins differ solely in the substitution-, oxygenation- and stereochemical pattern of a highly conserved 28-membered macrocyclic frame.[2,3] It is interesting to note that they are usually produced in form of either epimer at C-25, with myxovirescin A_1 (**1**) and A_2 (**2**) being a typical pair.[3] The obvious capacity of the operative biosynthetic machinery therefore holds great promise for metabolic engineering in order to obtain "non-natural" natural products with improved application profiles.[6,7]

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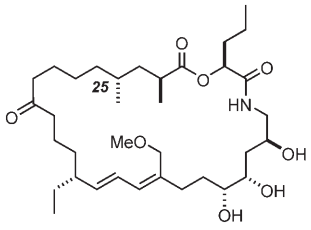
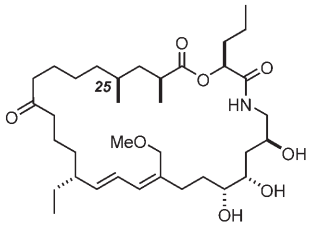


Myxovirescin A_1 (**1**)



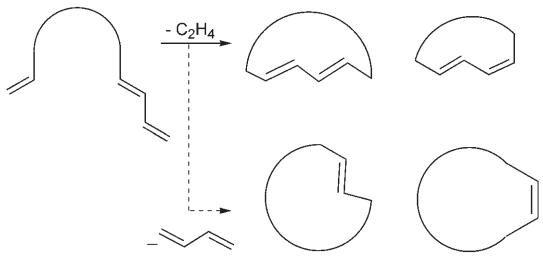
Myxovirescin A_2 (**2**)

The myxovirescins are broad spectrum antibiotics with considerable activity against Gram-negative bacteria.[3] They are believed to interfere with bacterial cell wall synthesis, most probably by inhibiting the translocation rather than the cross linking steps. Moreover, they are exceptionally adhesive to various surfaces, including dental tissue, which potentially qualifies them for the treatment of plaque and gingivitis in humans.[2–7] Preliminary investigations indicate considerable scope for structural modifications while maintaining appreciable antibacterial activity.[3,8]

In addition to the emerging mutasynthetic approaches,[7] "diverted total synthesis" represents another way for systematic structural editing once the natural leads have been conquered.[9] This latter challenge has been met by the groups of Williams and Seebach, who reported concise total syntheses of myxovirescin A_1, B and M_2.[10,11] The complex structures of these targets, however, provide ample opportunity for complementary studies, with the primary aim of cutting back on the number of steps, particularly those in the longest linear sequence.[12,13] Moreover, the published syntheses rely on chiral building blocks from nature as well as on macrolactonization or -lactamization strategies. Hence, we became interested in developing a largely reagent- and catalyst-controlled alternative route to myxovirescin A_1 (**1**) as the most potent antibiotic of this series.[14] The results of our "first-generation" approach are summarized below.

Results and Discussion

Strategic considerations: Despite the tremendous success of ring closing metathesis (RCM) for the formation of macrocyclic skeletons,[15,16] the preparation of cyclic 1,3-dienes remains a difficult task. Conjugated dienes can react with the standard metathesis catalysts either at the terminal or the internal double bond, thereby leading to mixtures that are difficult to separate and hence of limited synthetic utility (Scheme 1).[17,18] Moreover, as the stereochemical outcome of RCM-based macrocyclizations cannot yet be rigorously

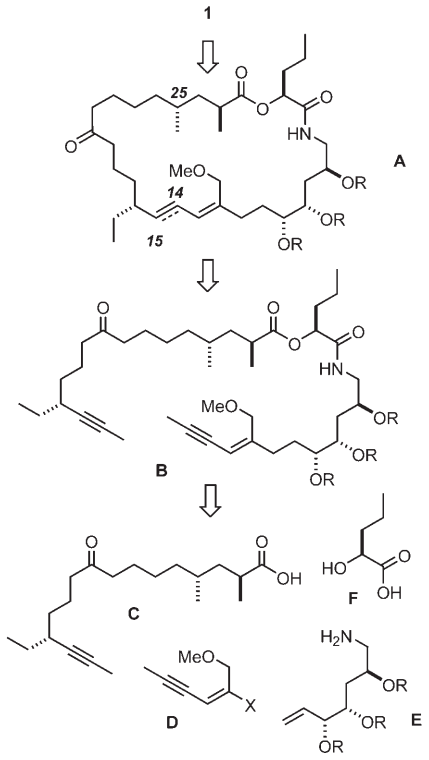


Scheme 1. Possible product spectrum arising from RCM reactions of diene–ene substrates.

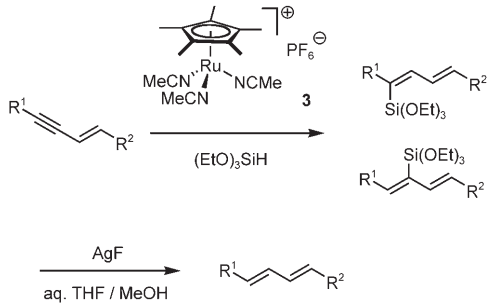
predetermined, the number of possible isomers may increase even further. Finally, one has to keep in mind that polar substituents in the substrate that are able to chelate the incipient metal carbene intermediates can strongly impact the effectiveness of RCM-based macrocyclizations.[19,20] Because these issues, collectively, discourage an RCM approach to **1**,[8] we envisaged the formation of its 28-membered ring at C-14/C-15 by an a priori less ambiguous ring closing alkyne metathesis (RCAM) reaction.[21,22]

However, this strategic decision also bore considerable risk. The metathesis of alkynes in general is much less explored, although a rapidly growing number of applications in the total synthesis arena[23–25] highlight the favorable application profile of the available catalysts.[26–28] Yet, successful cases of RCAM reactions of conjugated enynes, as required in the present context, remain extremely scarce.[29] This may be due to the fact that the catalyst must be able to rigorously distinguish between their conjugated double and triple bonds. Moreover, the catalytically competent high valent metal alkylidyne species are inherently Lewis acidic and hence responsive to donor sites within a given substrate. Therefore, it was by no means clear at the outset of this project if an enyne flanked by a methyl ether, as present in the cyclization precursor **B**, would be amenable to productive enyne–yne metathesis by any of the available systems (Scheme 2).[26–28]

Provided that this challenge could be met, the subsequent reduction of the produced cyclic enyne **A** to an (*E*,*Z*)-configured 1,3-diene also constitutes a non-trivial task. Although ruthenium catalyzed *trans*-hydrosilylation of the alkyne followed by proto-desilylation of the resulting vinylsilane may be viable (Scheme 3),[30,31] previous studies indicate that 1,3-enynes are at the edge of this emerging methodology, requiring not only fairly high catalyst loadings but also the reactions to be performed in neat silane in order to be effective.[31a] None of the few examples reported in the literature is anywhere close in complexity to the projected case. Therefore a model study was undertaken to assess the risk of this strategy prior to launching the actual total synthesis campaign.



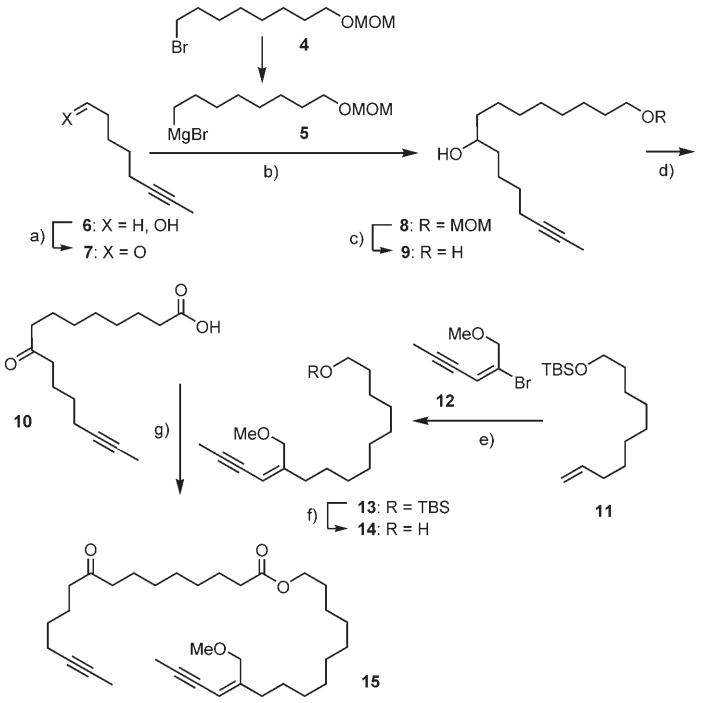
Scheme 2. Retrosynthetic analysis of **1** based on ring closing alkyne metathesis (RCAM) as the key transformation.



Scheme 3. Strategy for the conversion of enynes into 1,3-dienes by a ruthenium catalyzed *trans*-hydrosilylation and subsequent proto-desilylation.

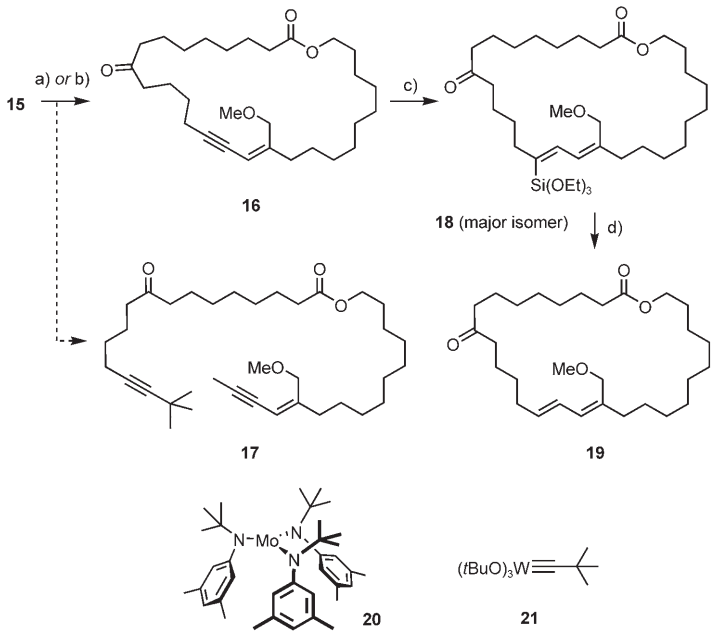
Model studies: The chosen model **15** was prepared as shown in Scheme 4. To this end, commercial 8-bromooctanol was MOM-protected and the resulting product **4** transformed into the corresponding Grignard reagent **5**. Addition of **5** to aldehyde **7**, cleavage of the MOM-acetal in **8**, and oxidation of the resulting diol **9** gave keto-acid **10** in good overall yield.

This compound was esterified with alcohol **14**, which was accessible by an alkyl-Suzuki reaction[32] of bromide **12** (see below) with the organoborane derived from **11** and 9-H-9-BBN. Although this transformation required optimization, it could be effected in high yield with catalytic amounts of [(dppf)$PdCl_2$] in the presence of Ph_3As and Cs_2CO_3. Gratifyingly, the molybdenum-based alkyne metathesis catalyst



Scheme 4. a) PDC, CH_2Cl_2, 59%; b) Mg, THF, reflux, then aldehyde **7**, RT, 73%; c) conc. HCl, MeOH, quant.; d) i) Dess-Martin periodinane, CH_2Cl_2; ii) $NaClO_2$, H_2NSO_3H, THF/H_2O (1:1), 78% (over both steps); e) 9-H-9-BBN, THF, 0 °C → RT; then bromide **12**, Cs_2CO_3, [(dppf)$PdCl_2$] (7 mol%), Ph_3As (15 mol%), aq. DMF, 90%; f) TBAF, THF, 90%; g) EDC, DMAP, CH_2Cl_2, 90%.

generated in situ from complex **20** and CH_2Cl_2 as previously described by our group,[27] smoothly converted compound **15** into the desired cyclic enyne **16** (Scheme 5). From this result



Scheme 5. a) Complex **20** (10 mol%), toluene, CH_2Cl_2, 80 °C, 80%; b) complex **21** (50 mol%), toluene, 80 °C, 40% (**16**) + 24% (**17**); c) $(EtO)_3SiH$, complex **3** (30 mol%); d) AgF, aq. THF/MeOH, 50% (over both steps).

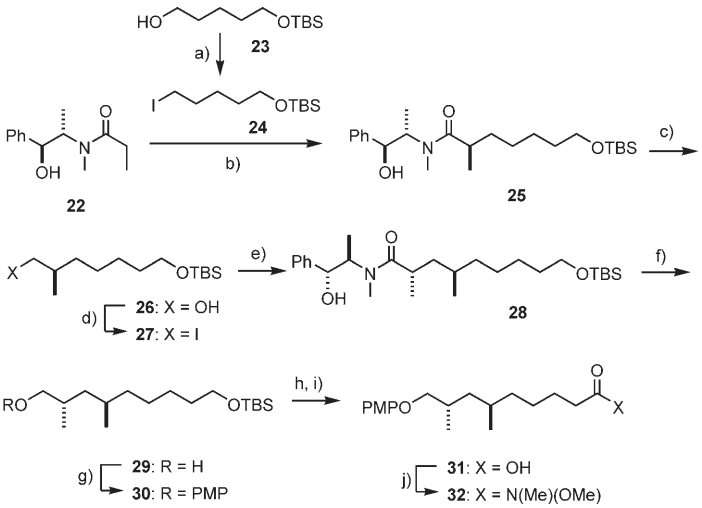
it must be concluded that the ether flanking the reacting alkyne does not interfere with productive RCAM, thus further attesting to the remarkable functional group tolerance of the chosen catalyst system.[27] For comparison, the now commercially available Schrock alkylidyne complex $[(t\text{BuO})_3\text{W}{\equiv}\text{CCMe}_3]$ (**21**)[26] has also been tested, yet found to be significantly less productive. In this case, substantial amounts of the alkyne cross metathesis product **17** were also formed, indicating that the reaction likely initiates at the alkyne- rather than the enyne site of the substrate.

The subsequent *trans*-hydrosilylation of **16** in neat $(\text{EtO})_3\text{SiH}$ required a fairly high loading of $[\text{Cp*Ru}(\text{MeCN})_3]\text{PF}_6$ (**3**, 30 mol%)[33] as precatalyst of choice. The resulting mixture of regioisomeric vinylsilanes was proto-desilylated with the aid of AgF in aqueous THF/MeOH as previously described,[31] affording the (*E*,*Z*)-configured diene **19** in 50% unoptimized yield over both steps.

Preparation of the building blocks—The Western fragment: Encouraged by this model study, the development of efficient fragment syntheses became the next immediate goal. Access to the required acid segment was based on an iterative use of the excellent asymmetric alkylation methodology developed by Myers and co-workers (Scheme 6).[34] Specifically, reaction of the pseudo-ephedrine derived propionamide **22** with iodide **24** mediated by LDA in the presence of LiCl afforded **25** in high yield and diastereoselectivity (de >99%) on a multigram scale. This product was converted into iodide **27**, which then served as electrophilic component in the next alkylation step with *ent*-**22**. The outcome of this reaction was equally rewarding, since the diastereomeric purity of the resulting product **28** was again close to the limits of detection (99% de). Routine oxidation state- and protecting group management readily afforded acid **31**, which was converted into the corresponding Weinreb amide[35] **32** under standard conditions.

The second fragment was equally well accessible upon alkylation of butyramide **33** with iodide **35** (Scheme 7). Subsequent conversion into aldehyde **38** followed by an alkylative Corey–Fuchs reaction[36] smoothly installed the end-capped alkyne **40**. Cleavage of the residual silyl ether and transformation of the resulting alcohol **41** into bromide **42** was straightforward. Addition of the Grignard reagent **43** to Weinreb amide **32** delivered ketone **44**,[37] which was readily elaborated into the western domain of myxovirescin A_1 by cleavage of the terminal *p*-methoxyphenyl ether[38] followed by oxidation of the released alcohol **45** to the corresponding carboxylic acid **46**.

Preparation of the enyne linchpin: A very satisfactory route to the required alkenyl bromide **12** was gleaned by an essentially quantitative and exquisitely *trans*-selective dibromination of commercial methyl propargyl ether **47** with pyridinium perbromide.[39] However, it is essential to perform the reaction in the dark, as exposure of the produced dibromide **48** to daylight induces isomerization to the thermodynamically more stable (*Z*)-isomer. Careful analysis and comparison of the NMR spectra of these isomers allowed for an unambiguous assignment of their double bond configuration.

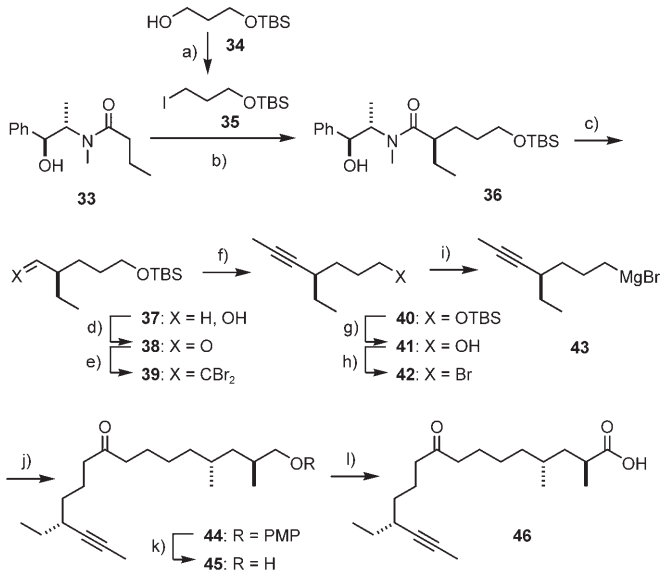


Scheme 6. a) I_2, PPh_3, imidazole, CH_2Cl_2, 97%; b) LDA, LiCl, THF, 0°C, 85% (> 99% de); c) LDA, then $BH_3{\cdot}NH_3$, THF, 0°C → RT, 81%; d) I_2, PPh_3, imidazole, CH_2Cl_2, 99%; e) *ent*-**22**, LDA, LiCl, THF, 0°C, 70% (99% de); f) LDA, then $BH_3{\cdot}NH_3$, THF, 0°C → RT, 86%; g) *p*-methoxyphenol, PPh_3, DEAD, THF, 80°C; h) TBAF, THF, 90% (over both steps); i) PDC, DMF, 74%; j) carbonyldiimidazole (CDI), Et_3N, NH(OMe)(Me)·HCl, CH_2Cl_2, 0°C, 87%.

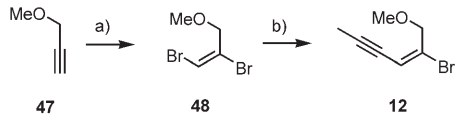
In the presence of catalytic amounts of $[\text{Pd}(\text{PPh}_3)_4]$, **48** reacted with propynylzinc chloride regioselectively at its sterically less hindered site to give enyne **12** (Scheme 8), conserving the internal bromine function. The excellent reproducibility and scalability of this Negishi coupling[40,41] were prerequisites for the success of the total synthesis campaign.

Preparation of the triol subunit: While the approaches to the polar segment of **1** pursued in the previous total syntheses relied on chiral building blocks derived from nature (D-ribose, D-mannose),[10,11] we developed a largely reagent- and catalyst-controlled entry. Advantage was taken from the practicality of a slightly modified Noyori hydrogenation for the production of large quantities of **50** (> 50 g per run) with high optical purity (96% *ee*).[42] Substitution of the chloride by azide and protection of the secondary alcohol in **51** (Scheme 9) as MOM-acetal using MOM-Br generated in situ[43] were also high yielding. The resulting ester **52** was then reduced to the corresponding aldehyde **53** with the aid of DIBAl-H in CH_2Cl_2 at −78°C; it is noteworthy that the azide group remains intact under these conditions. Although **53** is somewhat sensitive, it can be stored in pure form at −20°C under Argon for several weeks without noticeable decomposition.

An *anti*-selective oxyallylation was envisaged to open access to compound **61** featuring the correct oxygenation pattern and a terminal double bond. The latter provides a convenient handle for subsequent fragment coupling via an alkyl-Suzuki reaction[11,32] with bromide **12**. Of the different oxyallylation methods known in the literature,[44] the protocol pioneered by Brown was deemed most convenient.[45,46]



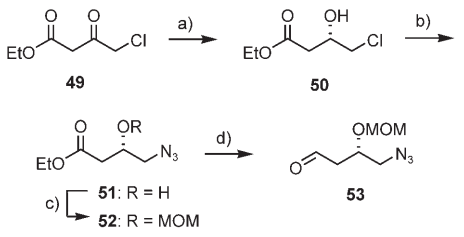
Scheme 7. a) I_2, PPh_3, imidazole, CH_2Cl_2, 96%; b) LDA, LiCl, THF, 0°C, 85% (> 97% de); c) LDA, then $BH_3{\cdot}NH_3$, THF, 0°C → RT, 88%; d) TMAP (5 mol%), NMO·H_2O, MS 4 Å, CH_2Cl_2, 86%; e) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 0°C, then **38**, −78°C; f) *n*BuLi, MeI, THF, −78°C→ −16°C, 98%; g) TBAF, THF, 95%; h) CBr_4, PPh_3, CH_2Cl_2, 77%; i) Mg, 1,2-dibromoethane cat., THF, 40°C; j) amide **32**, THF, 0°C, 77%; k) CAN, MeCN/H_2O, 0°C, 81%; l) i) 4-methoxy-TEMPO, KBr, NaOCl, $NaHCO_3$, H_2O/CH_2Cl_2, 0°C; ii) $NaClO_2$, *t*BuOH, 2-methylbutene, NaH_2PO_4, H_2O/CH_2Cl_2, 90% (> 99% de).



Scheme 8. a) Pyridine·HBr_3, CH_2Cl_2, quant.; b) 1-propynylmagnesium bromide, $ZnCl_2$, [$Pd(PPh_3)_4$] (5 mol%), THF/Et_2O, 0°C, 62%.

Thus, addition of the substituted allylborane **57**, generated from allenylboronate **56** and "Ipc_2BH", should deliver the correct stereoisomer upon oxidative work up (Scheme 10).

Despite considerable experience with the use of chiral allylboron reagents,[47] we encountered significant difficulties with this particular transformation. Although the diastereoselectivities observed in our preliminary assays were consistently high, the isolated yields were variable and mostly unsatisfactory; even more seriously, these problems increased further upon attempted up-scaling. During these initial trials, however, it was noticed that significant amounts of alcohol **62** were produced as a by-product, indicating that a reducing species must be present in the mixture that competes with allylborane **57** for the aldehyde substrate.[48] Suspecting that this competing nucleophile might either be unreacted "Ipc_2BH" or a borane derived thereof, we took a closer look at this classical and seemingly well established reagent.



Scheme 9. a) [((*R*)-binap)$RuCl_2$] (0.03 mol%); H_2 (100 bar), EtOH/acetone (1:1), 100°C, 96% (96% *ee*); b) NaN_3, DMF, 100°C, 77%; c) *p*TsOH·H_2O, LiBr, dimethoxymethane, 70%; d) DIBAl-H, CH_2Cl_2, −78°C, 89%.

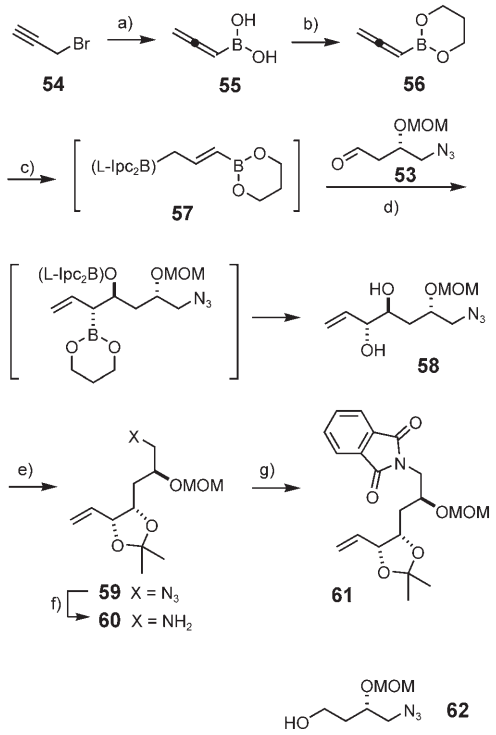
In fact, "Ipc_2BH" in THF solution consists of an equilibrating mixture of several boron-containing components (see below). Because of this complex composition, a careful empirical optimization of the conditions and the stoichiometry of the hydroboration reaction converting **56** into the required allylborane **57** was carried out. Only after this exercise (cf. Experimental Section) could the required oxyallylation product **58** be obtained in well reproducible 88% isolated yield and diastereomeric purities in excess of 92% de, whereas the amount of alcohol **62** was consistently lower than 10% in all runs. Conversion of the diol unit of **58** into the corresponding isopropylidene acetal **59**, reduction of the azide and protection of the resulting amine **60** as phthalimide **61** completed the preparation of the polar building block **E** in suitably protected form.

Interlude on "di(isopinocampheyl)borane": Di(isopinocampheyl)borane is a highly useful reagent for the preparation of a large variety of chiral products.[49] It is common practice in the literature to refer to it as the simple mononuclear boron derivative "Ipc_2BH", even though in the initial reports it was suggested that it probably exists as a dimer, *sym*-tetra(isopinocampheyl)diborane **63** (Scheme 11).[50]

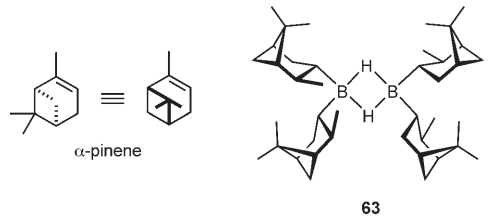
Surprisingly many optimized procedures for its preparation have been reported over the years.[50,51] A common feature is that in the hydroboration step an excess α-pinene is used, which does not have to be optically pure but becomes enriched upon incorporation into "Ipc_2BH" (thus, (+)-α-pinene of only 84% *ee* delivers (−)-"Ipc_2BH" of >98% *ee*).[51] At the same time, the excess of the olefin is thought to minimize the dissociation of *sym*-tetra(isopinocampheyl)-diborane (**63**) into tri(isopinocampheyl)diborane (**64**) and α-pinene (Scheme 12).

Despite this knowledge, numerous synthetic procedures described in the literature using "Ipc_2BH" completely disregard the possibility of serious interference from a deborylation reaction. Because we suspected that this could be responsible for the reduction of **53** to **62** and the other difficulties encountered in the preparation and use of the functionalized allylborane **57**, it was decided to have a closer look into the actual composition of this classical reagent.

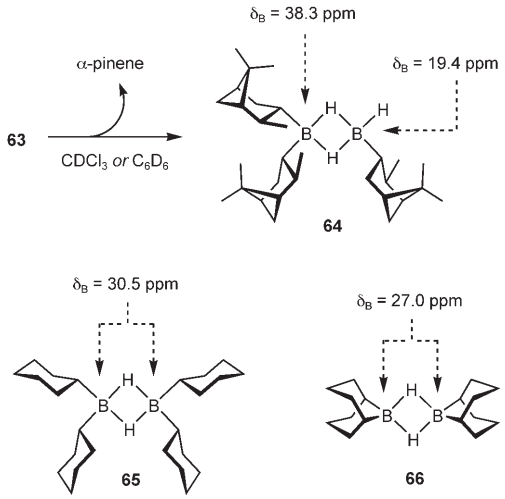
In line with the suggestions made in the early literature,[50] hydroboration of excess α-pinene with $BH_3{\cdot}SMe_2$ in THF generates a mixture of compounds, from which only one component crystallizes upon standing. This crystalline fraction consists of pure *sym*-tetra(isopinocampheyl)diborane



Scheme 10. a) i) Mg, cat. $HgCl_2$, Et_2O, reflux; ii) $B(OMe)_3$, −78 °C → 0 °C, then aq. HCl; b) 1,3-propanediol, 41 % (over three steps); c) crystalline $[(L\text{-}Ipc)_2BH]_2$ (**63**), Et_2O, 0 °C; d) i) aldehyde **53**, −78 °C; ii) MeOH, aq. H_2O_2 (30 % *w*/*w*), aq. NaOH (3 M), 0 °C → RT, 88 % (**58**); e) 2,2-dimethoxypropane, *p*TsOH·H_2O, 90 %; f) $LiAlH_4$, Et_2O, 0 °C → RT, 91 %; g) phthalic anhydride, toluene, MS 4 Å, 80 °C, 88 %.



Scheme 11. Dimeric constitution of "di(isopinocampheyl)borane" in the solid state.



Scheme 12. Deborylation upon dissolution of crystalline $[Ipc_2BH]_2$ (**63**), as evident by comparison of the ^{11}B NMR data with those of authentic tetraorganodiborane derivatives.

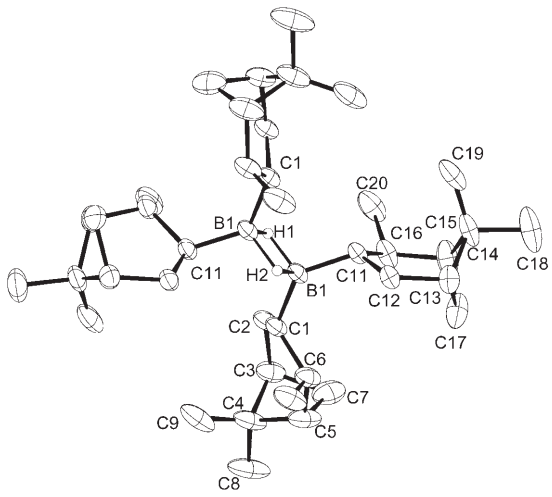


Figure 1. Molecular structure of **63** in the solid state. The molecule is situated on a crystallographic 2-fold axis. Anisotropic displacement parameter ellipsoids are shown at 50 % probability, hydrogen atoms except for the B-H-B bridge have been omitted for clarity. Disordered solvent is not shown.

(**63**) as unequivocally proven by single crystal X-ray diffraction (Figure 1). To exclude the unlikely scenario that the chosen crystal may not be representative for the bulk of the material, powdered samples were analyzed by FT-IR in attenuated total reflectance (ATR) mode, which showed only the band characteristic for bridging B-H-B entities ($\tilde{\nu}$ = 1517 cm^{-1}). When recorded in hexane solution, however, the IR spectrum is strikingly different, clearly featuring an additional band for a terminal B–H bond ($\tilde{\nu}$ = 2494 cm^{-1}).

Therefore, samples of analytically pure, crystalline **63** were dissolved in various solvents and inspected by ^{11}B NMR. To our surprise, the spectra recorded in $CDCl_3$ were totally inconsistent with the presence of any appreciable amount of **63** (for which a boron resonance in the 25–30 ppm range is expected), or any monomeric "Ipc_2BH" derived thereof. Rather, two major resonances at δ_B = 19.4 ppm and δ_B = 38.3 ppm were observed. These chemical shifts together with the recorded integral (≈1:1) are highly indicative of a triorganodiborane,[52] and are hence ascribed to tri(isopinocampheyl)diborane **64**, which obviously constitutes the only (or at least predominant) boron-containing species in the equilibrated solution. Hence, dimeric di(isopinocampheyl)borane (**63**) must have undergone an essentially *quantitative* mono-deborylation in $CDCl_3$ (Scheme 12). The clearly discernable olefinic proton in the corresponding ^1H NMR spectrum (δ_H = 5.20 ppm) corroborates this view. Exactly the same observations were made when C_6D_6 (δ_B = 18.7, 38.3; ≈1:1) rather than $CDCl_3$ was chosen as the solvent.

Despite the good literature precedence for the assignments of the observed ^{11}B shifts,[52] further independent confirmation was sought. To this end, we prepared tetracyclohexyldiborane (**65**),[53] confirmed its dimeric nature by X-ray crystallography (Figure 2), and recorded the corresponding ^{11}B NMR spectrum in $CDCl_3$ for comparison. **65**, which is not prone to undergo deborylation, shows the characteristic chemical shift of a tetraorganodiborane in $CDCl_3$ solution ($\delta_B = 30.5$ ppm), as does the well known 9-H-9-BBN dimer **66** ($\delta_B = 27.0$ ppm).

These results support the notion that tetraorganodiboranes and triorganodiboranes are easily distinguished by ^{11}B NMR spectroscopy. Therefore we must conclude that an equilibrated solution of "di(isopinocampheyl)borane" in $CDCl_3$ or C_6D_6 contains neither **63** nor the elusive "Ipc_2BH" frequently invoked in the literature, but rather consists of a 1:1 mixture of Ipc_2BH and $IpcBH_2$ associated in form of the hetero-dimer **64**. Even more complex is the composition of this reagent in ethereal solvents. While the dissolution of **63** in Et_2O is rather slow and the composition therefore variable with time,[54] clear solutions of analytically pure, recrystallized **63** in THF show four discernable peaks of similar intensity in ^{11}B NMR ($\delta_B = 12.4$, 20.3, 40.0, 43.3 ppm); while two of them again appear to correspond to **64**, the constitution of the other boron containing component(s) in this mixture cannot be assigned with certainty at this point.

In summary, this study shows that the famous "di(isopinocampheyl)borane" is dimeric in the solid state, but a complex reagent in solution as virtually quantitative deborylation and/or equilibration phenomena occur upon standing. Its successful use as a chiral reagent for hydroboration, as exemplified by the preparation of the functionalized allylborane **57** described above, therefore hinges critically upon the chosen stoichiometry, solvent, concentration, temperature, order and time of addition, and presence or absence of any additives able to coordinate to boron etc. We recommend that, when this reagent is used, the utmost attention is paid to an empirical optimization of these and other relevant parameters to ensure an appropriate degree of reproducibility. In certain cases, it may be beneficial to add excess pinene to a reaction mixture as this will retard or (partly) suppress the formation of **64** and hence have a positive effect on the chemical and/or optical yield as well as the robustness of the method. A good example for this is the optimized procedure for the preparation of the valuable reagent Ipc_2BOMe derived from **63** by methanolysis.[55]

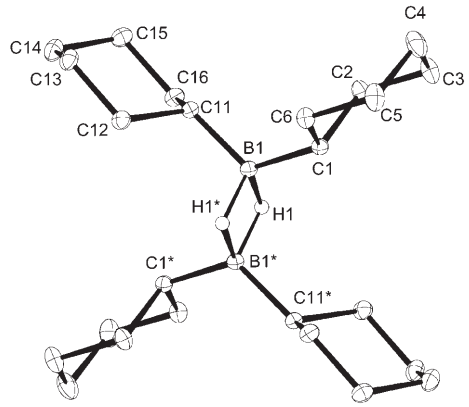
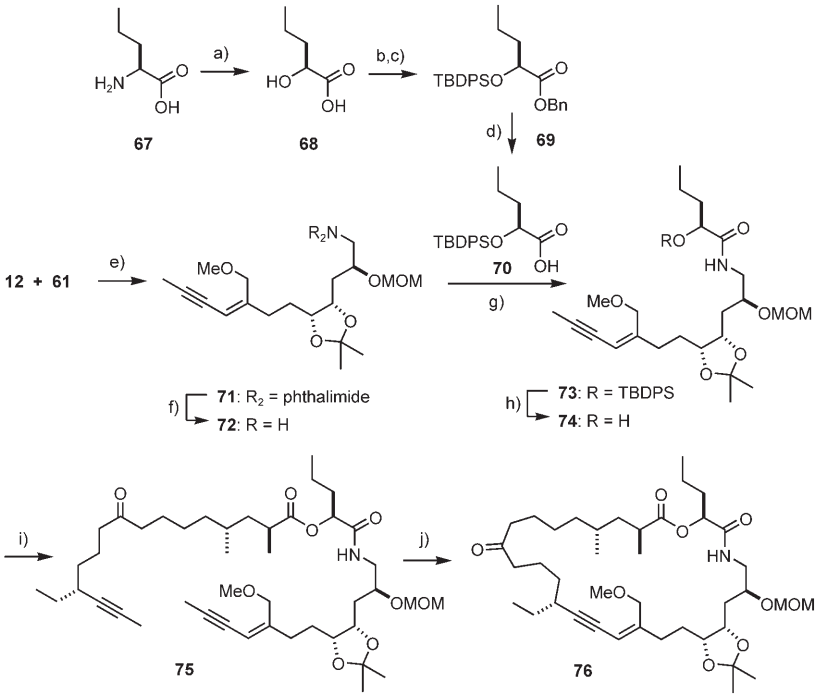


Figure 2. Molecular structure of **65** as found in the crystal. The molecule is situated on a crystallographic inversion centre. Anisotropic displacement parameter ellipsoids are shown at 50% probability, hydrogen atoms except for the B-H-B bridge have been omitted for clarity.

Fragment coupling and ring closing alkyne metathesis: With the access to the required building blocks now secured, the stage was set for the coupling of these fragments (Scheme 13). To this end, alkene **61** was reacted with 9-H-9-BBN dimer to give the corresponding alkylborane, which



Scheme 13. a) $NaNO_2$, H_2SO_4, H_2O, 0°C → RT, 80%; b) BnBr, $(nBu)_4NI$, K_2CO_3, acetone, 40°C, 69%; c) TBDPSCl, imidazole, CH_2Cl_2, 98%; d) Pd/C (10% *w*/*w*), EtOAc/EtOH (1:1), 63%; e) **61**, 9-H-9-BBN, THF, 0°C, then **12**, Cs_2CO_3, [(dppf)$PdCl_2$] (7 mol%), Ph_3As (15 mol%), aq. THF, 81%; f) H_2N-NH_2·H_2O, EtOH, 60°C; g) acid **70**, 1-HOBt, EDC·HCl, $(iPr)_2NEt$, CH_2Cl_2, 77% (over both steps); h) TBAF, THF, 90%; i) acid **46**, EDC·HCl, 1-HOBt, Et_3N, DMAP, 65–75%; j) Complex **20** (40–50 mol% in 3 portions), toluene, CH_2Cl_2, 80°C, 79%.

underwent a high yielding cross coupling reaction with alkenyl bromide **12** under the conditions successfully employed in the model study. In practical terms, it was advantageous that the by-products derived from the minor diastereomer formed in the oxyallylation step could be conveniently removed at this stage. Hydrazinolysis of the phthalimide in **71** and condensation of the resulting crude amine **72** with the TBDPS-protected 2-hydroxypentanoic acid **70**, which is readily available from L-norvaline **67** as shown in Scheme 13,[56] afforded amide **73** without incident.[57] The structure of acid **70** in the solid state is depicted in Figure 3.

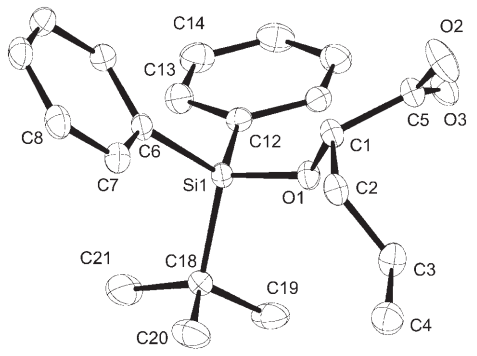


Figure 3. Molecular structure of **70** in the solid state. The proton of the carboxylic acid is disordered over atom positions O2 and O3. In the crystal, hydrogen bonded carboxylic acid dimers are formed incorporating a crystallographic 2-fold axis. Anisotropic displacement parameter ellipsoids are shown at 50% probability, hydrogen atoms have been omitted for clarity.

While the deprotection of the TBDPS-ether in **73** with TBAF posed no problem, the esterification of the released alcohol **74** with the western domain **46** proceeded in reasonable yields of up to 75% only when effected by EDC (*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide) and HOBt (1-hydroxy-7-azabenzotriazole), while the use of DCC or recourse to the Yamaguchi protocol were largely unsuccessful.

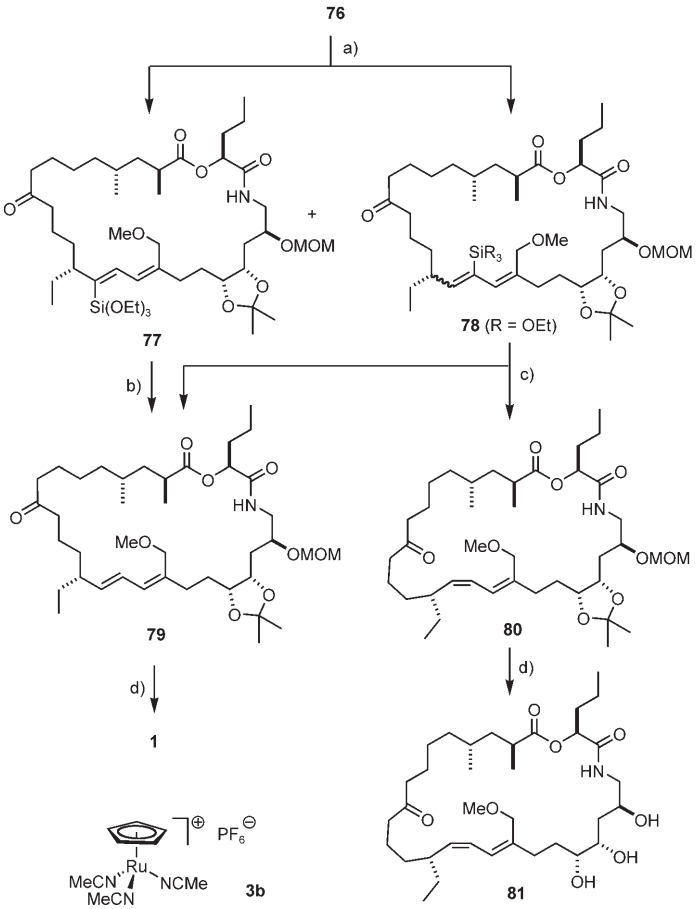
The highly functionalized enyne–yne derivative **75** could be cyclized to the corresponding 28-membered cycloalkyne **76** in well reproducible 79% yield with the aid of the molybdenum catalyst generated in situ from **20** and CH_2Cl_2 as previously described.[27] However, a fairly high catalyst loading was necessary to ensure complete conversion (40–50%, added in three portions). Whether this is due to the inherently lower intrinsic reactivity of conjugated enynes and/or the presence of a secondary amide linkage has not been addressed in detail.[58] In line with the results of the model study, however, the molybdenum based catalyst system was much more efficacious than the tungsten alkylidyne **21**,[26] which had previously been found equipotent in less demanding cases. Moreover, this particular RCAM reaction highlights again the truly remarkable capacity of the catalyst to distinguish between triple- and double bonds even if they are conjugated, which makes alkyne metathesis orthogonal to the more commonly practiced metathesis of alkenes in conceptual terms.

Semi-reduction and completion of the total synthesis: Whilst the semi-reduction of acetylenes to (*Z*)-alkenes is well established and opens a reliable entry into (*Z*)-cycloalkenes when combined with RCAM,[21–25] the stereo-complementary reduction to the corresponding (*E*)-isomers is considerably more challenging. Whereas the few classical solutions to this problem are hardly attractive, the recent discovery of Trost that $[Cp^*Ru(MeCN)_3]PF_6$ (**3**) catalyzes a *trans*-hydrosilylation of terminal as well as internal alkynes opens a potentially much more rewarding alternative. Proto-desilylation of the vinylsilanes primarily formed delivers the corresponding (*E*)-alkenes in good yields in many cases.[30]

We have previously combined this methodology with RCAM to produce (*E*)-cycloalkenes of various ring sizes with high stereochemical integrity.[31] Thereby, the use of AgF in aq. THF/MeOH turned out to be particularly effective in the proto-desilylation step. The method is applicable to conjugated enyne substrates, since the catalyzed hydrosilylation occurs selectively at the triple bond and leaves the pre-existing olefin intact (Scheme 3). However, the reactivity of enynes was found to be significantly lower than that of ordinary alkynes, a fact that can be partly compensated by conducting the hydrosilylation in neat silane and using a higher catalyst loading.[31]

Since this methodology had worked reasonably well in the model study summarized in Scheme 5, we were confident that it would equally apply to the actual total synthesis of myxovirescin A_1. Despite considerable experimentation, however, attempted hydrosilylation of the cyclic enyne **76** with $(EtO)_3SiH$ as the silane of choice and $[Cp^*Ru(MeCN)_3]PF_6$ (**3**) did not work well at all, remaining incomplete even when very high catalyst loadings were chosen, irrespective of whether the reaction was performed neat or in the presence of suitable co-solvents.

Puzzled by this unexpected failure, various other ruthenium catalysts were screened, amongst which the sterically less demanding analogue $[CpRu(MeCN)_3]PF_6$ (**3b**) performed best (Scheme 14). With its aid, **76** could be converted into three isomeric vinylsilanes that were isolated in a combined yield of 66% in two fractions (**77** and **78**). This outcome was surprising, as it implied that the course of the reaction had not been rigorously *trans*-selective; appreciable amounts of a *cis*-isomer also must have formed. In fact, subsequent proto-desilylation with AgF in aqueous THF/MeOH[31] furnished the desired (*E,Z*)-configured product **79** and the (*Z,Z*)-configured isomer **80** that were readily separable and could therefore be assigned with certainty. Deprotection of the acetal groups in **79** and **80** following the procedures established in the previous total syntheses[10,11] then afforded myxovirescin A_1 (**1**) and its hitherto unknown 14*Z*-configured analogue **81**, respectively. The spectroscopic and analytical data of the synthetic samples of **1** were in full accord with those of the natural product reported in the literature.[3,11] Although this synthetic endeavor was ultimately successful and the new route to myxovirescin A_1 is competitive in terms of the usual empirical indices (17 steps and $\approx$2% overall yield over the longest linear sequence, 46



Scheme 14. a) $(EtO)_3SiH$, toluene, $[CpRu(MeCN)_3]PF_6$ (**3b**, 30 mol%), **78** (53%) + **77** (13%); b) AgF, aq. THF/MeOH, 94% (**79**); c) AgF, aq. THF/MeOH, 25% (**79**) + 23% (**80**); d) $HClO_4$, aq. THF, MeOH, 38–52%.

steps overall),[12] it also revealed that the methodology for the formal *trans*-reduction of alkynes requires further investigation.

Conclusion

The complex macrolide antibiotic myxovirescin A_1 (**1**) served as template for the development of a convergent total synthesis that is flexible enough to accommodate systematic structural variations at a later stage. The chosen route is largely based on reagent- and catalyst-controlled transformations, of which the venerable Suzuki reaction and the more recent ring closing alkyne metathesis performed exceptionally well. Moreover, it was possible to improve the reliability of Brown's *anti*-oxyallylation methodology after studying the true nature of the classical "di(isopinocampheyl)borane (Ipc_2BH)" used for the preparation of the required allylborane reagent **57**. We believe that this investigation on "Ipc_2BH" will also positively impact many other transformations employing this classical hydroborating agent. Of the key steps employed en route to **1**, it was the late-stage ruthenium catalyzed *trans*-hydrosilylation that posed the most significant problems. Although this method did allow to covert cycloalkyne **76** produced by RCAM into the required *E*,*Z*-configured 1,3-diene, the observed selectivity and the isolated yield need further improvement. Hence, this study illustrates the notion that the total synthesis of complex target molecules remains the ultimate test for the performance, scope and limitations of any newly developed methodology.

Experimental Section

General: All reactions were carried out in flame-dried glassware under Ar. The solvents were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O, DME (Mg/anthracene), DMSO, CH_2Cl_2, MeCN, Et_3N, (CaH_2), MeOH (Mg), DMF (Desmodur, dibutyltin dilaurate), hexanes, pentanes, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded on Bruker DPX 300, AV 400, or DMX 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 ($CDCl_3$: $\delta_C \equiv 77.0$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.26$ ppm; CD_2Cl_2: $\delta_C \equiv 53.8$ ppm; residual CH_2Cl_2 in CD_2Cl_2: $\delta_H \equiv 5.32$ ppm). ^{11}B NMR chemical shifts are given relative to external $BF_3{\cdot}Et_2O$ ($\equiv 0$ ppm). Where indicated, the signal assignments are unambiguous; the numbering Scheme is arbitrary and is shown in the inserts. The assignments are based upon 1D and 2D spectra recorded using the following pulse sequences from the Bruker standard pulse program library: DEPT; COSY (cosygs and cosydqtp); HSQC (invietgssi) optimized for $^1J(C,H) = 145$ Hz; HMBC (inv4gslplrnd) for correlations via $^nJ(C,H)$; HSQC-TOCSY (invietgsml) using an MLEV17 mixing time of 120 ms. IR: Nicolet FT-7199 spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet). Melting points: Büchi melting point apparatus B-540 (corrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Fluka, Lancaster, Aldrich) were used as received.

Model studies

1-Bromo-8-methoxymethoxy-octane (4): Dimethoxymethane (30 mL) and 8-bromo-1-octanol (840 mg, 4.02 mmol) were added to a suspension of phosphorus pentoxide (3 g, 21.1 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred for 30 min before the solution was decanted and diluted with aq. sat. $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3×30 mL), the combined organic layers were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (pentanes/Et_2O 95:5) to give product **4** as a colorless oil (840 mg, 83%). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.55$ (s, 2H), 3.45 (t, $J = 6.6$ Hz, 2H), 3.34 (t, $J = 6.8$ Hz, 2H), 3.29 (s, 3H), 1.79 (m, 2H), 1.52 (m, 2H), 1.22–1.41 ppm (m, 8H); ^{13}C NMR (75 MHz): $\delta = 96.4$, 67.8, 55.1, 33.9, 32.8, 29.7, 29.2, 28.7, 28.1, 26.1 ppm; IR (KBr): $\tilde{\nu} = 2988$, 2931, 2856, 1465, 1215, 1145, 1112, 1048, 919, 645, 563 cm^{-1}; MS (EI): m/z (%): 253 [M^+] (0.7), 204 (3), 190 (3), 148 (3), 109 (6), 75 (15), 69 (14), 55 (12), 45 (100), 41 (12); HRMS (ESI+): m/z: calcd for $C_{10}H_{21}BrO_2$: 253.08033; found: 253.08002.

Oct-6-ynal (7): Oct-8-yn-1-ol (**6**, 1.22 g, 9.6 mmol) was slowly added to a suspension of pyridinium dichromate (5.44 g, 14.5 mmol) in CH_2Cl_2 (25 mL). The solution was stirred overnight before it was filtered through a pad of silica which was carefully rinsed with CH_2Cl_2. The combined filtrates were evaporated and the residue was purified by Kugelrohr distillation (100–115 °C, 1 mbar) to afford aldehyde **7** (707 mg, 59%) as a colorless oil. **7** easily oxidized in air to form the corresponding carboxylic acid and should therefore be kept in a refrigerator under inert atmosphere. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.76$ (t, $J = 1.7$ Hz, 1H), 2.43 (dt, $J = 7.3$ Hz, 1.7 Hz, 2H), 2.14 (m, 2H), 1.76 (t, $J = 2.6$ Hz, 3H), 1.72 (m,

2H), 1.50 ppm (m, 2H); ^{13}C NMR (75 MHz): δ=202.4, 78.5, 76.0, 43.4, 28.4, 21.2, 18.5, 3.4 ppm; IR (KBr): $\tilde{\nu}$=2940, 2921, 2722, 1724, 1437, 1334, 1077 cm^{-1}; MS (EI): *m/z* (%): 124 [M^+] (2), 123 (8), 109 (32), 95 (57), 91 (38), 79 (89), 67 (99), 53 (91), 41 (100), 27 (64). HRMS (ESI+): *m/z*: calcd for $C_8H_{13}O+H$: 125.09664; found: 125.09658.

16-Methoxymethoxy-hexadec-2-yn-8-ol (8): Magnesium turnings (150 mg, 6.2 mmol) were activated by stirring under reduced pressure with gentle heating; they were allowed to reach ambient temperature before being suspended in freshly distilled THF (15 mL). 1 mL of a solution of bromide **4** (647 mg, 2.56 mmol) in THF (9 mL) was added to the mixture at room temperature. Once the reaction had started, the remaining solution of **4** was added at such a rate as to maintain gentle reflux. Once the addition was complete, the mixture was refluxed for 2 h before it was cooled to room temperature. The solution of aldehyde **7** (220 mg, 1.77 mmol) in THF (7 mL) was introduced and the reaction mixture stirred overnight before being quenched with water. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL), the combined organic phases were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography to give alcohol **8** (389 mg, 73%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.54 (s, 2H), 3.52 (m, 1H), 3.44 (t, *J*=6.6 Hz, 2H), 3.29 (s, 3H), 2.06 (m, 2H), 1.70 (t, *J*=2.5 Hz, 3H), 1.15–1.55 ppm (m, 21H); ^{13}C NMR (100 MHz): δ=96.4, 79.1, 75.5, 71.8, 67.9, 55.0, 37.5, 37.0, 29.7, 29.6, 29.5, 29.3, 29.1, 26.2, 25.6, 24.9, 18.7, 3.4 ppm; IR (KBr): $\tilde{\nu}$=3435, 2929, 2856, 1463, 1214, 1146, 1112, 1044, 919 cm^{-1}; MS (EI): *m/z* (%): 304 [M^+] (0.4), 235 (2), 203 (2), 171 (20), 135 (8), 123 (16), 109 (12), 95 (24), 81 (41), 67 (36), 55 (39), 45 (100); HRMS: *m/z*: calcd for $C_{18}H_{34}O_3+Na$: 321.24056; found: 321.24062.

Hexadec-14-yne-1,9-diol (9): HCl (12 M, 100 μL) was added to a solution of compound **8** (386 mg, 1.21 mmol) in MeOH (10 mL), the resulting solution was heated under reflux for 3 h and then stirred overnight at room temperature. The reaction was quenched with aq. sat. $NaHCO_3$ (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to afford the desired diol **9** (307 mg, quant.) as a colorless oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.54 (t, *J*=6.6 Hz, 2H), 3.52 (m, 1H), 2.05 (m, 2H), 1.69 (t, *J*=2.5 Hz, 3H), 1.62 (brs, 2H), 1.16–1.53 ppm (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=79.1, 75.5, 71.8, 62.9, 37.4, 36.9, 32.7, 29.6, 28.5, 29.3, 29.0, 25.7, 25.6, 24.9, 18.7, 3.4 ppm; IR (KBr): $\tilde{\nu}$=3326, 2924, 2851, 1464, 1118, 1072, 858, 663 cm^{-1}; MS (EI): *m/z* (%): 254 [M^+] (0.1), 207 (2), 159 (23), 135 (16), 125 (32), 123 (30), 107 (32), 95 (30), 81 (98), 67 (87), 55 (100), 43 (82), 29 (21); HRMS (ESI+): *m/z*: calcd for $C_{16}H_{30}O_2+Na$: 277.21435, found: 277.21450.

9-Oxo-hexadec-14-ynoic acid (10): Dess–Martin periodinane (1.50 g, 3.54 mmol) was added to a solution of diol **9** (300 mg, 1.18 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 5 h before the reaction was quenched with aq. sat. NaOH (1 M, 3 mL). The organic phase was washed with aq. sat. $Na_2S_2O_5$ (5 mL), the aqueous layer was extracted with CH_2Cl_2 (3×5 mL), the combined organic phases were dried over Na_2SO_4 and evaporated to afford the corresponding aldehyde as a white solid, which was used in the next step without further purification. Characteristic data of this keto-aldehyde: ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.68 (t, *J*=1.9 Hz, 1H), 2.32 (m, 6H), 2.05 (m, 2H), 1.69 (t, *J*=2.5 Hz, 3H), 1.31–1.64 (m, 8H), 1.15–1.30 ppm (m, 6H); ^{13}C NMR (75 MHz): δ=211.0, 202.7, 78.7, 75.7, 43.8, 42.6, 42.2, 29.1, 29.0, 28.9, 28.5, 23.7, 23.0, 21.9, 18.5, 3.4 ppm; IR (KBr): $\tilde{\nu}$=2924, 2863, 2849, 1711, 1701, 1419, 1092, 718 cm^{-1}; MS (EI): *m/z* (%): 250 [M^+] (0.4), 235 (2), 175 (2), 155 (20), 138 (14), 123 (48), 109 (53), 95 (76), 81 (45), 67 (100), 55 (93), 41 (67).

H_2NSO_3H (140 mg, 1.44 mmol) and a solution of $NaClO_2$ (163 mg, 1.44 mmol) in H_2O (6 mL) were added to a solution of the crude aldehyde (300 mg, 1.2 mmol) in THF (6 mL), causing an immediate color change to yellow. After stirring for 1 h, the mixture was diluted with *tert*-butyl methyl ether (10 mL) and water, the aqueous layer was extracted with *tert*-butyl methyl ether, the combined organic phases were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 2:1) to give acid **10** (249 mg, 78% over both steps) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.32 (m, 4H), 2.27 (t, *J*=7.5 Hz, 2H), 2.05 (m, 2H), 1.69 (t, *J*=2.5 Hz, 3H), 1.15–1.64 ppm (m, 14H); ^{13}C NMR (100 MHz): δ=211.2, 179.7, 78.7, 75.7, 42.7, 42.2, 33.9, 29.0 (2 C), 28.8, 28.5, 24.5, 23.7, 23.0, 18.5, 3.4 ppm; IR (KBr): $\tilde{\nu}$=2934, 2924, 2908, 2862, 2849, 1701, 1419, 1305, 738 cm^{-1}; MS (EI): *m/z* (%): 266 [M^+] (1), 248 (6), 186 (12), 171 (50), 138 (55), 123 (70), 110 (20), 95 (81), 81 (41), 67 (58), 55 (100), 41 (48); HRMS (ESI+): *m/z*: calcd for $C_{16}H_{26}O_3+Na$: 289.17796; found: 289.17804; elemental analysis calcd (%) for $C_{16}H_{26}O_3$: C 72.14, H 9.84, found C 72.12, H 9.84.

(11*Z*)-11-Methoxymethylpentadec-11-en-13-ynyl-1-oxy(*tert*-butyl-dimethyl)-silane (13): 9-H-9-BBN (45 mg, 0.37 mmol) was added to a solution of alkene **11** (38 mg, 0.20 mmol) in THF (3 mL) at 0°C. The mixture was allowed to warm to ambient temperature and was stirred overnight. In a second Schlenk flask, vinyl bromide **12** (38 mg, 0.2 mmol), cesium carbonate (123 mg, 0.38 mmol), Ph_3As (9 mg, 0.03 mmol) and [$PdCl_2$-(dppf)·CH_2Cl_2] (12 mg, 0.015 mmol) were dissolved in DMF (3 mL). Before the solution of the alkylborane was transferred to this flask, water (100 μL) was added to quench excess 9-BBN. The resulting solution was stirred for 30 min before it was quenched with sat. aq. NH_4Cl (5 mL). A standard extractive work up followed by flash chromatography afforded the desired product **13** (69 mg, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.41 (m, 1H), 4.14 (s, 2H), 3.59 (t, *J*=6.6 Hz, 2H), 3.30 (s, 3H), 2.12 (m, 2H), 1.93 (d, *J*=2.3 Hz, 3H), 1.22–1.52 (m, 16H), 0.89 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.9, 108.1, 89.4, 76.3, 71.3, 63.3, 57.8, 33.5, 32.9, 29.6, 29.5, 29.43, 29.40, 29.3, 27.6, 26.0 (3C), 25.8, 18.3, 4.3, −5.3 ppm (2C); IR (KBr): $\tilde{\nu}$=2928, 2855, 2221, 1630, 1471, 1463, 1255, 1098, 836, 755, 662 cm^{-1}; MS (EI): *m/z* (%): 380 [M^+] (3), 365 (3), 350 (1), 323 (38), 308 (53), 217 (21), 161 (20), 147 (22), 109 (52), 93 (100), 75 (82), 55 (35), 41 (23); HRMS (ESI+): *m/z*: calcd for $C_{23}H_{44}O_2Si$: 380.31106, found: 380.31066.

(11*Z*)-11-Methoxymethyl-pentadec-11-en-13-yn-1-ol (14): TBAF (1 M in THF, 160 μL, 0.16 mmol) was added to a solution of compound **13** (60 mg, 0.16 mmol) in THF (2 mL). After stirring for 1 h, the reaction was quenched with aq. sat. $NaHCO_3$ (5 mL), the aqueous layer was extracted with *tert*-butyl methyl ether, the combined organic phases were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc 2:1) to give alcohol **14** (38 mg, 90%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.41 (m, 1H), 4.15 (s, 2H), 3.63 (t, *J*=6.6 Hz, 2H), 3.30 (s, 3H), 2.12 (m, 2H), 1.97 (d, *J*=2.3 Hz, 3H), 1.56 (m, 2H), 1.22–1.48 ppm (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=149.9, 108.1, 89.5, 76.3, 71.3, 63.1, 57.8, 33.5, 32.8, 29.5, 29.5, 29.4 (2C), 29.3, 27.6, 25.7, 4.4 ppm; IR (KBr): $\tilde{\nu}$=3372, 2926, 2854, 2220, 1628, 1465, 1375, 1087, 722 cm^{-1}; MS (EI): *m/z* (%): 266 [M^+] (8), 251 (5), 165 (2), 151 (5), 123 (18), 109 (100), 91 (10), 77 (7), 55 (6), 45 (7); HRMS (ESI+): *m/z*: calcd for $C_{17}H_{28}O_2$: 266.22458; found: 266.22423.

(11*Z*)-11-Methoxymethyl-pentadec-11-en-13-ynyl-9-oxo-hexadec-14-ynoate (15): Carboxylic acid **10** (72 mg, 0.27 mmol) was added to a solution of alcohol **14** (65 mg, 0.24 mmol), EDC (94 mg, 0.49 mmol) and DMAP (59 mg, 0.49 mmol) in CH_2Cl_2 (15 mL). The resulting mixture was stirred for 6 h before the reaction was quenched with aq. HCl (1 M). A standard extractive work up followed by flash chromatography (hexanes/EtOAc 4:1) afforded product **15** (117 mg, 90%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.40 (m, 1H), 4.13 (s, 2H), 4.03 (t, *J*=6.7 Hz, 2H), 3.28 (s, 3H), 2.37 (m, 4H), 2.26 (t, *J*=7.5 Hz, 2H), 2.11 (m, 4H), 1.95 (d, *J*=2.3 Hz, 3H), 1.75 (t, *J*=2.6 Hz, 3H), 1.17–1.72 ppm (m, 30H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=211.0, 173.8, 149.9, 108.1, 89.4, 78.7, 76.3, 75.7, 71.3, 64.4, 57.8, 42.7, 42.2, 34.3, 33.5, 29.4 (2C), 29.3, 29.2, 29.1, 29.0 (2C), 28.9, 28.6, 28.5, 27.6, 25.9, 24.9, 23.7, 23.0, 18.5, 4.3, 3.4 ppm; IR (KBr): $\tilde{\nu}$=2920, 2850, 2215, 1726, 1726, 1703, 1377, 1176, 1107, 719 cm^{-1}; MS (EI): *m/z* (%): 514 [M^+] (30), 499 (20), 482 (10), 402 (4), 249 (5), 133 (17), 123 (4), 109 (100), 105 (17), 81 (30), 55 (34), 43 (15); HRMS (ESI+): *m/z*: calcd for $C_{33}H_{54}O_4$: 514.40221; found: 514.40245; elemental analysis calcd (%) for $C_{33}H_{54}O_4$: C 76.99, H 10.57; found: C 76.81, H 10.65.

(17*Z*)-18-Methoxymethyl-oxa-cyclooctacos-17-en-15-yne-2,10-dione (16): Complex **20** (7.5 mg, 0.016 mmol)[20],[59] and CH_2Cl_2 (120 μL, 1.87 mmol) were successively added to a solution of diyne **15** (60 mg, 0.12 mmol) in toluene (85 mL) and the resulting mixture was stirred at 80°C for 15 h. For work up, the reaction was quenched with MeOH (5 mL), all volatile

materials were evaporated and the residue was purified by flash chromatography (hexanes/EtOAc 9:1) to afford macrocycle **16** (43 mg, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.44$ (m, 1H), 4.14 (s, 2H), 4.07 (t, $J = 6.2$ Hz, 2H), 3.30 (s, 3H), 2.32–2.47 (m, 6H), 2.28 (t, $J = 7.3$ Hz, 2H), 2.15 (t, $J = 6.9$ Hz, 2H), 1.19–1.81 ppm (m, 30H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.3$, 173.9, 149.7, 108.3, 93.5, 77.8, 71.3, 64.3, 57.8, 42.4, 42.3, 34.4, 33.2, 29.1, 29.0, 28.9 (3C), 28.8, 28.7, 28.5, 28.4, 28.0, 27.0, 25.7, 24.9, 23.7, 23.2, 19.2 ppm; IR (KBr): $\tilde{\nu} = 2927$, 2855, 2213, 1734, 1714, 1175, 1107, 1089 cm^{-1}; MS (EI): m/z (%): 460 [M^+] (98), 445 (14), 428 (100), 410 (25), 259 (10), 131 (62), 91 (68), 55 (98), 41 (43); HRMS (ESI+): m/z: calcd for $C_{29}H_{48}O_4$: 483.34503; found: 483.34506.

Compound 17: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.41$ (m, 1H), 4.15 (s, 2H), 4.05 (t, $J = 6.7$ Hz, 2H), 3.30 (s, 3H), 2.39 (m, 4H), 2.28 (t, $J = 7.5$ Hz, 2H), 2.13 (m, 4H), 1.97 (d, $J = 2.3$ Hz, 3H), 1.22–1.72 (m, 30H), 1.19 ppm (s, 9H); MS (EI): m/z (%): 556 [M^+] (54), 541 (16), 509 (17), 499 (30), 467 (19), 291 (11), 233 (7), 151 (24), 137 (29), 123 (32), 109 (100), 55 (46), 43 (25), 41 (20), 29 (6).

(15*E*,17*Z*)-18-Methoxymethyl-oxa-cyclooctacosa-15,17-diene-2,10-dione (18): A mixture of enyne **16** (27 mg, 0.059 mmol), $(EtO)_3SiH$ (50 μL, 0.36 mmol) and complex **3** (9 mg, 0.018 mmol) was vigorously stirred for 5 h before it was filtered through a short pad of silica which was carefully rinsed with Et_2O. The combined filtrates were evaporated and the residue was dissolved in THF (3 mL), MeOH (0.5 mL) and water (25 μL). AgF (10.3 mg, 0.081 mmol) was added and the resulting mixture was stirred in the dark for 5 h. Insoluble residues were filtered off through a plug of silica which was carefully rinsed with Et_2O, the combined filtrates were evaporated and the residue purified by flash chromatography (hexanes/Et_2O 10:1) to give the title compound as a colorless oil (13 mg, 50% over both steps). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.34$ (dd, $J = 11.0$, 14.9 Hz, 1H), 5.97 (d, $J = 11.0$ Hz, 1H), 5.62 (dt, $J = 7.1$, 14.9 Hz, 1H), 4.07 (t, $J = 6.4$ Hz, 2H), 4.01 (s, 2H), 3.29 (s, 3H), 2.38 (m, 4H), 2.29 (t, $J = 7.3$ Hz, 2H), 2.12 (m, 4H), 1.20–1.66 ppm (m, 30H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.5$, 173.9, 136.0, 134.2, 129.0, 126.2, 69.8, 64.4, 57.8, 42.7, 42.5, 35.0, 34.4, 32.4, 29.2, 29.1, 29.0, 28.9 (2C), 28.83 (2C), 28.75, 28.6, 28.5, 27.4, 25.8, 24.8, 23.7, 23.3 ppm; IR (KBr): $\tilde{\nu} = 3027$, 2928, 2855, 1734, 1713, 1655, 1617, 1187, 969 cm^{-1}; MS (EI): m/z (%): 463 (3), 462 [M^+] (8), 431 (32), 430 (100), 412 (7), 262 (3), 171 (7), 120 (30), 105 (21), 81 (18), 55 (31), 41 (14); HRMS (ESI+): m/z: calcd for $C_{29}H_{50}O_4$+Na: 485.36068; found: 485.36098.

Western segment

***tert*-Butyl((5-iodopentyl)oxy)dimethylsilane (24)**: Imidazole (3.30 g, 49 mmol) and I_2 (11.1 g, 43.7 mmol) were successively added to a vigorously stirred solution of PPh_3 (10.2 g, 38.9 mmol) in CH_2Cl_2 (100 mL). A solution of alcohol **23** (7.10 g, 32.5 mmol)[60] in CH_2Cl_2 (40 mL) was slowly added and the mixture stirred for 4 h before all volatile materials were evaporated and the residue purified by flash chromatography (hexanes/EtOAc 1:0 → 4:1) to give product **24** as a yellow liquid (10.36 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.61$ (t, $J = 6.2$ Hz, 2H), 3.19 (t, $J = 7.1$ Hz, 2H), 1.85 (quint, $J = 7.2$ Hz, 2H), 1.57–1.41 (m, 4H), 0.90 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 62.9$, 33.4, 31.7, 27.0, 26.0, 18.4, 6.9, −5.3 ppm; IR (film): $\tilde{\nu} = 2954$, 2930, 2886, 2857, 2737, 1471, 1462, 1255, 1213, 1103, 836, 812, 775 cm^{-1}; MS (EI): m/z (%): 271 (24), 215 (19), 185 (16), 143 (6), 101 (4), 75 (19), 70 (6), 69 (100), 45 (4), 41 (18); HRMS (CI): m/z: calcd for $C_{11}H_{26}IOSi$: 329.0798; found: 329.0801 [M^++H].

***tert*-Butyl(((6*R*)-7-iodo-6-methylheptyl)oxy)dimethylsilane (27)**: Prepared analogously from alcohol **26** (8.34 g, 32 mmol), imidazole (3.28 g, 48.2 mmol), I_2 (11.1 g, 43.7 mmol) and PPh_3 (10.11 g, 38.6 mmol). Flash chromatography (hexanes/EtOAc 10:1) provides product **27** as a yellow liquid (11.86 g, 99%). $[\alpha]_D^{20} = -1°$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.60$ (t, $J = 6.5$ Hz, 2H), 3.19 (ddd, $J = 5.3$, 9.6, 15.5 Hz, 2H), 1.54–1.17 (m, 9H), 0.97 (d, $J = 6.5$ Hz, 3H), 0.89 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 63.2$, 36.4, 34.7, 32.8, 26.7, 26.0, 25.9, 20.6, 18.4, 17.9, −5.3 ppm; IR (film): $\tilde{\nu} = 2955$, 2929, 2856, 2739, 1471, 1462, 1388, 1361, 1255, 1194, 1101, 835, 775 cm^{-1}; MS (EI): m/z (%): 313 (13), 215 (6), 185 (7), 111 (42), 83 (5), 75 (23), 73 (10), 70 (6), 69 (100), 59 (5), 57 (5), 55 (29), 43 (6), 41 (11); HRMS (ESI+): m/z: calcd for $C_{14}H_{31}INaOSi$: 393.1081; found: 393.1081 [M^++Na]; elemental analysis calcd (%) for $C_{14}H_{31}IOSi$: C 45.40, H 8.44; found: C 45.32, H 8.41.

***tert*-Butyl(3-iodopropoxy)dimethylsilane (35)**: Prepared analogously from alcohol **34** (13.3 g, 69.9 mmol), imidazole (7.10 g, 104 mmol), I_2 (24 g, 95 mmol) and PPh_3 (22 g, 84 mmol). Flash chromatographic purification of the crude material (hexanes) afforded iodide **35** as a yellow liquid (20.2 g, 96%). The analytical data are in good agreement with those reported in the literature.[61] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.67$ (t, $J = 5.7$ Hz, 2H), 3.28 (t, $J = 6.7$ Hz, 2H), 1.99 (m, 2H), 0.90 (s, 9H), 0.07 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 63.9$, 33.6, 26.2, 14.8, 7.2, −5.3 ppm; IR (film): $\tilde{\nu} = 2954$, 2929, 2895, 2857, 2738, 1471, 1425, 1386, 1361, 1256, 1182, 1138, 1102, 1053, 1006, 931, 835, 813, 777, 715, 663, 606 cm^{-1}; MS (EI): m/z (%): 244 (11), 243 (100), 215 (52), 186 (5), 185 (65), 115 (40), 101 (5), 75 (10), 73 (13), 58 (6), 57 (6), 45 (8), 41 (13), 29 (5); HRMS (CI): m/z: calcd for $C_9H_{22}IOSi$: 301.0485; found: 301.0488 [M^++H].

(2*R*)-7-((*tert*-Butyl(dimethyl)silyl)oxy)-*N*-((1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethylheptanamide (25): *n*BuLi (1.6 M in hexane, 13.1 mL, 21.0 mmol) was slowly added to a suspension of LiCl (2.54 g, 59.9 mmol) and $(iPr)_2NH$ (3.16 mL, 22.5 mmol) in THF (12 mL) at −78 °C before the resulting mixture was allowed to reach ambient temperature. After stirring for 10 min, the mixture was cooled to −78 °C before a pre-cooled (0 °C) solution of amide **22** (2.21 g, 9.99 mmol)[34] in THF (33 mL) was introduced. After stirring for 1 h at that temperature and for an additional 20 min at 0 °C, a solution of iodide **24** (4.92 g, 15.0 mmol) in THF (63 mL) was added dropwise at 0 °C over a period of 1 h and stirring continued until TLC showed complete conversion. The reaction was quenched with aq. sat. NH_4Cl (80 mL), the aqueous layer was extracted with EtOAc (3×100 mL), the combined organic phases were dried over $MgSO_4$ and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 10:1 → 2:1) to give product **25** as a pale yellow liquid (3.59 g, 85%). $[\alpha]_D^{20} = +54°$ ($c = 1.3$, $CHCl_3$); *de* > 99% (HPLC: column: 125 mm Purospher C18e (5 μm), ∅ 3.0 mm; MeOH/water 75:25, 0.5 mL min^{-1}; $T = 308$ K; 17.8 MPa; $t_R = 32.03$ min); ^{1}H NMR (400 MHz, $CDCl_3$, major rotamer): $\delta = 7.34$ (m, 5H), 4.60 (m, 2H), 4.41 (br s, 1H), 3.54 (t, $J = 6.5$ Hz, 2H), 2.84 (s, 3H), 2.58 (m, 1H), 1.64–0.98 (m, 8H), 1.14 (d, $J = 7.0$ Hz, 3H), 1.07 (d, $J = 6.7$ Hz, 3H), 0.89 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): $\delta = 179.1$, 142.6, 128.2, 127.5, 126.3, 76.4, 63.1, 57.8, 36.5, 34.0, 32.7, 27.2, 26.0, 25.9 (2C), 18.3, 17.3, 14.4, −5.3 ppm; IR (film): $\tilde{\nu} = 3386$, 3086, 3063, 3029, 2954, 2931, 2896, 2857, 2737, 1621, 1471, 1463, 1408, 1388, 1375, 1360, 1304, 1255, 1199, 1100, 1052, 1028, 1006, 988, 835, 775, 701 cm^{-1}; MS (EI): m/z (%): 406 (3), 366 (4), 365 (15), 364 (57), 315 (10), 314 (24), 258 (5), 257 (7), 230 (3), 148 (17), 115 (4), 101 (3), 97 (9), 89 (4), 75 (17), 73 (14), 59 (6), 58 (100), 55 (16); HRMS (ESI+): m/z: calcd for $C_{24}H_{43}NO_3Si$+Na: 444.2905; found: 444.2905 [M^++Na]; elemental analysis calcd (%) for $C_{24}H_{43}NO_3Si$: C 68.36, H 10.28, N 3.32; found: C 68.28, H 10.22, N 3.26.

(2*S*,4*R*)-9-((*tert*-Butyl(dimethyl)silyl)oxy)-*N*-((1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl)-*N*,2,4-trimethylnonanoic acid amide (28): Prepared analogously from *ent*-**22** (1.37 g, 6.19 mmol) and iodide **27** (3.44 g, 9.29 mmol) using LiCl (1.58 g, 37.3 mmol), $(iPr)_2NH$ (1.96 mL, 13.9 mmol) and *n*BuLi (1.6 M in hexane, 8.06 mL, 12.9 mmol). Flash chromatography (hexanes/EtOAc 10:1 → 4:1) afforded product **28** as a colorless liquid (2.00 g, 70%). $[\alpha] = -57°$ ($c = 0.9$, $CHCl_3$); *de* = 99% (HPLC: column: 125 mm Purospher C18e (5 μm), ∅ 3.0 mm; MeOH/water 85:15; 0.5 mL min^{-1}; $T = 308$ K; 14.4 MPa; $t_R = 13.97$ min (major diastereomer), 24.95 min (minor diastereomer)); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$–7.07 (m, 5H), 5.05 (br s, 1H), 4.56 (m, 1H), 4.22 (m, 1H), 3.57 (t, $J = 6.4$ Hz, 2H), 2.42 (m, 1H), 2.34 (s, 3H), 1.59–0.98 (m, 17H), 0.99 (s, 9H), 0.78 (d, $J = 6.4$ Hz, 3H), 0.08 ppm (s, 6H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 178.5$, 143.9, 128.3, 127.3, 126.8, 74.5, 63.3, 58.3, 41.6, 37.6, 34.4, 33.3, 30.9, 27.1, 26.7, 26.2 (2C), 19.8, 18.5, 17.4, 14.4, −5.1 ppm; IR (film): $\tilde{\nu} = 3383$, 3087, 3063, 3029, 2955, 2930, 2857, 2737, 1622, 1471, 1463, 1408, 1377, 1360, 1255, 1100, 1052, 1028, 836, 775, 701 cm^{-1}; MS (EI): m/z (%): 408 (7), 407 (24), 406 (79), 357 (13), 356 (33), 299 (6), 148 (20), 115 (5), 97 (6), 83 (12), 75 (15), 73 (9), 69 (9), 59 (6), 58 (100), 55 (10); HRMS (ESI+): m/z: calcd for $C_{27}H_{49}NNaO_3Si$: 486.3374; found:

486.3378 [M^++Na]; elemental analysis calcd (%) for $C_{27}H_{49}NO_3Si$: C 69.92, H 10.65; found: C 70.06, H 10.61.

(2*R*)-5-((*tert*-Butyl(dimethyl)silyl)oxy)-2-ethyl-*N*-((1*S*,2*S*)-2-hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methylpentanamide (36): Prepared analogously from **33** (2.35 g, 9.99 mmol) and iodide **35** (4.50 g, 15 mmol) using LiCl (2.54 g, 59.9 mmol), (iPr)$_2$NH (3.16 mL, 22.5 mmol) and nBuLi (1.6 M in hexane, 13.1 mL, 21.0 mmol). Flash chromatography (hexanes/EtOAc 10:1 → 2:1) afforded product **36** as a yellow liquid (3.45 g, 85 %). $[\alpha]_D^{20}$ = +71° (c = 1.2, $CHCl_3$); *de* > 97 % (^{13}C NMR); ^{1}H NMR (400 MHz, C_6D_6, major rotamer): δ = 7.34–7.06 (m, 5H), 5.17 (br s, 1H), 4.54 (m, 1H), 4.32 (m, 1H), 3.44 (m, 2H), 2.36 (s, 3H), 2.23 (m, 1H), 1.77–1.00 (m, 9H), 0.96 (s, 9H), 0.80 (t, J = 7.4 Hz, 3H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, C_6D_6, major rotamer): δ = 177.6, 143.9, 128.3, 127.3, 126.8, 76.2, 63.3, 58.2, 43.6, 30.9, 29.4, 26.4, 26.3, 26.2, 18.5, 14.5, 12.0, −5.2 ppm; IR (film): $\tilde{\nu}$ = 3382, 3087, 3063, 3029, 2957, 2930, 2857, 2738, 1618, 1472, 1462, 1409, 1386, 1361, 1305, 1255, 1195, 1143, 1098, 1051, 1006, 973, 939, 836, 775, 701, 662 cm^{-1}; MS (EI): m/z (%): 351 (13), 350 (50), 300 (14), 244 (21), 243 (100), 75 (12), 73 (22), 58 (32), 55 (10); HRMS (ESI+): m/z: calcd for $C_{23}H_{41}NNaO_3Si$: 430.2748; found: 430.2744 [M^++Na].

(2*R*)-7-((*tert*-Butyl(dimethyl)silyl)oxy)-2-methyl-1-heptanol (26): nBuLi (1.6 M in hexane, 76.3 mL, 122 mmol) was slowly added to a solution of (iPr)$_2$NH (18.5 mL, 132 mmol) in THF (130 mL) at −78 °C. The mixture was stirred at that temperature for 10 min and at 0 °C for another 10 min before BH_3·NH_3 (4.29 g, 90 %, 125 mmol) was introduced and stirring continued at ambient temperature for 30 min. The mixture was cooled to 0 °C before a solution of compound **25** (13.2 g, 31.3 mmol) in THF (220 mL) was added and stirring continued at ambient temperature for 2 h. For work up, the reaction was quenched by slow addition of aq. sat. NH_4Cl (150 mL). The mixture was stirred for 30 min before the aqueous layer was extracted with *tert*-butyl methyl ether (3×200 mL). The combined organic phases were washed with brine before they were dried over $MgSO_4$ and evaporated. Flash chromatography of the residue (hexanes/EtOAc 10:1) afforded product **26** as a pale yellow liquid (6.57 g, 81 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60 (t, J = 6.6 Hz, 2H), 3.46 (m, 2H), 1.65–1.25 (m, 9H), 1.09 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.4, 63.3, 35.8, 33.1, 32.8, 26.8, 26.1, 26.0, 18.4, 16.6, −5.3 ppm; IR (film): $\tilde{\nu}$ = 3348, 2953, 2930, 2857, 2737, 1472, 1463, 1387, 1361, 1255, 1101, 1034, 1006, 836, 813, 775 cm^{-1}; MS (EI): m/z (%): 203 (2), 157 (2), 115 (4), 112 (2), 111 (21), 105 (11), 101 (3), 93 (5), 89 (3), 77 (2), 76 (3), 75 (37), 73 (12), 70 (6), 69 (100), 67 (3), 61 (2), 59 (4), 57 (5), 56 (2), 55 (36), 45 (2), 43 (6), 41 (11), 31 (3), 29 (4); HRMS (ESI+): m/z: calcd for $C_{14}H_{32}NaO_2Si$: 283.2064; found: 283.2064 [M^++Na]; elemental analysis calcd (%) for $C_{14}H_{32}O_2Si$: C 64.55, H 12.38; found: C 64.50, H 12.46.

(2*S*,4*R*)-9-((*tert*-Butyl(dimethyl)silyl)oxy)-2,4-dimethyl-1-nonanol (29): Prepared analogously from substrate **28** (2.44 g, 5.26 mmol), using nBuLi (1.6 M in hexane, 12.8 mL, 20.5 mmol), (iPr)$_2$NH (3.1 mL, 22 mmol) and BH_3·NH_3 (722 mg, 90 %, 21.0 mmol). Flash chromatography (hexanes/EtOAc 10:1) afforded the title compound as a colorless liquid (1.37 g, 86 %). $[\alpha]_D^{20}$ = −14° (c = 1.5, $CHCl_3$); *de* > 99 % (HPLC: column: 125 mm Nucleodur 100–5-C18ce, ∅ 4.0 mm; MeOH/water 80:20; 0.8 mL min^{-1}; T = 308 K; 8.6 MPa; t_R = 17.74 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60 (t, J = 6.6 Hz, 2H), 3.44 (ddd, J = 6.2, 10.4, 17.1 Hz, 2H), 1.71 (m, 1H), 1.54–1.03 (m, 12H), 0.89 (s, 9H), 0.88 (d, J = 5.7 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.1, 63.3, 40.6, 38.0, 33.2, 32.9, 29.9, 26.8, 26.1, 26.0, 19.4, 18.4, 16.3, −5.3 ppm; IR (film): $\tilde{\nu}$ = 3346, 2954, 2929, 2857, 2737, 1471, 1463, 1385, 1255, 1102, 1038, 1006, 836, 813, 775 cm^{-1}; MS (EI): m/z (%): 245 (3), 129 (3), 115 (5), 111 (18), 109 (3), 105 (16), 101 (5), 98 (8), 97 (100), 95 (7), 93 (7), 89 (6), 85 (7), 84 (5), 83 (72), 81 (5), 75 (55), 73 (20), 71 (19), 70 (5), 69 (74), 59 (7), 57 (24), 56 (5), 55 (87), 43 (21), 41 (15), 29 (5); HRMS (ESI+): m/z: calcd for $C_{17}H_{38}NaO_2Si$: 325.2533; found: 325.2531 [M^++Na]; elemental analysis calcd (%) for $C_{17}H_{38}O_2Si$: C 67.48, H 12.66; found: C 67.43, H 12.64.

(2*R*)-5-((*tert*-Butyl(dimethyl)silyl)oxy)-2-ethyl-1-pentanol (37): Prepared analogously from substrate **36** (0.50 g, 1.2 mmol), using nBuLi (1.6 M in hexane, 3.0 mL, 4.8 mmol), (iPr)$_2$NH (0.72 mL, 5.1 mmol) and BH_3·NH_3 (168 mg, 90 %, 4.9 mmol). Flash chromatography (hexanes/EtOAc 10:1) afforded the title compound as a yellow liquid (265 mg, 88 %). $[\alpha]_D^{20}$ = +2° (c = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.61 (t, J = 6.5 Hz, 2H), 3.55 (br s, 2H), 1.58–1.51 (m, 2H), 1.47–1.29 (m, 6H), 0.90 (t, J = 7.4 Hz, 3H), 0.89 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.3, 63.5, 41.8, 29.9, 26.5, 26.0, 23.5, 18.4, 11.1, −5.3 ppm; IR (film): $\tilde{\nu}$ = 3349, 2957, 2930, 2858, 2738, 1472, 1463, 1387, 1361, 1255, 1099, 1039, 1006, 969, 939, 836, 813, 775, 712, 662 cm^{-1}; MS (EI): m/z (%): 105 (15), 101 (5), 97 (60), 89 (5), 75 (44), 73 (14), 69 (16), 59 (5), 56 (5), 55 (100), 43 (6), 29 (5); HRMS (ESI+): m/z: calcd for $C_{13}H_{30}NaO_2Si$: 269.1908; found: 269.1904 [M^++Na]; elemental analysis calcd (%) for $C_{13}H_{30}O_2Si$: C 63.35, H 12.27; found: C 63.39, H 12.24.

***tert*-Butyl(((6*R*,8*S*)-9-(4-methoxyphenoxy)-6,8-dimethylnonyl)-oxy)dimethylsilane (30)**: A solution of alcohol **29** (500 mg, 1.65 mmol), *para*-methoxyphenol (622 mg, 5.01 mmol), PPh_3 (569 mg, 2.17 mmol) and diethyl azodicarboxylate (0.34 mL, 2.16 mmol) in THF (6.3 mL) was stirred in a sealed tube at 80 °C for 30 min. The reaction was quenched with water (5 mL), the aqueous layer was extracted with *tert*-butyl methyl ether (3× 10 mL), and the combined organic phases were dried ($MgSO_4$) and evaporated. The crude product was used in the next step without further purification. Analytically pure samples obtained by flash chromatography (hexanes/EtOAc 10:1) analyzed as follows: $[\alpha]_D^{20}$ = −5° (c = 1.3, $CHCl_3$); *de* > 99 % (HPLC: column: 125 mm YMC ProC18, 120 A, 5 μm, ∅ 2.1 mm; MeCN/water 90:10; 0.2 mL min^{-1}; T = 308 K; 2.8 MPa; t_R = 31.58 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (s, 4H), 3.77 (s, 3H), 3.69 (ddd, J = 6.3, 8.9, 15.8 Hz, 2H), 3.60 (t, J = 6.6 Hz, 2H), 1.99 (m, 1H), 1.53 (m, 3H), 1.40–1.13 (m, 8H), 0.98 (d, J = 6.6 Hz, 3H), 0.90 (s, 9H), 0.86 (d, J = 6.6 Hz, 3H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6, 153.5, 115.4, 114.6, 74.6, 63.3, 55.8, 41.0, 37.9, 32.9, 30.8, 29.9, 26.9, 26.2, 26.0, 19.4, 18.4, 16.9, −5.3 ppm; IR (film): $\tilde{\nu}$ = 2954, 2929, 2856, 1592, 1509, 1469, 1442, 1388, 1361, 1288, 1232, 1181, 1102, 1045, 1006, 992, 939, 905, 835, 775, 748, 712, 662 cm^{-1}; MS (EI): m/z (%): 409 (6), 408 ([M^+], 20), 211 (8), 199 (9), 181 (16), 125 (8), 124 (100), 123 (5), 111 (13), 109 (13), 98 (5), 97 (59), 95 (7), 89 (5), 83 (42), 75 (36), 73 (18), 71 (12), 69 (34), 59 (6), 57 (15), 55 (41), 43 (12), 41 (11); HRMS (ESI+): m/z: calcd for $C_{24}H_{44}NaO_3Si$: 431.2952; found: 431.2954 [M^++Na]; elemental analysis calcd (%) for $C_{24}H_{44}O_3Si$: C 70.53, H 10.85; found: C 70.61, H 10.77.

(6*R*,8*S*)-9-(4-Methoxyphenoxy)-6,8-dimethylnonanoic acid (31): TBAF (1 M in THF, 1.82 mL, 1.82 mmol) was added to a solution of crude compound **30** (1.65 mmol) in THF (8.3 mL) and the resulting mixture was stirred for 18 h before it was adsorped on silica. Elution with hexanes/EtOAc 10:1 → 4:1 afforded (6*R*,8*S*)-9-(4-methoxyphenoxy)-6,8-dimethyl-1-nonanol as a pale yellow liquid (436 mg, 90 % over two steps) which analyzed as follows: $[\alpha]_D^{20}$ = −3° (c = 1.1, $CHCl_3$); *de* > 99 % (HPLC: column: 125 mm YMC ProC18, 120 A, 5 μm, ∅ 2.1 mm; eluent: MeOH/water 70:30; 0.2 mL min^{-1}; T = 308 K; 8.8 MPa; t_R = 28.30 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (s, 4H), 3.77 (s, 3H), 3.69 (ddd, J = 6.3, 9.0, 15.8 Hz, 2H), 3.64 (t, J = 6.6 Hz, 2H), 2.00 (m, 1H), 1.56 (m, 3H), 1.41–1.13 (m, 9H), 0.98 (d, J = 6.7 Hz, 3H), 0.86 ppm (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6, 153.5, 115.4, 114.6, 74.6, 63.1, 55.8, 41.0, 37.8, 32.8, 30.7, 29.9, 26.8, 26.0, 19.4, 16.9 ppm; IR (film): $\tilde{\nu}$ = 3337, 3047, 2929, 2857, 1614, 1591, 1509, 1466, 1231, 1043, 824, 748 cm^{-1}; MS (EI): m/z (%): 294 (14) [M^+], 125 (9), 124 (100), 109 (9), 69 (5), 55 (13), 43 (5), 41 (7); HRMS (ESI+): m/z: calcd for $C_{18}H_{30}NaO_3$: 317.2087; found: 317.2088 [M^++Na]; elemental analysis calcd (%) for $C_{18}H_{30}O_3$: C 73.43, H 10.27; found: C 73.50, H 10.32.

A mixture of this alcohol (100 mg, 0.340 mmol) and PDC (1.28 g, 3.40 mmol) in DMF (3.5 mL) was stirred for 15 h before it was quenched with water (10 mL) and extracted with Et_2O (5×5 mL). The combined organic layers were dried over $MgSO_4$ and evaporated, and the residue was purified by flash chromatography with hexanes/EtOAc 10:1 → 4:1 to give acid **31** as a yellow liquid (78 mg, 74 %). $[\alpha]_D^{20}$ = −9° (c = 1.5, $CHCl_3$); *de* > 99 % (HPLC: column: 125 mm Purospher RP-18e (5 μm), ∅ 3.0 mm; eluent: MeOH/0.1 % TFA 75:25; 0.5 mL min^{-1}; T = 308 K; 13.1 MPa; t_R = 11.52 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.79 (br s, 1H), 6.83 (s, 4H), 3.77 (s, 3H), 3.69 (ddd, J = 6.3, 8.9, 15.7 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 2.01 (m, 1H), 1.67–1.51 (m, 3H), 1.45–1.13 (m, 6H), 0.98 (d, J = 6.6 Hz, 3H), 0.86 ppm (d, J = 6.6 Hz, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$): $\delta = 179.7$, 153.6, 153.5, 115.4, 114.6, 74.6, 55.7, 40.9, 37.4, 34.0, 30.7, 29.8, 26.5, 24.9, 19.3, 16.8 ppm; IR (film): $\tilde{\nu} = 3044$, 2955, 2927, 2871, 2676, 2058, 1709, 1591, 1509, 1466, 1412, 1389, 1379, 1288, 1232, 1181, 1107, 1043, 948, 824, 748 cm^{-1}; MS (EI): *m/z* (%): 308 (9) [M^+], 125 (8), 124 (100), 123 (3), 109 (10), 83 (3), 69 (5), 55 (9), 43 (5), 41 (7); HRMS (ESI+): *m/z*: calcd for $C_{18}H_{28}NaO_4$: 331.1880; found: 331.1880 [M^++Na]; elemental analysis calcd (%) for $C_{18}H_{28}O_4$: C 70.10, H 9.15; found: C 70.14, H 9.12.

(6*R*,8*S*)-*N*-Methoxy-9-(4-methoxyphenoxy)-*N*,6,8-trimethylnonanoic acid amide (32): 1,1′-Carbonyldiimidazole (35 mg, 0.21 mmol) was added to a solution of acid **31** (50 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) at 0 °C and the resulting mixture was stirred at ambient temperature for 1 h. The solution was then cooled to 0 °C before Et_3N (73 μL, 0.52 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (26 mg, 0.26 mmol) were successively introduced. After stirring for 14 h, the reaction was quenched with aq. HCl (3 M, 1 mL), the aqueous phase was extracted with CH_2Cl_2 (3× 5 mL), the combined organic layers were washed with aq. sat. $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography of the residue (hexanes/EtOAc 10:1 → 4:1) furnished product **32** as a yellow liquid (50 mg, 87 %). $[\alpha]_D^{20} = -8°$ ($c = 1.1$, $CHCl_3$); *de* > 99 % (HPLC: column: 125 mm YMC ProC18, 120 A, 5 μm, ∅ 2.1 mm; eluent: MeOH/water 70:30; 0.2 mL min^{-1}; $T = 308$ K; 8.8 MPa; $t_R = 29.45$ min); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.82$ (s, 4H), 3.76 (s, 3H), 3.74–3.61 (m, 2H), 3.68 (s, 3H), 3.18 (s, 3H), 2.42 (t, $J = 7.5$ Hz, 2H), 2.00 (m, 1H), 1.67–1.12 (m, 9H), 0.97 (d, $J = 6.7$ Hz, 3H), 0.86 ppm (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.7$, 153.5, 153.4, 115.4, 114.5, 74.5, 61.1, 55.6, 40.9, 37.6, 32.1, 31.8, 30.7, 29.8, 26.8, 24.8, 19.3, 16.7 ppm; IR (film): $\tilde{\nu} = 2956$, 2930, 2870, 1667, 1591, 1509, 1466, 1442, 1414, 1384, 1289, 1232, 1180, 1106, 1042, 995, 824, 799, 748, 639, 523 cm^{-1}; MS (EI): *m/z* (%): 352 (5), 351 (24) [M^+], 228 (20), 124 (100), 83 (12), 69 (10), 55 (24), 41 (12); HRMS (ESI+): *m/z*: calcd for $C_{20}H_{34}NO_4$: 352.2482; found: 352.2484 [M^++H]; elemental analysis calcd (%) for $C_{20}H_{33}NO_4$: C 68.34, H 9.46, N 3.99; found: C 68.27, H 9.38, N 4.06.

***tert*-Butyl(((4*R*)-6,6-dibromo-4-ethyl-5-hexenyl)oxy)dimethyl-silane (39)**: A solution of *N*-methylmorpholin-*N*-oxide monohydrate (97 %, 588 mg, 4.87 mmol) and powdered molecular sieves (4 Å, 1.62 g) in CH_2Cl_2 (5 mL) was stirred for 10 min before a solution of alcohol **37** (800 mg, 3.25 mmol) in CH_2Cl_2 (5 mL) and tetra-*N*-propylammonium perruthenate (57 mg, 0.16 mmol, 5 mol %) were successively added. The resulting mixture was stirred for 30 min before it was passed through a short pad of Celite which was carefully rinsed with CH_2Cl_2. The combined filtrates were evaporated and the resulting crude aldehyde **38** (685 mg, 2.80 mmol, 86 %) immediately used in the next step without further purification.

PPh_3 (3.41 g, 13.0 mmol) was added in portions over a period of 20 min to a solution of CBr_4 (2.15 g, 6.48 mmol) in CH_2Cl_2 (22 mL) at 0 °C. After stirring for 10 min, the resulting clear orange-red solution was cooled to −78 °C before a solution of the crude aldehyde in CH_2Cl_2 (11 mL) was added dropwise. The resulting mixture was stirred for 40 min before it was transferred under stirring into a mixture of hexanes (460 mL) and Et_3N (2.28 mL, 16.22 mmol). The precipitates formed were filtered off over basic alumina, which was carefully rinsed with hexanes/EtOAc 1:1. The combined filtrates were evaporated and the crude product dissolved in CH_2Cl_2 (16.5 mL). To remove residual PPh_3, MeI (0.81 mL, 13 mmol) was added. After stirring for 1 h, the reaction was quenched with aq. sat. NH_4Cl (10 mL), the aqueous layer was extracted with *tert*-butyl methyl ether (3×15 mL), the combined organic phases were dried over $MgSO_4$ and evaporated, and the residue was purified by flash chromatography (hexanes) to give the title compound **39** as a colorless liquid (965 mg, 74 % over both steps). $[\alpha]_D^{20} = -1°$ ($c = 1.1$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.12$ (d, $J = 9.8$ Hz, 1H), 3.60 (t, $J = 6.2$ Hz, 2H), 2.31 (m, 1H), 1.54–1.42 (m, 4H), 1.37–1.26 (m, 2H), 0.91–0.88 (m, 3H), 0.90 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.3$, 88.1, 63.0, 45.1, 30.3, 30.2, 27.4, 26.0, 18.4, 11.5, −5.3 ppm; IR (film): $\tilde{\nu} = 2957$, 2928, 2895, 2857, 2738, 1617, 1471, 1462, 1386, 1361, 1255, 1188, 1101, 1006, 983, 939, 900, 835, 813, 775, 714, 661, 567 cm^{-1}; MS (EI): *m/z* (%): 345 (17), 343 (32), 341 (16), 169 (12), 167 (12), 147 (10), 139 (22), 137 (20), 108 (28), 107 (100), 93 (14), 91 (19), 83 (19), 81 (11), 79 (71), 75 (44), 73 (40), 67 (15), 65 (15), 59 (17), 57 (10), 55 (35), 41 (20), 29 (15); HRMS (ESI+): *m/z*: calcd for $C_{14}H_{28}Br_2NaOSi$: 421.0169; found: 421.0165 [M^++Na]; elemental analysis calcd (%) for $C_{14}H_{28}Br_2OSi$: C 42.01, H 7.05; found: C 41.87, H 7.02.

***tert*-Butyl(((4*R*)-4-ethyl-5-heptynyl)oxy)dimethylsilane (40)**: *n*BuLi (1.6 M in hexane, 2.67 mL, 4.27 mmol) was added over a period of 30 min to a solution of compound **39** (855 mg, 2.14 mmol) in THF (22 mL) at −78 °C. Once the addition was complete, the mixture was allowed to stir at −16 °C for 30 min before MeI (0.67 mL, 11 mmol) was introduced and stirring continued at that temperature for 60 min. An aqueous extractive work up followed by flash chromatography (hexanes) provided alkyne **40** as a colorless liquid (532 mg, 98 %). $[\alpha]_D^{20} = -7°$ ($c = 0.8$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.62$ (t, $J = 6.5$ Hz, 2H), 2.20 (m, 1H), 1.80 (d, $J = 2.4$ Hz, 3H), 1.76–1.32 (m, 6H), 0.97 (t, $J = 7.4$ Hz, 3H), 0.90 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 82.4$, 76.6, 63.2, 33.2, 31.3, 30.7, 28.4, 26.0, 18.4, 11.8, 3.5, −5.3 ppm; IR (film): $\tilde{\nu} =$ 2957, 2929, 2858, 2738, 1472, 1463, 1387, 1361, 1347, 1255, 1188, 1101, 1047, 1006, 968, 939, 836, 775, 662 cm^{-1}; MS (EI): *m/z* (%): 198 (7), 197 (41), 121 (13), 101 (8), 97 (7), 93 (5), 89 (5), 76 (7), 75 (100), 73 (17), 59 (7), 55 (9); HRMS (ESI+): *m/z*: calcd for $C_{15}H_{30}NaOSi$: 277.1958; found: 277.1961 [M^++Na]; elemental analysis calcd (%) for $C_{15}H_{30}OSi$: C 70.79, H 11.88; found: C 70.86, H 11.81.

(4*R*)-4-Ethyl-5-heptyn-1-ol (41): TBAF (1 M in THF, 2.3 mL, 2.3 mmol) was added to a solution of compound **40** (532 mg, 2.09 mmol) in THF (10 mL) and the resulting mixture was stirred for 14 h. A standard extractive work up followed by flash chromatographic purification of the crude material (hexanes/EtOAc 4:1) furnished product **41** as a yellow liquid (278 mg, 95 %). $[\alpha]_D^{20} = -6°$ ($c = 0.9$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.67$ (t, $J = 6.5$ Hz, 2H), 2.22 (m, 1H), 1.80 (d, $J = 2.4$ Hz, 3H), 1.78–1.34 (m, 6H), 0.98 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 82.2$, 76.9, 62.9, 33.3, 31.2, 30.7, 28.5, 11.8, 3.5 ppm; IR (film): $\tilde{\nu} =$ 3337, 2960, 2934, 2872, 2738, 1455, 1379, 1348, 1229, 1059, 1031, 925 cm^{-1}; MS (EI): *m/z* (%): 111 (7), 97 (9), 96 (66), 91 (29), 84 (10), 81 (100), 79 (62), 77 (48), 67 (33), 65 (15), 55 (40), 53 (39), 43 (27), 41 (48), 39 (25), 27 (17); HRMS (CI): *m/z*: calcd: 141.1279; found: 141.1281 [M^++H]; elemental analysis calcd (%) for $C_9H_{16}O$: C 77.09, H 11.50; found: C 77.14, H 11.46.

(4*R*)-7-Bromo-4-ethyl-2-heptyne (42): PPh_3 (2.27 g, 8.66 mmol) was added in portions to a solution of alcohol **41** (1.10 g, 7.86 mmol) and CBr_4 (2.87 g, 8.65 mmol) in CH_2Cl_2 (40 mL) and the resulting mixture was stirred for 5 h at ambient temperature. For work up, the solvents were carefully evaporated and the residue was purified by flash chromatography (hexanes/EtOAc 1:0 → 30:1) to give product **42** as a colorless liquid (1.23 g, 77 %). $[\alpha]_D^{20} = -17°$ ($c = 0.8$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.44$ (t, $J = 6.8$ Hz, 2H), 2.22 (m, 1H), 2.13–1.89 (m, 2H), 1.80 (d, $J = 2.4$ Hz, 3H), 1.63–1.55 (m, 1H), 1.51–1.35 (3H), 0.98 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 81.7$, 77.2, 33.9, 33.5, 32.8, 30.8, 28.4, 11.8, 3.5 ppm; IR (film): $\tilde{\nu} = 2962$, 2922, 2873, 2858, 1459, 1380, 1348, 1293, 1251, 1206, 649, 561 cm^{-1}; MS (GC-EI): *m/z* (%): 174 (7), 107 (6), 97 (5), 96 (68), 95 (20), 94 (11), 93 (16), 91 (18), 82 (7), 81 (100), 79 (57), 77 (33), 67 (31), 66 (9), 65 (17), 55 (23), 53 (46), 41 (40), 39 (28), 27 (20); HRMS (CI): *m/z*: calcd for $C_9H_{16}Br$: 203.0436; found: 203.0433 [M^++H]; elemental analysis calcd (%) for $C_9H_{15}Br$: C 53.22, H 7.44; found: C 53.31, H 7.52.

Compound 44: A solution of bromide **42** (168 mg, 0.827 mmol) in THF (3 mL) was added to a suspension of magnesium turnings (40 mg, 1.7 mmol, pre-activated with catalytic amounts of 1,2-dibromoethane) in THF (5 mL) and the mixture stirred at 40 °C for 100 min. The solution of the resulting Grignard reagent **43** was then transferred via canula under Ar to a solution of compound **32** (223 mg, 0.635 mmol) in THF (2 mL) at 0 °C. After stirring for 17 h at ambient temperature, the reaction was quenched with sat. aq. NH_4Cl (5 mL). A standard extractive work up followed by flash chromatography of the crude material (hexanes/EtOAc 30:1) provided product **44** as a colorless liquid (202 mg, 77 %). $[\alpha]_D^{20} =$ −11° ($c = 0.5$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.82$ (s, 4H), 3.77 (s, 3H), 3.69 (m, 2H), 2.39 (m, 4H), 2.20 (m, 1H), 1.99 (m, 1H), 1.79 (d, $J = 2.3$ Hz, 3H), 1.77–1.10 (m, 15H), 0.98 (d, $J = 6.6$ Hz, 3H), 0.97 (t, $J =$

7.4 Hz, 3H), 0.86 ppm (d, $J=6.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=211.3$, 153.7, 153.5, 115.5, 114.6, 82.1, 76.8, 74.6, 55.8, 42.8, 42.7, 41.0, 37.7, 34.5, 33.3, 30.8, 29.9, 28.3, 26.7, 24.2, 21.9, 19.4, 16.9, 11.8, 3.5 ppm; IR (film): $\tilde{\nu}=3045$, 2957, 2927, 2858, 2058, 1713, 1616, 1591, 1509, 1464, 1411, 1377, 1288, 1232, 1181, 1106, 1043, 992, 824, 748 cm^{-1}; MS (EI): m/z (%): 415 (5), 414 ([M^+], 17), 125 (8), 124 (100), 109 (9), 81 (4), 69 (4), 55 (9), 43 (5), 41 (5); HRMS (ESI+): m/z: calcd for $C_{27}H_{42}NaO_3$: 437.3026; found: 437.3029 [M^++Na]; elemental analysis calcd (%) for $C_{27}H_{42}O_3$: C 78.21, H 10.21; found: C 78.28, H 10.21.

Compound 45: A solution of CAN (80 mg, 0.15 mmol) in water (0.7 mL) was added to a solution of compound **44** (20 mg, 0.05 mmol) in MeCN (0.5 mL) at 0°C and the resulting mixture was stirred at that temperature for 45 min. For work up, the solution was diluted with water (5 mL) and extracted with EtOAc (5×5 mL), the combined organic phases were successively washed with aq. sat. $NaHCO_3$, aq. sat. Na_2SO_3 and brine before they were dried over $MgSO_4$ and evaporated. Purification of the crude product by flash chromatography (hexanes/EtOAc 10:1 → 4:1) furnished product **45** as a yellow liquid (12 mg, 81%). $[\alpha]_D^{20}=-19°$ ($c=0.8$, $CHCl_3$); *de* > 99% (HPLC: column: 125 mm Nucleodur 5-100-C18ec, ∅ 4.0 mm; eluent: MeOH/0.1% TFA 70:30; 0.8 mL min^{-1}; $T=308$ K; 8.1 MPa; $t_R=$ 22.79 min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=3.43$ (ddd, $J=13.7$, 10.4, 6.2 Hz, 2H), 2.40 (m, 4H), 2.18 (m, 1H), 1.79 (d, $J=2.3$ Hz, 3H), 1.74–1.02 (m, 16H), 0.96 (t, $J=7.4$ Hz, 3H), 0.88 (d, $J=6.7$ Hz, 3H), 0.83 ppm (d, $J=6.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=211.4$, 82.1, 76.8, 69.1, 42.8, 42.6, 40.6, 37.7, 34.5, 33.3, 33.2, 29.8, 28.3, 26.7, 24.1, 21.8, 19.3, 16.3, 11.8, 3.5 ppm; IR (film): $\tilde{\nu}=3422$, 2957, 2925, 2871, 2736, 1712, 1461, 1410, 1378, 1290, 1129, 1038, 987 cm^{-1}; MS (EI): m/z (%): 308 (3) [M^+], 167 (17), 166 (27), 151 (31), 149 (16), 137 (77), 124 (24), 123 (53), 110 (16), 109 (54), 108 (42), 107 (24), 95 (31), 93 (57), 83 (50), 82 (16), 81 (54), 79 (36), 71 (16), 69 (48), 67 (33), 57 (30), 55 (100), 53 (17), 43 (57), 41 (59), 31 (12), 29 (18); HRMS (ESI+): m/z: calcd for $C_{20}H_{36}NaO_2$: 331.2608; found: 331.2609 [M^++Na]; elemental analysis calcd (%) for $C_{20}H_{36}O_2$: C 77.87, H 11.76; found: C 77.83, H 11.68.

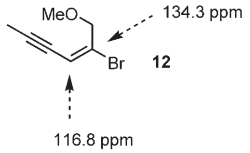
Acid 46: 4-Methoxy-TEMPO (4.3 mg, 23 μmol) was added to a vigorously stirred solution of alcohol **45** (35 mg, 0.11 mmol) and KBr (2.7 mg, 23 μmol) in CH_2Cl_2 (2.5 mL) and aq. sat. $NaHCO_3$ (5 mL) at 0°C. A solution of NaOCl (0.25 M, 0.60 mL, 0.15 mmol) was then introduced and the mixture stirred at 0°C for 7 h. For work up, the reaction was quenched with aq. sat. $Na_2S_2O_3$ (2.5 mL) and aq. sat. $NaHCO_3$ (50 mL), the aqueous layer was extracted with EtOAc (3×20 mL), the combined organic phases were dried over $MgSO_4$ and evaporated, and the resulting crude aldehyde was immediately used in the next step without further purification.

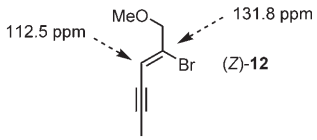
A solution of $NaClO_2$ (72 mg, 80%) and NaH_2PO_4 (38 mg) in water (1.4 mL) was added to a solution of *t*BuOH (3.35 mL) and 2-methylbutene (1.34 mL) and the resulting mixture was vigorously stirred for 10 min. An aliquot of this mixture (1.5 mL) was then added dropwise to a solution of the crude aldehyde in CH_2Cl_2 (0.5 mL). After stirring for 13 h, the mixture was diluted with water (10 mL) and extracted with EtOAc (3×10 mL). The combined organic phases were dried over $MgSO_4$ and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 10:1 → 4:1) to give acid **46** as a yellow liquid (32.9 mg, 90% over both steps). $[\alpha]_D^{20}=-1°$ ($c=1.0$, $CHCl_3$); *de* > 99% (HPLC: column: 125 mm Nucleodur 100-5-C18ec, ∅ 4.0 mm; eluent: MeOH/0.1% TFA 70:30; 0.8 mL min^{-1}; $T=308$ K; 8.3 MPa; $t_R=$ 19.34 min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=10.40$ (br s, 1H), 2.52 (m, 1H), 2.39 (m, 4H), 2.18 (m, 1H), 1.79 (d, $J=2.3$ Hz, 3H), 1.77–1.18 (m, 15H), 1.14 (d, $J=6.9$ Hz, 3H), 0.96 (t, $J=7.4$ Hz, 3H), 0.85 ppm (d, $J=$ 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=211.4$, 183.1, 82.0, 76.8, 42.7, 42.6, 40.7, 37.0, 36.7, 34.5, 33.3, 30.3, 28.3, 26.5, 24.0, 21.8, 19.2, 16.8, 11.7, 3.5 ppm; IR (film): $\tilde{\nu}=3096$, 2958, 2931, 2859, 2670, 1737, 1707, 1462, 1413, 1378, 1291, 1181, 949 cm^{-1}; MS (EI): m/z (%): 322 (1) [M^+], 266 (8), 241 (8), 171 (15), 166 (27), 153 (43), 151 (30), 141 (21), 137 (77), 123 (53), 109 (46), 108 (43), 107 (27), 97 (20), 95 (31), 93 (57), 83 (31), 81 (59), 79 (41), 69 (57), 67 (38), 57 (32), 55 (100), 53 (20), 45 (21), 43 (60), 41 (66), 29 (22); HRMS (ESI+): m/z: calcd for $C_{20}H_{34}NaO_3$: 345.2400; found: 345.2400 [M^++Na]; elemental analysis calcd (%) for $C_{20}H_{34}O_3$: C 74.49, H 10.63; found: C 74.42, H 10.57.

The enyne linchpin

(1*E*)-1,2-Dibromo-3-methoxy-1-propene (48): Ether **47** (4.00 g, 55.4 mmol) was added to a solution of pyridinium perbromide (95% w/w, 26.2 g, 77.8 mmol) in CH_2Cl_2 (80 mL) and the resulting mixture was stirred at ambient temperature in the dark for 91 h. Pentane (60 mL) was then added and the precipitates were filtered off through a short pad of Kieselgur which was carefully rinsed with pentanes. The combined filtrates were evaporated to give dibromide **48** as a yellow oil which was pure enough for use in the next step without further purification (12.73 g, quant.). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.69$ (s, 1H), 4.30 (s, 2H), 3.35 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=122.7$, 106.5, 72.1, 57.6 ppm; IR (film): $\tilde{\nu}=3081$, 2991, 2928, 2823, 1702, 1604, 1449, 1191, 1102, 1035, 912, 794, 706 cm^{-1}; MS (EI): m/z (%): 230 (13), 228 (7) [M^+], 199 (12), 151 (68), 149 (70), 121 (23), 119 (35), 117 (12), 107 (9), 105 (10), 95 (33), 93 (28), 69 (12), 55 (51), 45 (100), 41 (53), 39 (100), 37 (13), 29 (39), 27 (20), 26 (11); HRMS (EI): m/z: calcd for $C_4H_6Br_2O$: 227.8786; found: 227.8785; elemental analysis calcd (%) for $C_4H_6Br_2O$: C 20.90, H 2.63, Br 69.51; found: C 20.86, H 2.40, Br 69.36.

(2*E*)-2-Bromo-1-methoxy-2-hexen-4-yne (12): A solution of propynylmagnesium bromide (0.5 M in THF, 144 mL, 72.0 mmol) was slowly added to a solution of $ZnCl_2$ (1.0 M in Et_2O, 72 mL, 72 mmol) at 0°C. After stirring for 45 min at that temperature, $(PPh_3)_4Pd$ (3.20 g, 2.77 mmol, 5 mol%) was added to the white suspension, followed by bromide **48** (12.8 g, 55.7 mmol). After stirring for 15 h at 0°C, the mixture was filtered through a pad of Kieselgur which was rinsed with Et_2O. The combined filtrates were carefully reduced ($T\approx30$°C; $p=450$ mbar) to about $^1/_2$ of the original volume and the precipitated salts were again removed by filtration through Kieselgur. The filtrate was then evaporated and the residue purified by distillation to give product **12** as a pale yellow liquid (41–43°C, 10^{-3} mbar) (6.85 g, ≥95% (GC/MS), 62%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.12$ (app q, $J=2.5$ Hz, 1H), 4.34 (s, 2H), 3.36 (s, 3H), 1.96 ppm (d, $J=2.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 134.3, 116.8, 92.8, 75.1, 72.8, 57.5, 4.5 ppm; IR (film): $\tilde{\nu}=2916$, 2821, 224, 1726, 1449, 1375, 1282, 1190, 1099, 913, 859 cm^{-1}; MS (EI): m/z (%): 190 (14), 188 (15) [M^+], 109 (100), 78 (18), 77 (18), 66 (13), 65 (15), 53 (27), 51 (20), 45 (10), 39 (19); HRMS (EI): m/z: calcd for C_7H_9BrO: 187.9837; found: 187.9839; elemental analysis calcd (%) for C_7H_9BrO: C 44.47, H 4.80, Br 42.27; found: C 44.42, H 4.86, Br 42.34. The stereochemistry was confirmed by comparison with the data of the (*Z*)-configured isomer formed upon isomerization. The following ^{13}C NMR data are most characteristic, see graphic:





The hydroxylated sector

Ethyl (3*S*)-4-azido-3-hydroxybutanoate (51): A mixture of chloride **50** (21.3 g, 128 mmol[42]) and NaN_3 (17.9 g, 275 mmol) in DMF (300 mL) was stirred at 100°C for 48 h. After reaching ambient temperature, the mixture was diluted with *tert*-butyl methyl ether (300 mL) and extracted with aq. sat. NH_4Cl (3×200 mL). The aqueous layers were extracted with *tert*-butyl methyl ether, the combined organic phases were dried over Na_2SO_4 and evaporated, residual DMF was removed in high vacuum (40°C, 2×10^{-2} mbar), and the crude product purified by flash chromatography (hexane/EtOAc 7:3) to give product **51** as a colorless oil (17.1 g, 77%).

$[\alpha]_D^{20} = -12°$ ($c = 1.0$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.16$ (m, 3H), 3.35 (m, 2H), 3.14 (br s, 1H), 2.55 (m, 2H), 1.28 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.9$, 67.3, 60.9, 55.6, 38.5, 14.0 ppm; IR (film): $\tilde{\nu} = 3452$, 2983, 2933, 2097, 1717, 1374, 1270, 1164, 1094, 1024, 925 cm^{-1}; MS (EI): *m/z* (%): 128 (21), 117 (77), 89 (27), 75 (13), 71 (100), 56 (10), 47 (12), 45 (15), 44 (14), 43 (50), 30 (14), 29 (63), 27 (16); HRMS (CI): *m/z*: calcd for $C_6H_{12}N_3O_3$: 174.0879; found: 174.0881 [M^++H]; elemental analysis calcd (%) for $C_6H_{11}N_3O_3$: C 41.61, H 6.40, N 24.27; found: C 41.37, H 6.44, N 24.34.

Ethyl (3*S*)-4-azido-3-(methoxymethoxy)butanoate (52): LiBr (2.43 g, 28 mmol) and *p*TsOH·H_2O (2.5 g, 13 mmol) were added to a solution of compound **51** (19.4 g, 112 mmol) in dimethoxymethane (350 mL) and the resulting mixture was stirred for 116 h. The reaction was quenched with water (200 mL), the aqueous phase was extracted with *tert*-butyl methyl ether (3×100 mL), the combined organic phases were washed with brine and dried over $MgSO_4$, the solvent was evaporated and the residue purified by flash chromatography (hexanes/EtOAc 10:1) to give product **52** (16.96 g, 70%) as a colorless oil and a second fraction of recovered starting material (5.04 g, 21%). $[\alpha]_D^{20} = +3°$ ($c = 1.1$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.71$ (q, $J = 7.0$ Hz, 2H), 4.14 (q, $J = 7.2$ Hz, 2H), 4.13 (m, 1H), 3.43 (dq, $J = 12.8$, 5.0 Hz, 2H), 3.39 (s, 3H), 2.60 (dq, $J = 16.0$, 6.4 Hz, 2H), 1.26 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.5$, 96.5, 73.6, 60,7, 55.7, 54.3, 37.8, 14.1 ppm; IR (film): $\tilde{\nu} = 2939$, 2099, 1731, 1377, 1284, 1149, 1024, 918 cm^{-1}; MS (EI): *m/z* (%): 161 (11), 117 (2), 84 (4), 71 (2), 56 (3), 46 (2), 45 (100), 43 (3), 41 (3), 31 (2), 29 (11), 27 (3); HRMS (ESI+): *m/z*: calcd for $C_8H_{15}N_3NaO_4$: 240.0955; found: 240.0955 [M^++Na]; elemental analysis calcd (%) for $C_8H_{15}N_3O_4$: C 44.23, H 6.96, N 19.34; found: C 44.26, H 6.97, N 19.42.

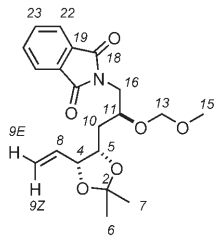
(3*S*)-4-Azido-3-(methoxymethoxy)butanal (53): DIBAl-H (1.0 M in CH_2Cl_2, 8.9 mL, 8.9 mmol) was slowly added to a solution of compound **52** (1.62 g, 7.46 mmol) in CH_2Cl_2 (15 mL) at −78 °C and the resulting mixture was stirred at that temperature of 1 h. For work up, the reaction was quenched with EtOAc (5 mL) and sat. aq. potassium sodium tartrate, and the resulting mixture was stirred at ambient temperature for 30 min until a clear separation of the phases was reached. The aqueous layer was extracted with EtOAc (3×15 mL), the combined organic layers were dried over $MgSO_4$ and evaporated, and the residue adsorbed on Florisil and purified by flash chromatography (hexanes/EtOAc 10:1 → 4:1) to give product **53** as a yellow liquid (1.15 g, 89%). The aldehyde is sensitive and must be kept under Ar at −20 °C. $[\alpha]_D^{20} = -12°$ ($c = 1.1$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.75$ (m, 1H), 4.69 (s, 2H), 4.20 (m, 1H), 3.39 (m, 2H), 3.35 (s, 3H), 2.72 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.5$, 96.4, 71.9, 55.7, 54.1, 46.5 ppm; IR (film): $\tilde{\nu} = 2897$, 2097, 1721, 1444, 1369, 1287, 1151, 1102, 1024, 916 cm^{-1}; MS (EI): *m/z* (%): 117 (16), 45 (100), 41 (4), 31 (4), 29 (10), 27 (3); HRMS (CI): *m/z*: calcd for $C_6H_{12}N_3O_3$: 174.0879; found: 174.0880 [M^++H].

Compound 58: Allenylboronate **56** (587 mg, 4.74 mmol)[45a] was added to a suspension of crystalline $[Ipc_2BH]_2$ (1.45 g, 2.53 mmol) in Et_2O (9.5 mL) at 0 °C and the resulting mixture was stirred at that temperature for 1 h until a clear solution had formed. After cooling to −78 °C, a solution of aldehyde **53** (410 mg, 2.37 mmol) in Et_2O (2.4 mL) was added via syringe pump over a period of 20 min and stirring was continued for 2.5 h once the addition was complete. MeOH (0.88 mL, 20.9 mmol) was introduced at −78 °C and the mixture was then stirred at 0 °C for 15 min before H_2O_2 (30% *w/w*, 1.8 mL) and aq. NaOH (3 M, 3.3 mL, 9.9 mmol) were successively added. The resulting mixture was stirred at ambient temperature for 90 min. For work up, the aqueous layer was extracted with CH_2Cl_2 (7×10 mL), the combined organic phases were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (pentanes/Et_2O 2:1) to give product **58** as a colorless liquid (484 mg, 88%). $[\alpha]_D^{20} = -40°$ ($c = 1.2$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.90$ (ddd, $J = 17.0$, 10.6, 6.3 Hz, 1H), 5.28 (m, 2H), 4.74 (q, $J = 6.4$ Hz, 2H), 4.15 (m, 1H), 3.95 (m, 1H), 3.90 (m, 1H), 3.42 (s, 3H), 3.42 (dd, $J = 12.5$, 4.2 Hz, 1H), 3.32 (dd, $J = 12.7$, 5.9 Hz, 1H), 2.91 (br s, 1H), 2.46 (br s, 1H), 1.68 (ddd, $J = 14.5$, 9.1, 2.5 Hz, 1H), 1.56 ppm (ddd, $J = 14.4$, 10.5, 3.56 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 136.1$, 117.5, 97.4, 75.9, 74.9, 70.1, 55.9, 55.3, 34.3 ppm; IR (film): $\tilde{\nu} = 3247$, 2955, 2892, 2827, 2150, 2101, 1438, 1377, 1348, 1293, 1231, 1150, 1107, 1069, 1043, 1001, 939, 920, 911, 807, 761 cm^{-1}; MS (EI): *m/z* (%): 145 (4), 113 (22), 84 (3), 71 (4), 70 (4), 69 (14), 58 (3), 57 (10), 46 (3), 45 (100), 43 (3), 42 (4), 41 (14), 31 (4), 30 (4), 29 (10), 27 (4); HRMS (CI): *m/z*: calcd for $C_9H_{18}N_3O_4$: 232.1297; found: 232.1295 [M^++H]; elemental analysis calcd (%) for $C_9H_{17}N_3O_4$: C 46.74, H 7.41, N 18.17; found: C 46.85, H 7.48, N 18.23.

1-Azido-1,3,6,7-tetradeoxy-2-*O*-(methoxymethyl)-4,5-*O*-(1-methylethylidene)-D-*arabino*-hept-6-enitol (59): A solution of diol **58** (0.39 g, 1.69 mmol) and *p*TsOH·H_2O (5 mg, 26 μmol, 1.5 mol%) in 2,2-dimethoxypropane (5 mL) was stirred for 30 min. For work up, the solution was diluted with EtOAc (3 mL) and hexane (7 mL) before it was passed through a pad of silica that was carefully rinsed with the same solvents. The combined filtrates were evaporated to give product **59** as a colorless oil, which was pure enough for immediate use in the next step (0.414 g, 90%). $[\alpha]_D^{20} = +12°$ ($c = 1.1$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.77$ (m, 1H), 5.28 (m, 2H), 4.72 (s, 2H), 4.52 (t, $J = 6.9$ Hz, 1H), 4.32 (ddd, $J = 10.6$, 6.3, 2.6 Hz, 1H), 3.89 (dt, $J = 8.9$, 4.2 Hz, 1H), 3.52 (dd, $J = 12.8$, 4.1 Hz, 1H), 3.41 (s, 3H), 3.27 (dd, $J = 12.8$, 4.9 Hz, 1H), 1.60 (m, 2H), 1.46 (s, 3H), 1.34 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 134.0$, 118.4, 108.4, 96.6, 79.4, 74.4 (× 2), 55.8, 55.1, 34.0, 28.1, 25.6 ppm; IR (film): $\tilde{\nu} = 2935$, 2098, 1371, 1214, 1102, 1033, 919 cm^{-1}; MS (EI): *m/z* (%): 157 (7), 125 (5), 98 (36), 95 (25), 83 (11), 69 (11), 67 (5), 57 (5), 55 (7), 45 (100), 43 (27), 41 (16), 39 (5), 29 (6); HRMS (ESI+): *m/z*: calcd for $C_{12}H_{21}N_3NaO_4$: 294.1424; found: 294.1422 [M^++Na]; elemental analysis calcd (%) for $C_{12}H_{21}N_3O_4$: C 53.12, H 7.80, N 15.49; found: C 53.15, H 7.84, N 15.62.

1-Amino-1,3,6,7-tetradeoxy-2-*O*-(methoxymethyl)-4,5-*O*-(1-methylethylidene)-D-*arabino*-hept-6-enitol (60): A solution of azide **59** (414 mg, 1.53 mmol) in Et_2O (10 mL) was slowly added to a suspension of $LiAlH_4$ (200 mg, 5.27 mmol) in Et_2O (10 mL) at 0 °C. The mixture was allowed to stir at ambient temperature for 2 h before the reaction was carefully quenched with water (9 mL) and NaOH (3 M, 7.5 mL). After stirring until a clear separation of the phases was reached, the aqueous layer was extracted with Et_2O (3×20 mL), and the combined organic phases were dried over Na_2SO_4 and evaporated to give amine **60** as a yellow liquid which was used in the next step without further purification (339 mg, 91%). $[\alpha]_D^{20} = +2°$ ($c = 1.0$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.78$ (ddd, $J = 17.2$, 10.4, 7.6 Hz, 1H), 5.27 (m, 2H), 4.71 (s, 2H), 4.51(m, 1H), 4.32 (ddd, $J = 9.6$, 6.3, 3.5 Hz, 1H), 3.71 (quint, $J = 4.5$ Hz, 1H), 3.40 (s, 3H), 2.88 (d, $J = 3.4$ Hz, 1H), 2.70 (br s, 1H), 1.84–1.50 (m, 4H), 1.47 (s, 3H), 1.35 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 134.3$, 118.2, 108.2, 96.5, 79.6, 77.6, 74.6, 55.6, 46.1, 33.7, 28.2, 25.6 ppm; IR (film): $\tilde{\nu} = 2985$, 2933, 1597, 1455, 1370, 1239, 1214, 1150, 1098, 1031, 917, 874 cm^{-1}; MS (EI): *m/z* (%): 230 (11), 156 (6), 113 (11), 108 (10), 98 (17), 96 (5), 95 (16), 85 (5), 83 (9), 70 (5), 69 (13), 68 (7), 67 (8), 59 (12), 56 (10), 55 (6), 45 (100), 43 (17), 41 (14), 30 (53), 29 (5); HRMS (ESI+): *m/z*: calcd for $C_{12}H_{23}NNaO_4$: 268.1519; found: 268.1520 [M^++Na]; elemental analysis calcd (%) for $C_{12}H_{23}NO_4$: C 58.75, H 9.45, N 5.71; found: C 58.67, H 9.45, N 5.79.

1,3,6,7-Tetradeoxy-1-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-*O*-(methoxymethyl)-4,5-*O*-(1-methylethylidene)-D-*arabino*-hept-6-enitol (61): Phthalic anhydride (330 mg, 2.20 mmol) was added to a suspension of amine **60** (650 mg, 2.65 mmol) and molecular sieves (4 Å, 1.1 g) in toluene (4.4 mL) and the resulting mixture was stirred at 80 °C for 48 h. For work up, the molecular sieves were filtered off, the filtrate was evaporated and the residue purified by flash chromatography (hexanes/EtOAc 4:1 → 2:1) to give product **61** as a pale yellow liquid (732 mg, 88%). ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.86$ (m, 2H, H-22), 7.72 (m, 2H, H-23), 5.77 (ddd, $J = 17.1$, 10.3, 7.8 Hz, 1H, H-8), 5.30 (ddd, $J = 17.1$, 1.6, 1.1 Hz, 1H, H-9Z), 5.17 (ddd, $J = 10.3$, 1.6, 0.9 Hz, 1H, H-9E), 4.60 (d, $J = 7.0$ Hz, 1H, H-13a), 4.57 (d, $J = 7.0$ Hz, 1H, H-13b), 4.55 (ddt, $J = 7.7$, 6.2, 1.8 Hz, 1H, H-4), 4.46 (ddd, $J = 8.4$, 6.1, 5.1 Hz, 1H, H-5), 4.06 (dq, $J = 6.2$, 4.4 Hz, 1H, H-11), 3.91 (dd, $J = 14.3$, 6.5 Hz, 1H, H-16a), 3.76 (dd, $J = 14.3$,



4.4 Hz, 1H, H-16b), 3.22 (s, 3H), 1.80 (ddd, $J=14.4$, 8.4, 6.1 Hz, 1H, H-10a), 1.71 (ddd, $J=14.3$, 5.9, 5.1 Hz, 1H, H-10b), 1.48 (s, 3H, H-6), 1.37 ppm (s, 3H, H-7); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=168.5$ (C-18), 134.3 (C-8), 134.0 (C-23), 132.1 (C-19), 123.2 (C-22), 118.6 (C-9), 108.4 (C-2), 95.9 (C-13), 79.8 (C-4), 74.4 (C-5), 73.0 (C-11), 55.7 (C-15), 41.0 (C-16), 33.9 (C-10), 28.2 (C-6), 25.7 ppm (C-7); IR (film): $\tilde{\nu}=3082$, 2986, 2936, 2897, 2824, 1775, 1715, 1645, 1615, 1468, 1430, 1396, 1381, 1325, 1239, 1216, 1191, 1155, 1134, 1102, 1038, 920, 867, 725, 714, 530 cm^{-1}; MS (EI): m/z (%): 360 (22), 256 (11), 206 (7), 205 (37), 188 (11), 186 (10), 175 (6), 174 (11), 173 (75), 161 (13), 160 (97), 157 (13), 153 (12), 133 (5), 125 (9), 121 (7), 113 (6), 109 (7), 104 (6), 99 (7), 98 (91), 95 (33), 85 (7), 83 (17), 77 (8), 70 (6), 69 (22), 67 (5), 59 (9), 58 (7), 55 (8), 45 (100), 43 (22), 41 (12); HRMS (ESI+): m/z: calcd for $C_{20}H_{25}NNaO_6$: 398.1574; found: 398.1576 [M^++Na]; elemental analysis calcd (%) for $C_{20}H_{25}NO_6$: C 63.99, H 6.71, N 3.73; found: C 64.11, H 6.67, N 3.71.

The α-hydroxyacid segment

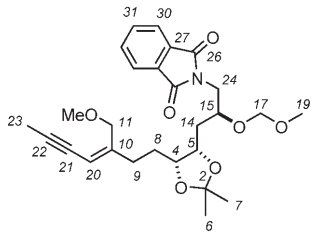
Benzyl (2*S*)-2-hydroxypentanoate: nBu$_4$NI (1.28 g, 0.347 mmol) and benzyl bromide (4.75 mL, 39.9 mmol) were added to a suspension of acid **68** (4.10 g, 34.7 mmol)[56] and K_2CO_3 (5.50 g, 39.9 mmol) in acetone (175 mL) and the resulting mixture was stirred under reflux for 24 h. After reaching ambient temperature, all insoluble materials were filtered off through a pad of Celite which was carefully rinsed with acetone, the combined filtrates were evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 20:1 → 10:1) to give the title compound as a colorless liquid (5.0 g, 69%). $[\alpha]_D^{20}=-5°$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.40$–7.34 (m, 5H), 5.21 (s, 2H), 4.23 (dd, $J=7.6$, 4.2 Hz, 1H), 2.7 (br s, 1H), 1.81–1.73 (m, 1H), 1.69–1.59 (m, 1H), 1.50–1.38 (m, 2H), 0.93 ppm (t, $J=4.05$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.3$, 135.2, 128.6, 128.5, 128.3, 70.3, 67.2, 36.4, 18.0, 13.7 ppm; IR (film): $\tilde{\nu}=3464$, 2960, 2874, 1731, 1456, 1262, 1195, 1128, 1073, 736, 696 cm^{-1}; MS (EI): m/z (%): 208 (8) [M^+], 108 (3), 107 (3), 92 (24), 91 (100), 79 (4), 77 (5), 73 (54), 65 (12), 56 (3), 55 (72), 51 (3), 43 (24), 41 (5), 39 (6), 31 (10), 29 (6), 27 (5); HRMS (EI): m/z: calcd for $C_{12}H_{16}O_3$: 208.1100; found: 208.1097; elemental analysis calcd (%) for $C_{12}H_{16}O_3$: C 69.21, H 7.74; found: C 69.09, H 7.65.

Benzyl (2*S*)-2-((*tert*-butyl(diphenyl)silyl)oxy)pentanoate (69): A solution of benzyl (2*S*)-2-hydroxypentanoate (2 g, 96 mmol), imidazole (0.85 g, 13 mmol), and TBDPSCl (2.8 mL, 11 mmol) in CH_2Cl_2 (50 mL) was stirred for 5 h before it was adsorbed on silica. The product was isolated by flash chromatography (hexanes/EtOAc 20:1) in form of a colorless liquid (4.2 g, 98%). $[\alpha]_D^{20}=-37°$ ($c=1.1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.66$–7.61 (m, 4H), 7.43–7.29 (m, 9H), 7.20–7.18 (m, 2H), 4.93 (d, $J=12.3$ Hz, 1H), 4.89 (d, $J=12.3$ Hz, 1H), 4.28 (t, $J=5.7$ Hz, 1H), 1.78–1.62 (m, 2H), 1.47–1.26 (m, 2H), 1.08 (s, 9H), 0.83 ppm (t, $J=7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=173.1$, 136.0, 135.8, 135.7, 133.5, 133.3, 129.7, 129.7, 128.4, 128.2, 128.1, 127.6, 127.5, 72.6, 66.1, 37.3, 26.9, 19.4, 17.8, 13.9 ppm; IR (film): $\tilde{\nu}=3070$, 3048, 3034, 2998, 2959, 2932, 2893, 2858, 1754, 1734, 1589, 1498, 1487, 1472, 1457, 1428, 1390, 1362, 1313, 1268, 1213, 1185, 1136, 1113, 1043, 999, 939, 895, 822, 741, 701, 613, 508, 488 cm^{-1}; MS (EI): m/z (%): 390 (5), 389 (16), 361 (12), 221 (11), 199 (6), 183 (6), 135 (7), 92 (8), 91 (100); HRMS (ESI+): m/z: calcd for $C_{28}H_{34}NaO_3Si$: 469.2169; found: 469.2169 [M^++Na]; elemental analysis calcd (%) for $C_{28}H_{34}O_3Si$: C 75.29, H 7.67; found: C 75.38, H 7.65.

(2*S*)-2-((*tert*-Butyl(diphenyl)silyl)oxy)pentanoic acid (70): A mixture containing compound **69** (9.17 g, 20.5 mmol) and palladium on charcoal (10% *w*/*w*, 1.31 g) in EtOAc (100 mL) and EtOH (100 mL) was stirred for 30 h under an atmosphere of H_2. For work up, the catalyst was filtered off through a short pad of Celite which was carefully rinsed with EtOH, the combined filtrates were evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 10:1 → 4:1) to give product **70** as colorless crystals (4.58 g, 63%). Crystals suitable for X-ray analysis were obtained by recrystallization from hexane. M.p. 96–97°C; $[\alpha]_D^{20}=-14°$ ($c=0.7$, $CHCl_3$); *de* > 99% (HPLC: column: 250 mm Chiralpak AD, ∅ 4.6 mm; eluent: *n*-heptane/2-propanol/TFA 99:1:0.1; 0.5 mL min^{-1}; $T=298$ K; 1.6 MPa; $t_R=34.40$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.60$ (br s, 1H), 7.69–7.64 (m, 4H), 7.48–7.36 (m, 6H), 4.30 (t, $J=5.2$ Hz, 1H), 1.75–1.66 (m, 1H), 1.63–1.41 (m, 2H), 1.37–1.23 (m, 1H), 1.13 (s, 9H), 0.82 ppm (t, $J=7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=176.9$, 135.8, 135.7, 132.9, 132.3, 130.1, 127.8, 72.5, 36.7, 26.9, 19.3, 17.3, 13.8 ppm; IR (film): $\tilde{\nu}=3072$, 3019, 2963, 2932, 2859, 2688, 2579, 1712, 1589, 1473, 1464, 1430, 1273, 1230, 1145, 1112, 1090, 1039, 892, 824, 816, 745, 708, 686, 611, 505, 487 cm^{-1}; MS (EI): m/z (%): 300 (11), 299 (46), 271 (10), 200 (18), 199 (100), 139 (44); HRMS (ESI+): m/z: calcd for $C_{21}H_{28}NaO_3Si$: 379.1700; found: 379.1695 [M^++Na]; elemental analysis calcd (%) for $C_{21}H_{28}NaO_3Si$: C 70.74, H 7.92, Si 7.88; found: C 70.66, H 7.85, Si 7.78.

Fragment couplings and completion of the total synthesis

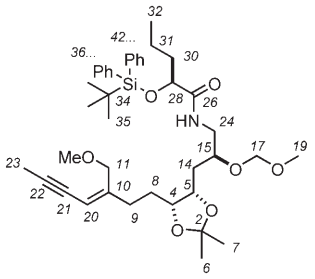
Compound 71: 9-H-9-BBN dimer (330 mg, 0.7 mmol of dimer) was added to a solution of compound **61** (676 mg, 1.80 mmol) in THF



(2.6 mL) at 0°C and the resulting mixture was stirred at ambient temperature for 2 h. Excess 9-H-9-BBN was quenched with water (0.4 mL) and the resulting solution was transferred via canula into a mixture of bromide **12** (511 mg, 2.70 mmol), Cs_2CO_3 (1.09 g, 3.35 mmol), Ph_3As (97%, 85 mg, 0.27 mmol) and [$PdCl_2$(dppf)]·CH_2Cl_2 (103 mg, 0.126 mmol) in THF (15 mL) and water (0.5 mL). The mixture was stirred at ambient temperature for 17 h before the solvent was evaporated and the residue purified by flash chromatography (hexanes/EtOAc 50:1 → 4:1) to give product **71** as a pale yellow liquid (696 mg, 81%). $[\alpha]_D^{20}=-1°$ ($c=0.8$, $CHCl_3$); *de* > 99% (HPLC: column: 125 mm Nucleodur 100-5-C18ec, ∅ 4.0 mm; eluent: MeCN/H_2O 45:55; 0.8 mL min^{-1}; $T=308$ K; 5.5 MPa; $t_R=38.23$ min); ^{1}H NMR (600 MHz, CD_2Cl_2): $\delta=7.84$ (m, 2H, H-30), 7.73 (m, 2H, H-31), 5.43 (m, 1H, H-20), 4.65 (d, $J=6.9$ Hz, 1H, H-17a), 4.60 (d, $J=6.9$ Hz, 1H, H-17b), 4.21 (ddd, $J=10.8$, 5.7, 2.7 Hz, 1H, H-5), 4.14 (d, $J=12.0$ Hz, 1H, H-11a), 4.12 (d, $J=12.0$ Hz, 1H, H-11b), 4.09 (dddd, $J=9.7$, 7.0, 4.9, 3.2 Hz, 1H, H-15), 4.02 (ddd, $J=9.4$, 5.7, 4.3 Hz, 1H, H-4), 3.82 (dd, $J=14.1$, 7.0 Hz, 1H, H-24a), 3.72 (dd, $J=14.1$, 5.0 Hz, 1H, H-24b), 3.28 (s, 3H, H-13), 3.15 (s, 3H, H-19), 2.32 (ddd, $J=15.0$, 10.0, 5.0 Hz, 1H, H-9a), 2.12 (ddd, $J=15.0$, 10.0, 6.0 Hz, 1H, H-9b), 1.97 (d, $J=2.4$ Hz, 3H, H-23), 1.65 (ddd, $J=14.1$, 10.8, 3.2 Hz, 1H, H-14a), 1.58 (m, 1H, H-8a), 1.54 (ddd, $J=14.1$, 9.8, 2.6 Hz, 1H, H-14b), 1.51 (m, 1H, H-8b), 1.34 (s, 3H, H-6), 1.28 ppm (s, 3H, H-7); ^{13}C NMR (150 MHz, CD_2Cl_2): $\delta=168.7$ (C-26), 149.7 (C-10), 134.3 (C-31), 132.6 (C-27), 123.4 (C-30), 108.7 (C-20), 108.0 (C-2), 97.2 (C-17), 90.3 (C-22), 77.6 (C-4), 76.3 (C-21), 74.4 (C-5), 73.9 (C-15), 71.6 (C-11), 58.1 (C-13), 56.0 (C-19), 42.5 (C-24), 34.4 (C-14), 30.6 (C-9), 28.6 (C-6), 28.5 (C-8), 26.1 (C-7), 4.4 ppm (C-23); IR (film): $\tilde{\nu}=2984$, 2932, 2824, 2220, 1774, 1716, 1615, 1467, 1432, 1396, 1324, 1243, 1218, 1191, 1155, 1134, 1100, 1072, 1036, 964, 918, 866, 794, 725, 714, 530 cm^{-1}; MS (ESI+): 508 [M^++Na]; HRMS (ESI+): m/z: calcd for $C_{27}H_{35}NNaO_7$: 508.2306; found: 508.2308 [M^++Na]; elemental analysis calcd (%) for $C_{27}H_{35}NO_7$: C 66.79, H 7.27, N 2.88; found: C 66.84, H 7.23, N 2.88.

Compound 73: Hydrazine monohydrate (16 μL, 0.32 mmol) was added to a solution of compound **71** (52.2 mg, 108 μmol) in EtOH (1.1 mL) and the mixture was stirred for 2.5 h at 60°C. The precipitate formed was filtered off and the filtrate was evaporated to give crude amine **72** which was immediately used in the next step without further purification.

A solution of this crude amine, EDC·HCl (57.7 mg, 0.301 mmol), 1-HOBt (42 mg, 0.31 mmol), (iPr)$_2$NEt (71 μL, 0.43 mmol) and acid **70** (77 mg, 0.22 mmol) in CH_2Cl_2 (0.5 mL) was stirred for 8 h at ambient temperature. The mixture was adsorbed on silica and the product was purified by flash chromatography (hexanes/EtOAc 7:1 → 4:1) to give compound **73** as a colorless liquid (57.6 mg, 77% over both steps). $[\alpha]_D^{20}=$

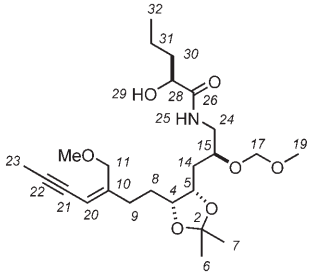


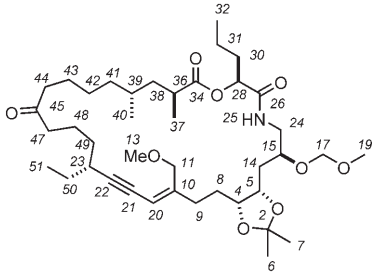
$-24°$ ($c=0.5$, $CHCl_3$); ^1H NMR (600 MHz, CD_2Cl_2): $\delta=7.67$ (m, 2H, H-37), 7.61 (m, 2H, H-43), 7.46 (m, 1H, H-39), 7.45 (m, 1H, H-45), 7.39 (m, 2H, H-38), 7.38 (m, 2H, H-44), 7.12 (t, $J=6.0$ Hz, 1H, H-25), 5.38 (m, $J=2.4$ Hz, 1H, H-20), 4.70 (d, $J=6.7$ Hz, 1H, H-17a), 4.67 (d, $J=6.7$ Hz, 1H, H-17b), 4.23 (dd, $J=5.3$, 4.1 Hz, 1H, H-28), 4.20 (dt, $J=7.5$, 5.9 Hz, 1H, H-5), 4.11 (d, $J=12.0$ Hz, 1H, H-11a), 4.09 (d, $J=12.0$ Hz, 1H, H-11b), 3.99 (ddd, $J=10.0$, 5.8, 3.6 Hz, 1H, H-4), 3.83 (m, 1H, H-15), 3.55 (ddd, $J=13.9$, 6.1, 4.2 Hz, 1H, H-24a), 3.37 (s, 3H, H-19), 3.27 (s, 3H, H-13), 3.21 (ddd, $J=13.9$, 6.0, 4.8 Hz, 1H, H-24b), 2.32 (ddd, $J=15.0$, 10.0, 5.0 Hz, 1H, H-9a), 2.11 (ddd, $J=15.0$, 10.0, 6.0 Hz, 1H, H-9b), 1.96 (d, $J=2.4$ Hz, 3H, H-23), 1.62 (m, 1H, H-30a), 1.54 (m, 2H, H-14), 1.52 (m, 1H), 1.43 (m, 1H, H-8), 1.39 (s, 3H, H-6), 1.38 (m, 1H, H-31a), 1.37 (m, 1H, H-30b), 1.30 (s, 3H, H-7), 1.17 (m, 1H, H-31b), 1.11 (s, 9H, H-35), 0.74 ppm (t, $J=7.3$ Hz, 3H, H-32); ^{13}C NMR (150 MHz, CD_2Cl_2): $\delta=173.2$ (C-26), 149.7 (C-10), 136.2 (C-37), 136.1 (C-43), 133.6 (C-36), 133.2 (C-42), 130.4 (2 C, C-39, C-45), 128.2 (C-44), 128.1 (C-38), 108.7 (C-20), 108.0 (C-2), 96.9 (C-17), 90.3 (C-22), 77.6 (C-4), 76.4 (C-21), 75.1 (C-15), 74.7 (C-28), 74.5 (C-5), 71.6 (C-11), 58.1 (C-13), 55.9 (C-19), 43.2 (C-24), 37.2 (C-30), 33.9 (C-14), 30.5 (C-9), 28.7 (C-6), 28.5 (C-8), 27.2 (C-35), 26.1 (C-7), 19.5 (C-34), 17.2 (C-31), 14.1 (C-32), 4.4 ppm (C-23); IR (film): $\tilde{\nu}=3432$, 3072, 3049, 2958, 2931, 2859, 2821, 2220, 1720, 681, 1589, 1518, 1488, 1463, 1428, 1379, 1368, 1346, 1246, 1218, 1153, 1111, 1036, 919, 895, 863, 822, 742, 703, 612, 506 cm^{-1}; MS (EI): m/z (%): 694 (5), 693 (9) [M^+], 638 (15), 637 (45), 636 (100), 604 (13), 578 (13), 546 (22), 338 (11), 298 (13), 213 (11), 199 (45), 197 (19), 183 (14), 139 (14), 135 (50), 91 (11), 45 (31); HRMS (ESI+): m/z: calcd for $C_{40}H_{59}NNaO_7Si$: 716.3953; found: 716.3945 [M^++Na]; elemental analysis calcd (%) for $C_{40}H_{59}NO_7Si$: C 69.23, H 8.57, N 2.02; found: C 69.17, H 8.48, N 1.88.

Compound 74: A solution of compound **73** (57.7 mg, 83.1 μmol) and TBAF (1.0 M in THF, 108 μL, 108 μmol) in THF (0.5 mL) was stirred for 14 h. Evaporation of the solvent followed by flash chromatography of the crude material (hexanes/EtOAc 1:1 → 1:2) gave product **74** as a colorless liquid (34.3 mg, 90%). $[\alpha]_D^{20}=-17°$ ($c=0.9$, $CHCl_3$); ^1H NMR (600 MHz, CD_2Cl_2): $\delta=6.95$ (m, 1H, H-25), 5.44 (m, 1H, H-20), 4.71 (d, $J=6.7$ Hz, 1H, H-17a), 4.67 (d, $J=6.7$ Hz, 1H, H-17b), 4.20 (ddd, $J=9.3$, 5.8, 4.3 Hz, 1H, H-5), 4.15 (d, $J=12.0$ Hz, 1H), 4.13 (d, $J=12.0$ Hz, 1H, H-11), 4.06 (ddd, $J=8.0$, 5.1, 3.8 Hz, 1H, H-28), 4.04 (ddd, $J=9.2$, 5.7, 4.6 Hz, 1H, H-4), 3.80 (m, 1H, H-15), 3.52 (ddd, $J=14.0$, 6.2, 3.7 Hz, 1H, H-24a), 3.39 (s, 3H, H-19), 3.28 (s, 3H, H-13), 3.23 (ddd, $J=14.0$, 6.2, 5.3 Hz, 1H, H-24b), 2.78 (d, $J=5.2$ Hz, 1H, H-29), 2.31 (ddd, $J=15.0$, 10.0, 5.0 Hz, 1H, H-9a), 2.11 (ddd, $J=15.0$, 10.0, 6.0 Hz, 1H, H-9b), 1.96 (d, $J=2.4$ Hz, 3H, H-23), 1.75 (m, 1H, H-30a), 1.58 (m, 1H), 1.57 (m, 1H, H-30b), 1.56 (m, 2H, H-14), 1.53 (m, 1H, H-8), 1.44 (m, 2H, H-31), 1.39 (s, 3H, H-6), 1.30 (s, 3H, H-7), 0.94 ppm (t, $J=7.4$ Hz, 3H, H-32); ^{13}C NMR (150 MHz, CD_2Cl_2): $\delta=174.2$ (C-26), 149.5 (C-10), 108.9 (C-20), 108.0 (C-2), 97.4 (C-17), 90.4 (C-22), 77.6 (C-4), 76.3 (C-21), 76.2 (C-15), 74.4 (C-5), 72.1 (C-28), 71.6 (C-11), 58.0 (C-13), 55.9 (C-19), 43.7 (C-24), 37.5 (C-30), 34.0 (C-14), 30.5 (C-9), 28.7 (C-6), 28.6 (C-8), 26.1 (C-7), 18.7 (C-31), 14.0 (C-32), 4.4 ppm (C-23); IR (film): $\tilde{\nu}=3398$, 2982, 2957, 2931, 2874, 2822, 2220, 1715, 1654, 1534, 1454, 1379, 1369, 1246, 1218, 1154, 1101, 1059, 1034, 917, 868 cm^{-1}; MS (EI): m/z (%): 456 (5), 455 (18) [M^+], 199 (15), 187 (16), 186 (24), 175 (25), 143 (24), 135 (19), 133 (21), 131 (17), 130 (20), 119 (15), 109 (19), 105 (22), 101 (18), 93 (18), 91 (25), 55 (29), 45 (100), 43 (25), 30 (54); HRMS (EI): m/z: calcd for $C_{24}H_{41}NO_7$: 455.2883; found: 455.2882; elemental analysis calcd (%) for $C_{24}H_{41}NO_7$: C 63.27, H 9.07, N 3.07; found: C 63.18, H 8.92, N 3.02.

Compound 75: A solution containing compound **74** (24.4 mg, 53.6 μmol), acid **70** (13.3 mg, 41.2 μmol), Et_3N (11.6 μL, 82.4 μmol), DMAP (10.1 mg, 82.4 μmol), EDC·HCl (15.8 mg, 82.4 μmol) and 1-HOBt (11.4 mg, 82.4 μmol) in CH_2Cl_2 (0.2 mL) was stirred for 1 h before additional EDC·HCl (11.8 mg, 61.6 μmol) and DMAP (15.2 mg, 124.4 μmol) were introduced and stirring continued for 18 h. The mixture was then adsorbed on silica and the product purified by flash chromatography (hexanes/EtOAc 10:1 → 4:1) to give compound **75** as a colorless liquid (20.3 mg, 65%). $[\alpha]_D^{20}=-5°$ ($c=0.1$, $CHCl_3$); ^1H NMR (600 MHz, CD_2Cl_2): $\delta=6.62$ (t, $J=5.6$ Hz, 1H), 5.44 (m, 1H), 5.07 (dd, $J=6.1$ Hz, 1H), 4.70 (d, $J=6.6$ Hz, 1H), 4.66 (d, $J=6.6$ Hz, 1H), 4.18 (m, 1H), 4.15 (d, $J=12.0$ Hz, 1H), 4.12 (d, $J=12.0$ Hz, 1H), 4.02 (ddd, $J=9.7$, 5.7, 4.3 Hz, 1H), 3.78 (m, 1H), 3.54 (ddd, $J=14.0$, 6.2, 3.6 Hz, 1H), 3.38 (s, 3H), 3.28 (s, 3H), 3.18 (dt, $J=14.0$, 5.7 Hz, 1H), 2.58 (m, 1H), 2.36 (m, 5H), 2.16 (m, 2H), 1.96 (d, $J=2.3$ Hz, 3H), 1.78 (d, $J=2.4$ Hz, 3H), 1.82–1.23 (m, 23H), 1.39 (s, 3H), 1.30 (s, 3H), 1.17 (d, $J=7.0$ Hz, 3H), 0.96 (t, $J=7.3$ Hz, 3H), 0.92 (t, $J=7.3$ Hz, 3H), 0.85 ppm (d, $J=6.2$ Hz, 3H); ^{13}C NMR (150 MHz, CD_2Cl_2): $\delta=210.8$, 175.8, 170.0, 149.4, 108.4, 107.7, 97.0, 90.0, 82.1, 77.3, 76.7, 76.0, 75.8, 74.1, 73.8, 71.4, 57.8, 55.5, 43.4, 42.7, 42.6, 40.6, 37.4, 37.1, 34.6, 34.1, 33.6, 33.4, 30.4, 30.3, 28.4 (2 C), 28.2, 26.6, 25.8, 24.1, 21.9, 19.0, 18.3, 16.8, 13.6, 11.6, 4.1, 3.1 ppm; IR (film): $\tilde{\nu}=3446$, 3349, 2957, 2925, 2873, 2856, 2823, 2220, 1739, 1713, 1688, 1527, 1459, 1409, 1378, 1245, 1218, 1153, 1106, 1061, 1034, 964, 918, 865 cm^{-1}; MS (ESI+): 782 [M^++Na]; HRMS (ESI+): m/z: calcd for $C_{44}H_{73}NNaO_9$: 782.5178; found: 782.5186 [M^++Na]; elemental analysis calcd (%) for $C_{44}H_{73}NO_9$: C 69.53, H 9.68, N 1.84; found: C 69.70, H 9.57, N 1.77.

Compound 76: A solution of complex **20** (12.7 mg, 20.3 μmol) in toluene (6 mL) and CH_2Cl_2 (78 μL, 1.2 mmol) was added to a solution of substrate **75** (31 mg, 41 μmol) in toluene (35 mL) and the resulting mixture was stirred at 80 °C for 14 h. A standard extractive work up followed by flash chromatography (hexanes/EtOAc 4:1 → 3:1) gave product **76** as a pale yellow liquid (22.6 mg, 79%). $[\alpha]_D^{20}=-9°$ ($c=0.9$, toluene); ^1H NMR (600 MHz, C_6D_6): $\delta=6.17$ (br dd, $J=6.4$, 4.4 Hz, 1H, H-25), 5.66 (m, 1H, H-20), 5.24 (dd, $J=7.7$, 5.0 Hz, 1H, H-28), 4.55 (d, $J=6.7$ Hz, 1H, H-17a), 4.53 (d, $J=6.7$ Hz, 1H, H-17b), 4.37 (d, $J=11.9$ Hz, 1H, H-11a), 4.34 (d, $J=11.9$ Hz, 1H, H-11b), 4.18 (m, 1H, H-5), 3.97 (m, 1H, H-4), 3.88 (m, 1H, H-15), 3.55 (ddd, $J=14.0$, 7.2, 3.2 Hz, 1H, H-24a), 3.41 (dt, $J=13.9$, 4.5 Hz, 1H, H-24b), 3.26 (s, 3H, H-13), 3.17 (s, 3H, H-19), 2.58 (m, 1H, H-36), 2.52 (m, 1H, H-9a), 2.30 (m, 1H, H-9b), 2.25 (m, 1H, H-23), 2.22 (m, 1H, H-47a), 2.18 (m, 1H, H-44a), 2.15 (m, 1H, H-44b), 2.09 (m, 1H, H-47b), 1.85 (m, 3H, H-30, H-48a), 1.73–1.52 (m, 8H, H-8, H-

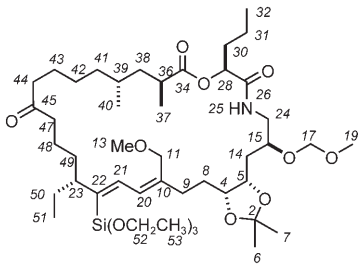




14, H-38a, H-43, H-48b), 1.49 (m, 1H, H-39), 1.44–1.21 (m, 10H, H-31, H-38b, H-41a, H-42, H-49, H-50), 1.41 (s, 3H, H-6), 1.27 (s, 3H, H-7), 1.13 (d, J=6.9 Hz, 3H, H-37), 1.08 (m, 1H, H-41b), 0.98 (t, J=7.4 Hz, 3H, H-51), 0.83 (d, J=6.9 Hz, 3H, H-40), 0.81 ppm (t, J=7.4 Hz, 3H, H-32); ^{13}C NMR (150 MHz, C_6D_6): δ=209.0 (C-45), 175.7 (C-34), 169.8 (C-26), 149.9 (C-10), 109.0 (C-20), 107.7 (C-2), 97.4 (C-22), 96.5 (C-17), 79.7 (C-21), 77.2 (C-4), 74.8 (C-15), 74.5 (C-5), 74.3 (C-28), 71.9 (C-11), 57.9 (C-13), 55.4 (C-19), 42.8 (C-47), 42.6 (C-24), 41.9 (C-44), 41.2 (C-38), 37.7, 36.9 (C-41), 34.6 (C-23, C-49), 34.3 (C-30), 33.3 (C-14), 30.7 (C-9, C-36), 30.5 (C-39), 28.8 (C-6, C-50), 28.4 (C-8), 26.7 (C-42), 26.1 (C-7), 24.2 (C-43), 23.0 (C-48), 19.9 (C-40), 18.7 (C-31), 17.2 (C-37), 13.8 (C-32), 12.1 ppm (C-51); IR (film): $\tilde{\nu}$=3445, 3342, 2960, 2930, 2874, 2822, 2209, 1739, 1710, 1691, 1525, 1459, 1406, 1378, 1218, 1153, 1099, 1034, 918, 863 cm^{-1}; MS (ESI+): 728 [M^++Na]; HRMS (ESI+): m/z: calcd for $C_{40}H_{68}NO_9$: 706.4889; found: 706.4891 [M^++H].

Hydrosilylation: A mixture of substrate **76** (9.3 mg, 13 μmol), $(EtO)_3SiH$ (95%, 5.1 μL, 26 μmol), $[CpRu(MeCN)_3]PF_6$ (**3b**) (1.7 mg, 3.9 μmol, 30 mol%) in toluene (65 μL) was vigorously stirred for 75 min. For work up, tris(hydroxymethyl)phosphine (1 mg, 8 μmol) was introduced and stirring continued for 30 min before the mixture was filtered through a short pad of silica which was carefully rinsed with EtOAc (3 mL). Evaporation of the solvent, removal of residual silane in high vacuum, and purification of the residue by preparative TLC (hexanes/EtOAc 1.5:1) gave two product containing fractions. The faster moving fraction consisted of two isomeric products (**78**, 6.0 mg, 53%), whereas the slower moving fraction contained isomer **77** in pure form (1.5 mg, 13%).

Isomer 77: ^{1}H NMR (600 MHz, C_6D_6): δ=7.19 (d, J=11.8 Hz, 1H, H-21), 7.01 (d, J=11.7 Hz, 1H, H-20), 6.22 (dd, J=6.6, 5.0 Hz, 1H, H-25),

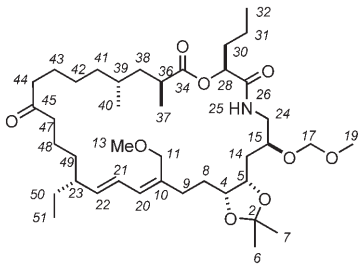


5.24 (dd, J=7.5, 5.1 Hz, 1H, H-28), 4.56 (d, J=6.6 Hz, 1H, H-17a), 4.55 (d, J=6.6 Hz, 1H, H-17b), 4.21 (m, 1H, H-5), 4.16 (dd, J=12.0, 0.6 Hz, 1H, H-11a), 4.12 (d, J=12.0 Hz, 1H, H-11b), 4.02 (ddd, J=9.7, 5.9, 3.9 Hz, 1H, H-4), 3.91 (m, 1H, H-15), 3.91 (q, J=7.0 Hz, 6H, H-52), 3.53 (ddd, J=14.1, 6.9, 3.5 Hz, 1H, H-24a), 3.45 (ddd, J=13.9, 4.5, 4.4 Hz, 1H, H-24b), 3.22 (s, 3H, H-13), 3.17 (s, 3H, H-19), 2.59 (m, 1H, H-9a), 2.58 (m, 1H, H-36), 2.39 (m, 1H, H-9b), 2.38 (m, 1H, H-23), 2.25 (m, 1H, H-47a), 2.14 (m, 2H, H-44), 2.13 (m, 1H, H-47b), 1.86 (m, 2H, H-30), 1.77 (m, 2H, H-48a, H-50a), 1.75 (m, 1H, H-8a), 1.74 (m, 1H, H-49a), 1.67 (m, 1H, H-8b), 1.65 (m, 1H, H-38a), 1.62 (m, 2H, H-14), 1.57 (m, 1H, H-48b), 1.56 (m, 1H, H-50b), 1.54 (m, 2H, H-43), 1.50 (m, 1H, H-39), 1.49 (m, 1H, H-49b), 1.45 (s, 3H, H-6), 1.39 (m, 2H, H-31), 1.36 (m, 1H, H-38b), 1.30 (s, 3H, H-7), 1.29 (m, 1H), 1.26 (t, J=7.0 Hz, 9H, H-53), 1.21 (m, 2H, H-42), 1.12 (d, J=6.9 Hz, 3H, H-37), 1.06 (m, 1H, H-41), 1.00 (t, J=7.4 Hz, 3H, H-51), 0.82 (d, J=6.6 Hz, 3H, H-40), 0.81 ppm (t, J=7.4 Hz, 3H, H-32); ^{13}C NMR (150 MHz, C_6D_6): δ=209.3 (C-45), 175.7 (C-34), 169.8 (C-26), 140.0 (C-10), 139.8 (C-22), 139.6 (C-21), 128.9 (C-20), 107.7 (C-2), 96.5 (C-17), 77.4 (C-4), 74.9 (C-15), 74.6 (C-5), 74.2 (C-28), 69.7 (C-11), 58.6 (C-52), 57.8 (C-13), 55.3 (C-19), 48.8 (C-23), 43.4 (C-47), 42.7 (C-24), 41.9 (C-44), 41.2 (C-38), 37.6 (C-36), 36.9 (C-41), 34.4 (C-49), 34.3 (C-30), 33.4 (C-14), 33.2 (C-9), 30.4 (C-39), 29.5 (C-8), 29.1 (C-50), 28.9 (C-6), 26.7 (C-42), 26.2 (C-7), 24.1 (C-43), 23.1 (C-48), 19.8 (C-40), 18.7 (C-31), 18.6 (C-53), 17.1 (C-37), 13.8 (C-32), 12.6 ppm (C-51).

Isomeric compounds **78**: ^{1}H NMR (600 MHz, C_6D_6): δ=6.77 (dd, J=6.1, 5.2 Hz, 1H), 6.12 (dd, J=9.5, 1.9 Hz, 1H), 6.11 (s, 1H), 5.49 (dd, J=8.1, 4.6 Hz, 1H), 4.65 (d, J=6.2 Hz, 1H), 4.63 (d, J=6.2 Hz, 1H), 4.33 (m, 1H), 4.23 (ddd, J=9.6, 5.8, 4.0 Hz, 1H), 4.16 (d, J=11.3 Hz, 1H), 4.11 (d, J=11.2 Hz, 1H), 3.97 (m, 1H), 3.90 (q, J=7.0 Hz, 6H), 3.77 (ddd, J=14.0, 6.5, 3.2 Hz, 1H), 3.30 (ddd, J=14.0, 7.0, 5.0 Hz, 1H), 3.26 (s, 3H), 3.19 (s, 3H), 2.64 (m, 1H), 2.61 (m, 1H), 2.47 (m, 1H), 2.45 (m, 1H), 2.11 (m, 2H), 2.07 (m, 2H), 1.95 (m, 1H), 1.87 (m, 1H), 1.86 (m, 1H), 1.78 (m, 1H), 1.76 (m, 1H), 1.64 (m, 2H), 1.60 (m, 2H), 1.57 (m, 2H), 1.52 (m, 1H), 1.43 (s, 3H), 1.42–1.35 (m, 4H), 1.34 (s, 3H), 1.27 (m, 1H), 1.26 (m, 1H), 1.22 (t, J=7.0 Hz, 9H), 1.22 (m, 2H), 1.16 (m, 1H), 1.15 (m, 1H), 1.11 (d, J=6.9 Hz, 3H), 0.99 (m, 1H), 0.93 (t, J=7.4 Hz, 3H), 0.85 (d, J=6.6 Hz, 3H), 0.80 ppm (t, J=7.4 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ=208.7, 175.6, 169.6, 151.5, 137.7, 133.0, 126.6, 107.8, 97.6, 77.2, 76.8, 74.4, 74.2, 71.5, 58.9, 58.2, 55.2, 43.8, 42.7, 42.6, 41.8, 41.2, 37.2, 36.5, 34.5 (2 C), 34.2, 31.2, 30.7, 28.8, 28.6, 28.0, 27.2, 26.2, 24.0, 22.2, 20.2, 18.8, 18.5, 17.9, 13.8, 12.0 ppm.

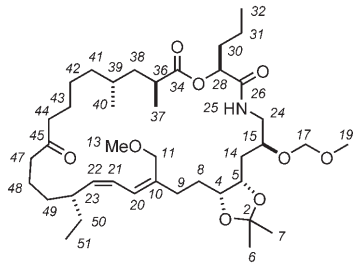
Compounds 79 and 80: A suspension of AgF (1.8 mg, 14 μmol) in MeOH (14 μL) and water (0.7 μL) was sonicated in an ultrasound laboratory cleaning bath for 15 min. A solution of compounds **78** (isomeric mixture, 6.0 mg, 6.9 μmol) in THF (35 μL) and MeOH (10 μL) was added and the resulting mixture was stirred for 75 min in the dark at ambient temperature. For work up, the mixture was passed through a short pad of silica which was carefully rinsed with Et_2O (3 mL) and EtOAc (2 mL), the combined filtrates were evaporated and the products purified by preparative TLC (hexanes/EtOAc 1.5:1) to give product **79** (1.2 mg, 25%) and product **80** (1.1 mg, 23%) as a pale yellow liquid each. If performed with pure isomer **77**, the analogous proto-desilylation reaction delivered product **79** in 94% yield as a pale yellow liquid.

Product 79: ^{1}H NMR (600 MHz, C_6D_6): δ=6.43 (dd, J=15.0, 10.8 Hz,



1H, H-21), 6.21 (br s, 1H, H-25), 6.16 (d, J=10.8 Hz, 1H, H-20), 5.38 (dd, J=15.0, 9.1 Hz, 1H, H-22), 5.20 (dd, J=6.9, 5.7 Hz, 1H, H-28), 4.56 (s, 2H, H-17), 4.18 (m, 1H, H-5), 4.05 (d, J=11.8 Hz, 1H, H-11a), 4.02 (d, J=11.8 Hz, 1H, H-11b), 3.99 (m, 1H, H-4), 3.90 (m, 1H, H-15), 3.52 (ddd, J=14.1, 6.9, 3.7 Hz, 1H, H-24a), 3.44 (ddd, J=14.0, 4.6, 4.3 Hz, 1H, H-24b), 3.17 (s, 3H, H-19), 3.15 (s, 3H, H-13), 2.60 (m, 1H, H-36), 2.50 (ddd, J=14.5, 10.6, 5.2 Hz, 1H, H-9a), 2.31 (ddd, J=14.5, 10.2, 5.7 Hz, 1H, H-9b), 2.10 (m, 1H, H-47a), 2.08 (m, 1H, H-44a), 2.01 (m, 2H, H-44b, H-47b), 1.86 (m, 2H, H-30), 1.82 (m, 1H, H-23), 1.73–1.00 (m, 21H, H-8, H-14, H-31, H-38, H-39, H-41, H-42, H-43, H-48, H-49, H-50), 1.44 (s, 3H, H-6), 1.29 (s, 3H, H-7), 1.13 (d, J=6.9 Hz, 3H, H-37), 0.86 (t, J=7.4 Hz, 3H, H-51), 0.82 (d, J=6.2 Hz, 3H, H-40), 0.82 ppm (d, J=7.4 Hz, 3H, H-32); ^{13}C NMR (150 MHz, C_6D_6): δ=209.1 (C-45), 175.8 (C-34), 169.7 (C-26), 138.9 (C-22), 136.5 (C-10), 128.9 (C-20), 126.6 (C-21), 107.7 (C-2), 96.6 (C-17), 77.8 (C-4), 75.0 (C-15), 74.6 (C-5), 74.2 (C-28), 70.4 (C-11), 57.6 (C-13), 55.3 (C-19), 45.3 (C-23), 43.1 (C-47), 42.8 (C-24), 41.8 (C-44), 41.3 (C-38), 37.6 (C-36), 36.7 (C-41), 34.9 (C-49), 34.3 (C-30), 33.5 (C-14), 32.1 (C-9), 30.4 (C-39), 29.5 (C-8), 28.8 (C-6), 28.7 (C-50), 26.7 (C-42), 26.1 (C-7), 24.0 (C-43), 22.8 (C-48), 20.0 (C-40), 18.7 (C-31), 17.3 (C-37), 13.8 (C-32), 12.0 ppm (C-51); MS (ESI+): 730 [M^++Na]; HRMS (ESI+): m/z: calcd for $C_{40}H_{69}NNaO_9$: 730.4865; found: 730.4867 [M^++Na].

Compound 80: ^{1}H NMR (600 MHz, C_6D_6): δ=6.60 (t, J=5.6 Hz, 1H), 6.49 (A-part of ABMX system, J=11.6, 1.5 Hz (extracted by simulation), 1H, H-20a), 6.46 (B-part of ABMX-system, J=11.6, −11.4 Hz (extracted by simulation), 1H, H-20b), 5.47 (dd, J=8.0, 4.6 Hz, 1H, H-28), 5.03 (X-



part of ABMX-system, t, $J=10.0$ Hz (measured), $J=-11.4$, 1.5 Hz (extracted by simulation), 1H, H-22), 4.62 (d, $J=6.5$ Hz, 1H, H-17a), 4.60 (d, $J=6.5$ Hz, 1H, H-17b), 4.37 (ddd, $J=10.4$, 5.7, 2.9 Hz, 1H, H-5), 4.13 (ddd, $J=10.5$, 5.8, 3.5 Hz, 1H, H-4), 3.99 (m, 1H, H-15), 3.98 (d, $J=11.4$ Hz, 1H, H-11a), 3.92 (d, $J=11.5$ Hz, 1H, H-11b), 3.56 (ddd, $J=13.8$, 5.0, 3.6 Hz, 1H, H-24a), 3.53 (ddd, $J=13.8$, 6.4, 4.6 Hz, 1H, H-24b), 3.20 (s, 3H, H-19), 3.16 (s, 3H, H-13), 2.58 (m, 1H, H-36), 2.45 (M-part of ABMX-system, m, 1H, H-23), 2.37 (dt, $J=14.0$, 8.2 Hz, 1H, H-9), 2.22–1.04 (m, 27H), 1.43 (s, 3H, H-6), 1.35 (s, 3H, H-7), 1.08 (d, $J=6.9$ Hz, 3H, H-37), 0.84 (t, $J=7.4$ Hz, 3H, H-51), 0.83 (d, $J=6.6$ Hz, 3H, H-40), 0.79 ppm (t, $J=7.4$ Hz, 3H, H-32); ^{13}C NMR (150 MHz, C_6D_6): $\delta=212.4$ (C-45), 175.7 (C-34), 169.7 (C-26), 138.4 (C-10), 136.3 (C-22), 125.1 (C-20), 125.0 (C-21), 107.8 (C-2), 96.9 (C-17), 77.0 (C-4), 75.7 (C-15), 74.3 (C-5), 74.1 (C-28), 70.0 (C-11), 57.9 (C-13), 55.3 (C-19), 43.1 (C-24), 42.9 (C-47), 42.1 (C-44), 41.4 (C-38), 38.8 (C-23), 37.0 (C-36), 36.8 (C-41), 35.3 (C-49), 34.5 (C-30), 33.5 (C-14), 32.6 (C-9), 30.4 (C-39), 29.2 (C-50), 28.9 (C-6, C-8), 27.2 (C-42), 26.3 (C-7), 24.1 (C-43), 22.5 (C-48), 20.0 (C-40), 18.7 (C-31), 17.2 (C-37), 13.8 (C-32), 12.1 ppm (C-51); MS (ESI+): 730 [M^++Na]; HRMS (ESI+): m/z: calcd for $C_{40}H_{69}NNaO_9$: 730.4865; found: 730.4868 [M^++Na].

Myxovirescin A_1 (1): $HClO_4$ (70%, 32 μL) was added to a solution of compound **79** (7.50 mg, 10.6 μmol) in THF (1.1 mL), water (150 μL) and MeOH (32 μL) and the resulting mixture was stirred at 40°C for 22 h before the reaction was carefully quenched with aq. sat. $NaHCO_3$. Extraction of the product with CH_2Cl_2 (5 mL), drying ($MgSO_4$) and evaporation of the organic phase, followed by purification of the residue by preparative TLC (EtOAc) afforded myxovirescin A_1 as a colorless solid (2.5 mg, 38%). The spectroscopic data were in full agreement with those published in the literature.[3,11] ^{1}H NMR (600 MHz, C_6D_6): $\delta=6.44$ (brs, 1H), 6.35 (dd, $J=14.9$, 10.9 Hz, 1H), 6.12 (d, $J=10.9$ Hz, 1H), 5.30 (m, 2H), 4.02 (d, $J=11.3$ Hz, 1H), 4.00 (brm, 1H), 3.84 (brm, 1H), 3.79 (br s, 1H), 3.74 (d, $J=11.3$ Hz, 1H), 3.58 (brm, 1H), 3.52 (ddd, $J=13.6$, 6.6, 3.8 Hz, 1H), 3.27 (dt, $J=13.6$, 5.6 Hz, 1H), 3.04 (s, 3H), 3.01 (brs, 1H), 2.80 (brs, 1H), 2.57 (m, 1H), 2.37 (m, 1H), 2.29 (m, 1H), 2.12–0.98 (m, 28H), 1.09 (d, $J=6.9$ Hz, 3H), 0.87 (t, $J=7.4$ Hz, 3H), 0.83 (d, $J=6.6$ Hz, 3H), 0.82 ppm (t, $J=7.4$ Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6): $\delta=210.2$, 175.9, 170.8, 139.2, 135.9, 130.0, 126.6, 74.1, 73.8, 72.2, 71.1, 69.3, 57.9, 45.7, 45.6, 42.9, 42.3, 41.4, 37.4, 36.7 (×2), 35.0, 34.3, 31.2, 31.1, 30.6, 28.8, 26.8, 24.0, 22.4, 19.9, 18.6, 17.6, 13.8, 12.1 ppm; MS (ESI+): 646 [M^++Na]; HRMS (ESI+): m/z: calcd for $C_{35}H_{61}NNaO_8$: 646.4289; found: 646.4290 [M^++Na].

Compound 81: Prepared analogously from compound **80** (3.9 mg, 5.5 μmol); colorless solid (1.3 mg, 38%). ^{1}H NMR (600 MHz, C_6D_6): $\delta=$ 6.66 (dd, $\Sigma J=11.3$ Hz, 1H, H-25), 6.51 (app d, $J=11.7$ Hz, 1H, H-20), 6.49 (app dd, $J=11.7$, 9.8 Hz, 1H, H-21), 5.49 (dd, $J=7.9$, 4.5 Hz, 1H, H-28), 5.04 (app t, $J=9.9$ Hz, 1H, H-22), 4.04 (brs, 1H, H-15), 3.97 (d, $J=11.6$ Hz, 1H, H-11a), 3.94 (brs, 1H, H-5), 3.92 (brs, 1H, 15-OH), 3.91 (d, $J=11.5$ Hz, 1H, H-11b), 3.68 (m, 1H, H-4), 3.63 (ddd, $J=13.5$, 6.7, 3.2 Hz, 1H, H-24a), 3.25 (ddd, $J=13.6$, 7.4, 4.7 Hz, 1H, H-24b), 3.10 (s, 3H, H-13), 3.08 (brs, 1H, 5-OH), 2.75 (brs, 1H, 4-OH), 2.56 (m, 2H, H-9a, H-36), 2.50 (ddd, $J=13.6$, 10.0, 5.6 Hz, 1H, H-9b), 2.39 (m, 1H, H-23), 1.94 (m, 1H), 1.92 (m, 1H, H-44a), 1.87 (m, 1H, H-30), 1.84 (m, 2H, H-47), 1.83 (m, 2H, H-38a, H-44b), 1.70 (m, 1H, H-8a), 1.67 (m, 2H, H-14), 1.66 (m, 1H, H-8b), 1.56–1.08 (m, 14H), 1.08 (d, $J=6.9$ Hz, 3H, H-37), 0.94 (m, 1H, H-41), 0.90 (m, 1H, H-49a), 0.89 (t, $J=7.4$ Hz, 3H, H-51), 0.84 (d, $J=6.6$ Hz, 3H, H-40), 0.81 ppm (t, $J=7.4$ Hz, 3H, H-32); ^{13}C NMR (150 MHz, C_6D_6): $\delta=212.8$ (C-45), 175.7 (C-34), 170.5 (C-26), 138.4 (C-10), 136.0 (C-22), 125.7 (C-20), 125.3 (C-21), 74.1 (C-28), 73.2 (C-4), 72.6 (C-5), 70.0 (C-11), 69.2 (C-15), 57.9 (C-13), 45.5 (C-24), 43.1 (C-47), 42.5 (C-44), 41.8 (C-38), 39.4 (C-23), 37.0 (C-36), 36.5 (C-41), 36.3 (C-14), 35.6 (C-49), 34.5 (C-30), 32.2 (C-9), 30.6 (C-39), 29.9 (C-8), 29.4 (C-50), 26.9 (C-42), 23.9 (C-43), 21.9 (C-48), 20.0 (C-40), 18.7 (C-31), 18.1 (C-37), 13.8 (C-32), 12.2 ppm (C-51); MS (ESI+): 646 [M^++Na]; HRMS (ESI+): m/z: calcd for $C_{35}H_{61}NNaO_8$: 646.4289; found: 646.4287 [M^++Na].

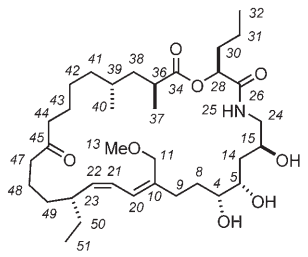
X-ray crystallographic study: Diffraction data for the compounds were collected using a Nonius KappaCCD diffractometer employing CCD scans. The structures were solved by direct methods using SHELXS-97; atomic positions and displacement parameters were refined using full matrix least-squares based on F^2 using SHELXL-97.[62]

Selected X-ray crystallographic data for compound 63: $C_{46}H_{84}B_2$, $M=$ 658.75 g mol^{-1}, colorless, crystal dimensions $0.20\times0.16\times0.04$ mm, monoclinic $C2$ (no. 5), at 100 K $a=21.4010(8)$, $b=7.8170(3)$, $c=12.6936(5)$ Å, $\beta=107.790(2)$, $V=2021.99(13)$ Å^3, $Z=2$, $\rho=1.082$ Mg m^{-3}, $\mu=$ 0.059 mm^{-1}, $\lambda=0.71073$ Å. Data completeness to $\theta_{max}=27.15°$ 98.6%, integration of raw data yielded a total of 14502 reflections, merged into 4423 unique reflections with $R_{int}=0.036$. Refinement of 218 parameters using all reflections converged at $R=0.076$, $wR=0.204$, highest residual electron density peak 0.3 Å^3.

Selected X-ray crystallographic data for compound 65: $C_{24}H_{46}B_2$, $M=$ 356.23 g mol^{-1}, colorless, crystal dimensions $0.42\times0.12\times0.10$ mm, monoclinic $C2/c$ (no. 15), at 100 K $a=20.1816(4)$, $b=6.31770(10)$, $c=$ 17.8640(3) Å, $\beta=95.6790(10)$, $V=2266.50(7)$ Å^3, $Z=4$, $\rho=1.044$ Mg m^{-3}, $\mu=0.056$ mm^{-1}, $\lambda=0.71073$ Å. Data completeness to $\theta_{max}=36.35°$ 99.5%, integration of raw data yielded a total of 42637 reflections, merged into 5496 unique reflections with $R_{int}=0.048$. Refinement of 122 parameters using all reflections converged at $R=0.037$, $wR=0.109$, highest residual electron density peak 0.4 Å^3.

Selected X-ray crystallographic data for compound 70: $C_{21}H_{28}O_3Si$, $M=$ 356.52 g mol^{-1}, colorless, crystal dimensions $0.18\times0.13\times0.04$ mm, monoclinic $C2$ (no. 5), at 100 K $a=16.7363(7)$, $b=8.2671(4)$, $c=14.5748(6)$ Å, $\beta=100.540(2)$, $V=1982.55(15)$ Å^3, $Z=4$, $\rho=1.194$ Mg m^{-3}, $\mu=$ 0.134 mm^{-1}, $\lambda=0.71073$ Å. Data completeness to $\theta_{max}=31.42°$ 99.4%, integration of raw data yielded a total of 21530 reflections, merged into 6514 unique reflections with $R_{int}=0.034$. Refinement of 230 parameters using all reflections converged at $R=0.037$, $wR=0.088$, highest residual electron density peak 0.3 Å^3.

CCDC-649747, -649748, and -650025 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



Acknowledgement

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[1] For an excellent overview, see: F. von Nussbaum, M. Brands, B. Hinzen, S. Weigand, D. Häbich, *Angew. Chem.* **2006**, *118*, 5194–5254; *Angew. Chem. Int. Ed.* **2006**, *45*, 5072–5129, and references therein.

[2] a) W. Trowitzsch, V. Wray, K. Gerth, G. Höfle, *J. Chem. Soc. Chem. Commun.* **1982**, 1340–1341; b) K. Gerth, H. Irschik, H. Reichenbach, W. Trowitzsch, *J. Antibiot.* **1982**, *35*, 1454–1459.

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