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Total Synthesis and NMR Investigations of Cylindramide

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Dedicated to Professor Gerhard Erker on the occasion of his 60th birthday

Abstract: Cylindramide (**1**) was built up from three components: a hydroxyornithine derivative **7**, a tetrazolylsulfone **8**, and a substituted pentalene subunit **9**. Derivative **7** was prepared in a six-step reaction sequence involving the Wittig reaction and a Sharpless asymmetric dihydroxylation starting from *N*-Boc-3-aminopropanal (**12**). Tetrazolylsulfone **8** was accessible in four steps from dioxinone **22**. The synthesis of the pentalene fragment **9** started from cycloocta-1,5-diene **26**, that was converted into enantiopure bicyclo[3.3.0]octanedione **29**. The latter was functionalized to give derivative **9**. The total synthesis was accomplished by inducing C–C bond formation by Sonogashira coupling of derivatives **9** and **7** followed by olefination with tetrazolylsulfone **8** under Julia–Kocienski conditions, macrocyclization, and subsequent Lacey–Dieckmann condensation to form the tetramic acid unit. As indicated by extensive ^{1}H and ^{13}C NMR spectroscopic investigations (DQF-COSY, ROESY spectra), the stereochemistry of synthetic cylindramide (**1**) corresponds with that of the naturally occurring product. ROE data were used for molecular modeling of the lowest-energy structures for cylindramide.

Keywords: lactams · macrocycles · NMR spectroscopy · tetramic acid · total synthesis

Introduction

Marine organisms have been found to be a rich source of many natural products with pharmacological relevance.[1] During such bioprospecting cylindramide (**1**) was isolated in 1993 by Fusetani and co-workers from the Okinawan sponge *Halichondria cylindrata*.[2]

Cylindramide belongs to the class of complex tetramic acid lactams and displays prominent cytotoxicity against human B16 melanoma cells.[2] Other members of this class are discodermide (**6**) from the Caribbean marine sponge *Discodermia dissoluta*,[3] alteramide A (**3**) from the bacterium *Alteromonas* sp., an endosymbiotic species of the sponge *Halichondria okadai*,[4] aburatubolactam A (**4**) produced by a *Streptomyces* species of a japanese marine mollusc,[5,6] maltophilin (**5**) from *Stenotrophomonas maltophilia*,[7,8] and geodin A magnesium salt (**2**) that was recently isolated from the southern australian marine sponge *Geodia* (Scheme 1).[9]

Characteristic structural features of these compounds are the substituted bicyclo[3.3.0]octane unit and the tetramic acid moiety. Despite the cytotoxic, antibiotic, and fungicidal activities of compounds **1**–**6**,[2–9] the chemistry remains unexplored, and only a model study[10] as well as two total syntheses of the structurally related ikarugamycin[11,12] have been published so far. This prompted us to investigate the tetramic acid lactams in more detail. Our efforts recently resulted in the enantioselective total synthesis of cylindramide **1** (Scheme 2).[13]

The key steps are a Sonogashira coupling of the hydroxyornithine moiety **7**, a Julia–Kocienski olefination of the *N*-phenyl-tetrazolylsulfone **8**, and a Lacey–Dieckmann cyclization. The highly functionalized pentalene system **9** was obtained from pentalenone **10** through a tandem Michael-addition/electrophilic-trapping reaction. At the start of our experiments the stereoselective formation of the bicyclo[3.3.0]octane unit and the macrolactamization were considered as the most critical steps, and thus, several strategies were evaluated. The results of these studies and the total

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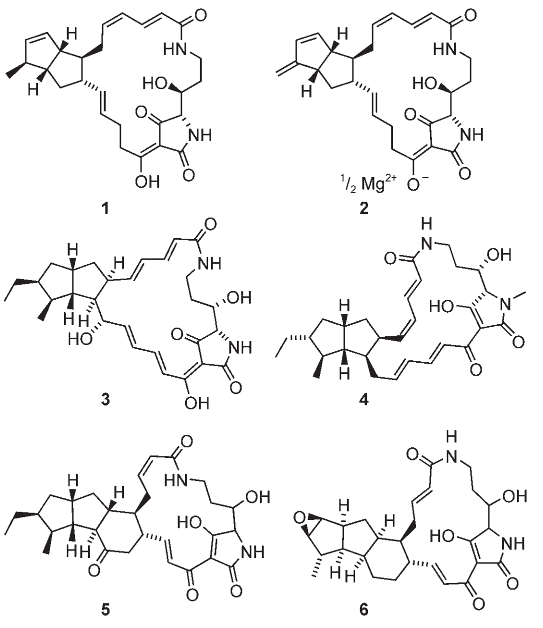
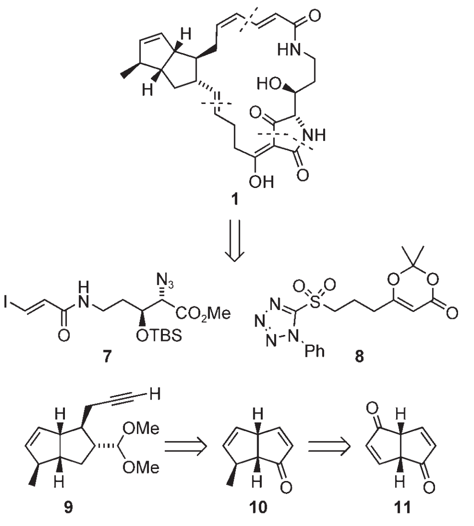


Scheme 1. Cylindramide (**1**) and related structures of compounds **2**–**6** from the class of tetramic acid lactams.

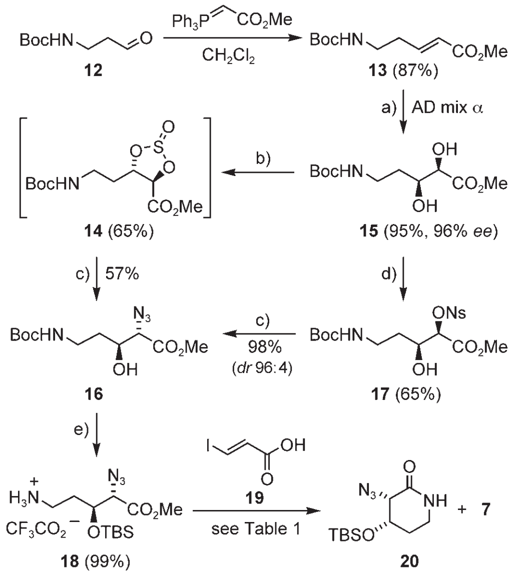


Scheme 2. Retrosynthetic pathway of cylindramide **1**.

synthesis are reported below. During our initial investigations the NMR spectra of the target compound **1** turned out to be surprisingly complex.[13] In order to understand the observed phenomena in more detail, the behavior of compound **1** was thoroughly investigated by NMR spectroscopy and the results are also discussed.

Results and Discussion

Formation of the hydroxyornithine subunit 7: The synthesis strategy for compound **7** is outlined in Scheme 3. *N*-Boc-3-aminopropanal (**12**) was converted to the α,β-unsaturated ester **13** in 87% yield by using a Wittig reaction. Ester **13** was further subjected to Sharpless asymmetric dihydroxylation[14] giving diol **15** in 95% yield and 96% *ee*. Conversion to the α-azido ester **16** was achieved through formation of the cyclic sulfite intermediate **14** and treatment with NaN_3 in DMF[15] in 38% yield over two steps.



Scheme 3. Preparation of the hydroxyornithine subunit **7**. a) AD-mix-α, *t*BuOH, H_2O, $MeSO_2NH_2$, 0 °C, 18 h; b) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C, 30 min; c) NaN_3, DMF, 50 °C, 16 h; d) NsCl, NEt_3, CH_2Cl_2, 4 °C, 12 h; e) 1. TBSCl, DMAP, DMF, RT, 24 h; 2. TFA, CH_2Cl_2, 0 °C, 2 h.

The deactivation of the β-hydroxy group in diol **15** by an intramolecular hydrogen bond[16] leading to regioselective nosylation of the α-hydroxy function was more effective. Subsequent treatment of nosylate **17** with NaN_3 in DMF yielded α-azido ester **16** in 98% with a diastereomeric ratio 96:4. After silylation of the remaining hydroxy group with *tert*-butyldimethylsilylchloride (TBSCl), the diastereomers could be separated by chromatography. Final deprotection of the amino group with trifluoroacetic acid in dichloromethane gave derivative **18** quantitatively after removal of all volatile materials by azeotropic distillation with benzene. However, considerable experimentation was required to couple derivative **18** with 3-iodoacrylic acid **19**[17] (Table 1).

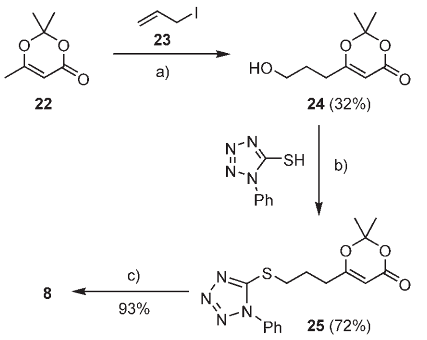
Under classical coupling conditions with 1-[3-(dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt)[18] or with mesitylsulfochloride as the coupling agent only lactam **20**[19] could be

Table 1. Coupling of hydroxyornithine derivative **18** to fragment **7**.

	Conditions	**20** Yield (%)	**7** Yield (%)
19	EDC, HOBt, THF, RT, 3 h	75	–
19	NEt_3, mesitylsulfochloride, CH_2Cl_2, RT, 5 h	>70	–
	3-iodoacrylic acid chloride, DMAP, pyridine, CH_2Cl_2, RT, 3 h	>70	5
	CH_2Cl_2, NEt_3, RT, 10 min	99	–
19	DEPC, DMF, NEt_3, 0 °C, 18 h	–	83
19	FDPP, DMF, *i*Pr_2NEt, RT, 3 h	–	81

isolated (Table 1). When 3-iodoacrylic acid chloride was employed, lactam **20** was obtained as the major product (>70%) together with 5% of the desired acyclic target compound **7**. Neutralization of derivative **18** with NEt_3 in dichloromethane caused complete aminolysis to lactam **20** within 10 min. By using diethyl cyanophosphonate (DEPC) and pentafluorophenyl diphenylphosphinate (FDPP)[20,21] we were finally able to overcome this problem. Both reagents completely suppressed the lactam formation and the amide **7** could be isolated in 83 and 81% yield, respectively.

Formation of the tetrazolylsulfone 8: As shown in Scheme 4, deprotonation of dioxinone **22** with lithium diisopropylamide (LDA) followed by allylation and ozonolysis in MeOH/CH_2Cl_2/pyridine with reductive workup yielded alcohol **24** in 32% total yield over two steps. Treatment of alcohol **24** with phenyltetrazolylsulfide under Mitsunobu conditions[22] gave derivative **25** in 72% yield. The latter was oxidized in the presence of catalytic amounts of ammonium molybdate and aqueous H_2O_2[23] to afford the desired *N*-phenyltetrazolylsulfone **8** in 93% yield. Recrystallization of **8** from MeOH gave single crystals suitable for X-ray crystallographic analysis (Figure 1).[24]



Scheme 4. Preparation of subunit **8**. a) 1. LDA, DMPU, THF, **22**, 0°C, 1 h, **23**, −40°C→RT, 16 h, 50%; 2. O_3, MeOH/CH_2Cl_2/pyridine 4:4:1, −78°C, $NaBH_4$, 64%; b) PPh_3, DEAD, THF, 0°C, 1 h; c) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, 0°C→RT, 3 h.

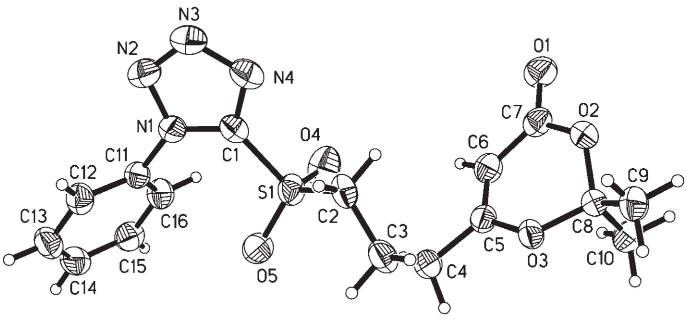
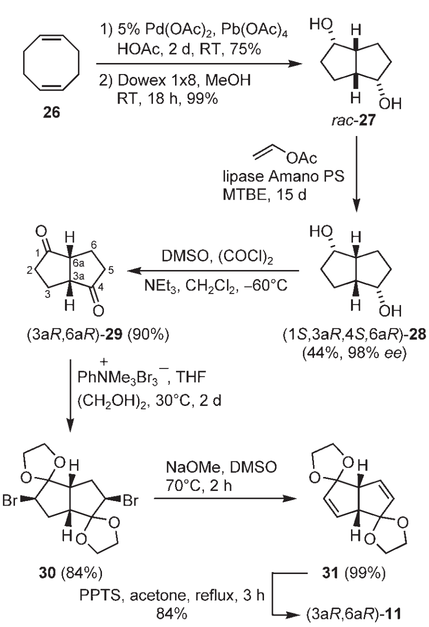


Figure 1. ORTEP view of *N*-phenyltetrazolylsulfone **8**.

Formation of the bicyclo[3.3.0]octane precursor 11: The synthesis approach to pentalene derivative **11** starting from commercially available cycloocta-1,5-diene (**26**) analogous to a literature procedure is depicted in Scheme 5. Diene **26** undergoes a transannular Pd-catalyzed ring-closure with $Pb(OAc)_4$ in HOAc.[25] Removal of the acetyl groups[26] and subsequent enzymatic resolution with lipase Amano PS and vinyl acetate in methyl *tert*-butyl ether[26,27] gave the diol (1*S*,3a*R*,4*S*,6a*R*)-**28** in 44% yield and both the corresponding monoacetate (8% yield) and the (1*R*,3a*S*,4*R*,6a*S*)-configured diacetate (38%), that could be separated by chromatography. Diol (1*S*,3a*R*,4*S*,6a*R*)-**28** was converted into enantiopure bicyclo[3.3.0]octanedione (3a*R*,6a*R*)-**29**[28] by Swern oxidation[29] with DMSO, $(COCl)_2$. This route allowed the preparation of dione **29** on a 50 g-scale that was purified by distillation.



Scheme 5. Preparation of enantiomerically pure dienedione (3a*R*,6a*R*)-**11**.

Next, we attempted to convert diketone **29** directly into the dienedione **11**.[30] For example, treatment of **29** with potassium hexamethyldisilazane (KHMDS) and phenylselenylbromide followed by H_2O_2 oxidation[31] gave 30% of an inseparable 1:1:1 mixture of starting material **29**, dienedione **11**, and the corresponding bicyclo[3.3.0]oct-3-ene-2,6-dione. Enol ether formation with trimethylsilyl triflate (TMSOTf), NEt_3,[32] and Saegusa oxidation with $Pd(OAc)_2$/benzoquinone[33] resulted in a complex mixture containing 41% of derivative **11**, whereas a modified procedure[34] gave no trace of the target compound **11**. Direct oxidation with HIO_3 in DMSO[35] or 2-iodoxybenzoic acid (IBX) in DMSO[35] gave 35–40% of a mixture of enedione and dienedione **11**. Further procedures[36,37] again gave only mixtures of starting material **29**, enedione, and dienedione **11**, or poor yields.

Due to the failure of the direct oxidation, an alternative approach to obtain enantiomerically pure diketone (3a*R*,6a*R*)-**11** was carried out by using the modified Farnum route (Scheme 5).[30] Bromoacetalization[38] of (3a*R*,6a*R*)-**29** to dibromo derivative **30** (84% yield) was achieved with $PhN^+Me_3Br_3^-$ instead of pyridinium tribromide and ethylene glycol. Base-induced elimination of the bromo-substituents occurred to give dienediacetal **31** in 99% yield, and subsequent cleavage of the acetal groups with pyridinium *p*-toluenesulfate (PPTS) resulted in enantiopure dienedione (3a*R*,6a*R*)-**11** (83% yield over two steps). Recrystallization of both enantiopure dibromide **30** and dienedione **11** gave single crystals which were suitable for X-ray crystal-structure analysis, confirming the absolute configuration of derivative (3a*R*,6a*R*)-**11** (Figures 2 and 3).[24]

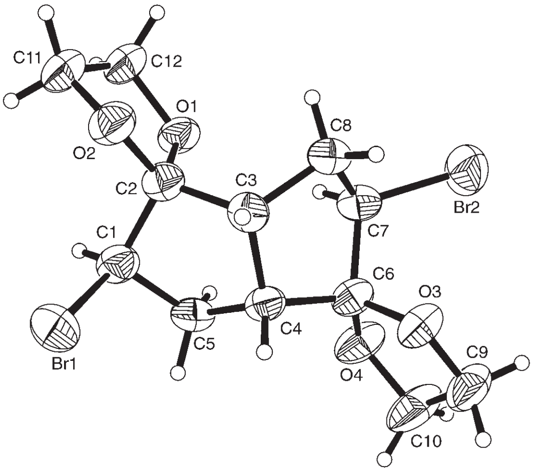


Figure 2. ORTEP view of dibromo acetal **30** derived from enantiopure (3a*R*,6a*R*)-**29**.

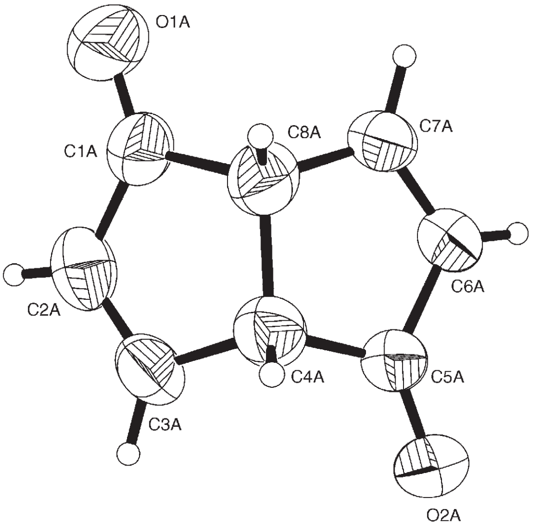
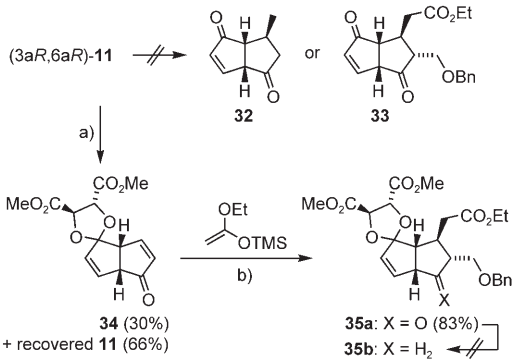


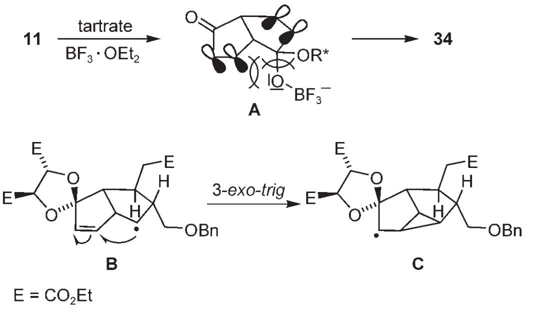
Figure 3. ORTEP view of enantiomerically pure dienedione (3a*R*,6a*R*)-**11**.

Functionalization of the bicyclo[3.3.0]octane moiety: Despite the apparently straightforward manipulation, dienedione (3a*R*,6a*R*)-**11** did not provide a suitable synthesis route (Scheme 6). Neither direct 1,4-addition of cuprates to give β-methylketone **32** nor the tandem Michael-addition/electrophilic-trapping reaction to afford derivative **33** were successful. Only polymerization of derivative (3a*R*,6a*R*)-**11**[39] or quantitative recovery of the starting material was observed. In an effort to avoid these problems, dienedione **11** was converted to the tartrate-derived monoacetal **34** in only 30% yield along with 66% of recovered starting material **11**. Any attempt to improve the conversion of the starting material failed. Monoacetal **34** underwent the Lewis acid catalyzed tandem Michael-addition/electrophilic-trapping reaction to result in the functionalized ketone **35a** (X = O). $Sc(OTf)_3$ effectively catalyzed the Michael reaction of the silyl ketene acetal and monoacetal **34**. The intermediate silyl enol ether was treated with formaldehyde dibenzylacetal $(BnO)_2CH_2$ in the presence of triflate TMSOTf and 2,6-di-*tert*-butylpyridine to give the ketone **35a** building block.[40] Unfortunately, removal of the ketone group by Mozingo desulfurization[41] and by reduction of the tosylhydrazone,[42] respectively, failed. Under the conditions of thioacetalization only decomposition was observed, whereas ketone **35a** did not react to produce the tosylhydrazone even at higher temperature. Also reduction and subsequent Barton–McCombie deoxygenation[43] did not give the desired product **35b** (X = H_2).



Scheme 6. Attempted functionalization of dienedione (+)-**11**. a) (*R*,*R*)-dimethyl tartrate, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C→RT, 2 d; b) $Sc(OTf)_3$, CH_2Cl_2, −78°C, then $(BnO)_2CH_2$, TMSOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, −78°C→RT.

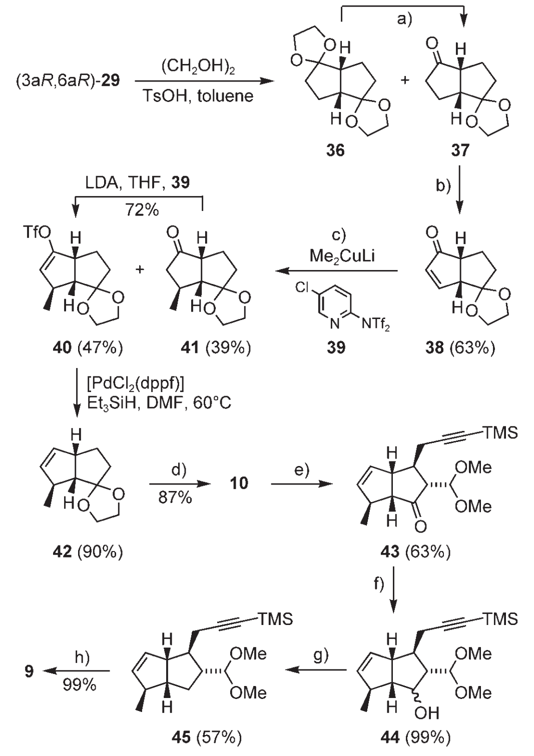
The sluggish reactivity of compound **11** towards acetal formation might be due to orbital repulsion in the preceding tetrahedral intermediate **A** between the π-orbitals of the convex pentalene system and the lone pairs of the OBF_3 group (Scheme 7). A possible reason for the failure of the Barton–McCombie deoxygenation might be the intermediate carbon radical **B**. Instead of hydrogen abstraction it might undergo a 3-*exo-trig* cyclization to the cyclopropylmethyl radical **C**. According to the Baldwin rules[44] this cyc-



Scheme 7. Hypothesis for the low reactivity of compound **11** towards acetal formation and for the failure of Barton–McCombie deoxygenation.

lization is allowed and the butterfly-shape of the pentalene system provides some steric preorganization.

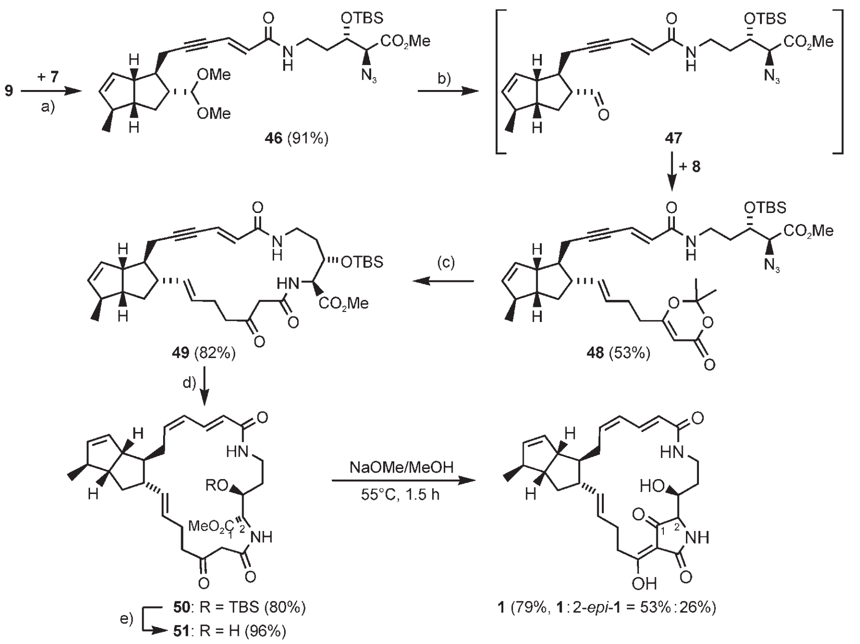
Owing to these difficulties we had to change our synthesis strategy as outlined in Scheme 8. Diketone (3a*R*,6a*R*)-**29** was treated with ethylene glycol (1.2 equiv) in the presence of toluenesulfonic acid to give a mixture of mono- (**37**) (80 %) and diacetal **36** (13 %), that could be converted into ketone **37** in 85 % yield by reaction with aqueous HCl in THF. Ketone **37** was oxidized to the corresponding enone **38** according to Nicolaou's procedure[36] by using IBX for the oxidation of the intermediate silyl enol ether generated from ketone **37** with LDA and trimethylsilyl chloride (TMSCl). The 1,4-addition of Me_2CuLi followed by trapping of the intermediate lithium enolate with Comins' reagent[45] yielded 47 % of the desired triflate **40** together with 39 % of ketone **41**. The latter was converted to **40** (72 % yield) by repeated deprotonation and quenching with Comins' reagent. Due to the butterfly-shaped pentalene the attack from the convex side is favored, resulting exclusively in diastereomer **40**. Pd-catalyzed reduction of the triflate moiety with Et_3SiH[46] afforded pentalene **42** in 90 % yield. Removal of the acetal group[47] and subsequent Nicolaou oxidation gave enone **10** in 87 % yield.



Scheme 8. Synthesis of the functionalized pentalene fragment **9**. a) 1 N HCl, THF, RT, 30 min, 85 % (**37**); b) LDA, THF, TMSCl, −78→−20 °C, 4-methoxypyridin-*N*-oxide (MPO), IBX, DMSO, CH_2Cl_2, RT, 45 min; c) Me_2CuLi, THF, then **39**, −78→0 °C; d) 1. PPTS, acetone, H_2O, reflux, 3 h, quant, 2. LDA, THF, TMSCl, −78 °C→−20 °C, then MPO, IBX, DMSO, CH_2Cl_2, RT, 30 min; e) TMS-C≡CCH_3, *t*BuLi, TMEDA, THF, −78 °C, 1 h, CuI, THF, −78→0 °C; **10**, TMSCl, −40→−15 °C, 2 h, then BF_3•OEt_2, $HC(OMe)_3$, CH_2Cl_2, −20 °C, 1 h; f) $NaBH_4$, MeOH, 0 °C; g) 1. $(Im)_2CS$ (5 equiv), DMAP (5 equiv), DCE, 80 °C, 18 h; 2. Bu_3SnH, AIBN, toluene, 110 °C, 45 min; h) K_2CO_3, MeOH, RT, 20 h.

Product **10** was treated with TMS-protected propynyl cuprate followed by orthoformate in the presence of BF_3•OEt_2 to give ketone **43** in 63 % yield. The carbonyl group in ketone **43** was removed following the Barton–McCombie[43] procedure. After reduction with $NaBH_4$, the alcohol **44** was isolated as a 1:1 mixture of diastereoisomers, that was subjected to Barton deoxygenation using a five-fold excess of thiocarbonyldiimidazole at 80 °C to afford the pentalene derivative **45** in 57 % yield over both steps. Desilylation of derivative **45** with K_2CO_3 in MeOH finally gave the desired fragment **9** in 99 % yield.

Elaboration of the coupling and macrocyclization conditions: Next, we followed our synthesis route to prepare the macrocycle in order to complete the synthesis of cylindramide **1** (Scheme 9). The reaction sequence started with a Sonogashira coupling[48] of the pentalene fragment **9** with the freshly prepared hydroxyornithine unit **7** to give the corresponding enyne **46** in 91 % yield. After hydrolysis of the dimethyl acetal group with PPTS[47] and subsequent Julia–Kocienski olefination[49] of intermediate aldehyde **47** with tetrazolylsulfone **8** (3 equiv) in the presence of NaHMDS, the *E*-configured product **48** was isolated exclusively in 53 % yield over both steps. Further isomers such as the corresponding *cis*-olefin or products epimerized in the α-position could not be detected. Staudinger reduction of the azide group with PPh_3[50] led to the free amine intermediate, which cyclized to lactam **49** in 82 % yield over two steps under dilution (2.5×10^{-4} M) and heating the dilute solution at reflux. Under these conditions the trimethyldioxinone function underwent a retro Diels–Alder reaction to form an acylketene, that was trapped by the free amino group under cyclization. The Lindlar reduction[51] of the enyne **49** giving the corresponding *Z*,*E*-diene **51**, after deprotection of the TBS ether **50**, turned out to be difficult. The amount of catalyst and the reaction times had to be carefully monitored, and incomplete conversion was essential, otherwise considerable overreduction was observed. Overreduction could be suppressed by using the smallest amount possible of the catalyst $Pd/BaSO_4$ that must be activated by hydrogen saturation prior to addition of substrate, and the *Z*,*E*-diene **50** was isolated in 80 % yield at



Scheme 9. Coupling of the fragments **9**, **7**, and **8**, and final macrocyclization. a) **7**, $[Pd(PPh_3)_4]$, CuI, NEt_3, THF, RT, 1 h; b) 1. PPTS, acetone, H_2O, reflux, 3 h, 2. NaHMDS, DME, −55 °C, 1 h, then **8** (3 equiv), −55 °C→RT, 18 h; c) 1. PPh_3, THF, H_2O, RT, 24 h, 2. toluene, 2.5×10^{-4} M, reflux, 7 h; d) H_2, $Pd/BaSO_4$, quinoline, MeOH, 51 % conversion (based on recovered starting material); e) HF/MeCN, RT, 2 h.

51 % conversion (based on recovered **49**). Subsequent desilylation with HF gave macrolactam **51** in 96 % yield. Thus, the overall yield starting from enyne **48** was 63 %. Lacey–Dieckmann cyclization[52] of macrolactam **51** finally gave cylindramide **1** in 79 % yield as an epimeric mixture **1**/2-*epi*-**1** 53 %:26 %, that could be separated by reversed-phase chromatography on an RP18 phase. This isomeric ratio was observed independently of reaction time, amount of NaOMe, and conversion, thus reflecting the thermodynamic equilibrium in favor of the natural isomer **1**.

NMR studies of cylindramide: The current analysis was performed in MeOD and builds on a previous NMR investigation of cylindramide in MeOD/$CDCl_3$ 1:1 by Kanazawa and co-workers.[2] For the chemical shift assignment, the protons from the high-field-shifted methyl group $H17^{Me}$ (δ = 0.96 ppm, referenced relative to MeOH) could be easily identified by peak integration of the proton one-dimensional spectrum. The spin system could be identified by continuous correlation peaks from protons H7–H24 as shown in the $\{^1H\}^1H$ DQF-COSY spectrum in Figure 4c and d. The second spin system, from protons H2–H5, is also visible in the DQF-COSY spectrum.

The proton chemical shifts of H2 and H3 are not resolved even at 900 MHz, but can be separated in the heteronuclear correlation experiment ($\{^1H\}^{13}C$ HSQC, Figure 4b). The chemical shift assignment for most of the carbon resonances could be achieved in a straightforward manner since most of proton chemical shifts are resolved. The quaternary carbons C1, C7, C25, C26, and C27 could be assigned by long-range correlation in the $\{^1H\}^{13}C$ HMBC experiments.

The proposed stereochemistry is supported by the semi-quantitative analysis of cross-peak intensities in the ROESY and COSY experiments. Figure 4e and f show selected regions in the $\{^1H\}^1H$ ROESY spectrum. The indicated peaks are in agreement with the relative stereochemistry of the ring atoms C13, C14, C18, and C20. The $^3J(H,H)$ coupling constants of protons H8–H11, H21, and H22 extracted from IP-COSY[53] data support the depicted stereochemistry of the double bonds ($^3J(H8,H9)$ = 16.8 Hz, *E*; $^3J(H9,H10)$ = 10.5 Hz, *E*; $^3J(H10,H11)$ = 7.8 Hz, *Z*; $^3J(H21,H22)$ = 15 Hz). A qualitative analysis of the cross-peak intensity due to scalar couplings in the $\{^1H\}^1H$ COSY allowed a prediction of the relative configuration of the stereochemistry of the bicyclo[3.3.0]octane unit. In addition, we can differentiate between the diastereotopic protons at the C19 center. Proton H18 shows a stronger cross-peak signal to the *trans* H19b than to the *cis* H19a proton, and H19b gives a more intense cross-peak signal to proton H20. The cross-peak signals H20/H13 and H13/H14 also strongly support a *trans* configuration between protons H20 and H13. Table 2 summarizes all NMR data extracted from the recorded spectra.

The expected configuration derived from the analysis of the COSY spectra is in good agreement with the intensities in the $\{^1H\}^1H$ ROESY spectrum (Figures 4e and f). Only proton H19b in a *trans* configuration to proton H18 shows ROE peaks to the protons H13, H21, and H22. A strong ROE peak is also observed for H14 to the protons H12a, H12b, and H11. The relative configuration around the stereogenic centers C2 and C3 cannot be determined from the NMR data because of the overlap of H3 and H2 protons and a missing correlation from proton H2 in the NOESY and HMBC spectra.

To further support the stereospecific assignment of the stereogenic centers, long-range C–H coupling constants were also interpreted. Long-range $J(C,H)$ coupling constants were obtained from quantitative analysis of the cross-peak signals in the $\{^1H\}^{13}C$ HMBC spectra compared with the $^1J(C,H)$ coupling constants determined in coupled $\{^1H\}^{13}C$ HSQC experiments[54] ($^2J(C1,H2)=4.0$; $^3J(C27,H2)=2.4$; $^3J(C4,H2)=3.1$; $^3J(C5,H3)=3.3$; $^3J(C7,H9)=9.5$; $^2J(C8,H9)=8.9$; $^2J(C10,H9)=8.9$; $^2J(C15,H14)=8.3$; $^3J(C16,H14)=8.3$ Hz).

Distances derived from ROE data were used as experimental restraints for an initial structure calculation (given in

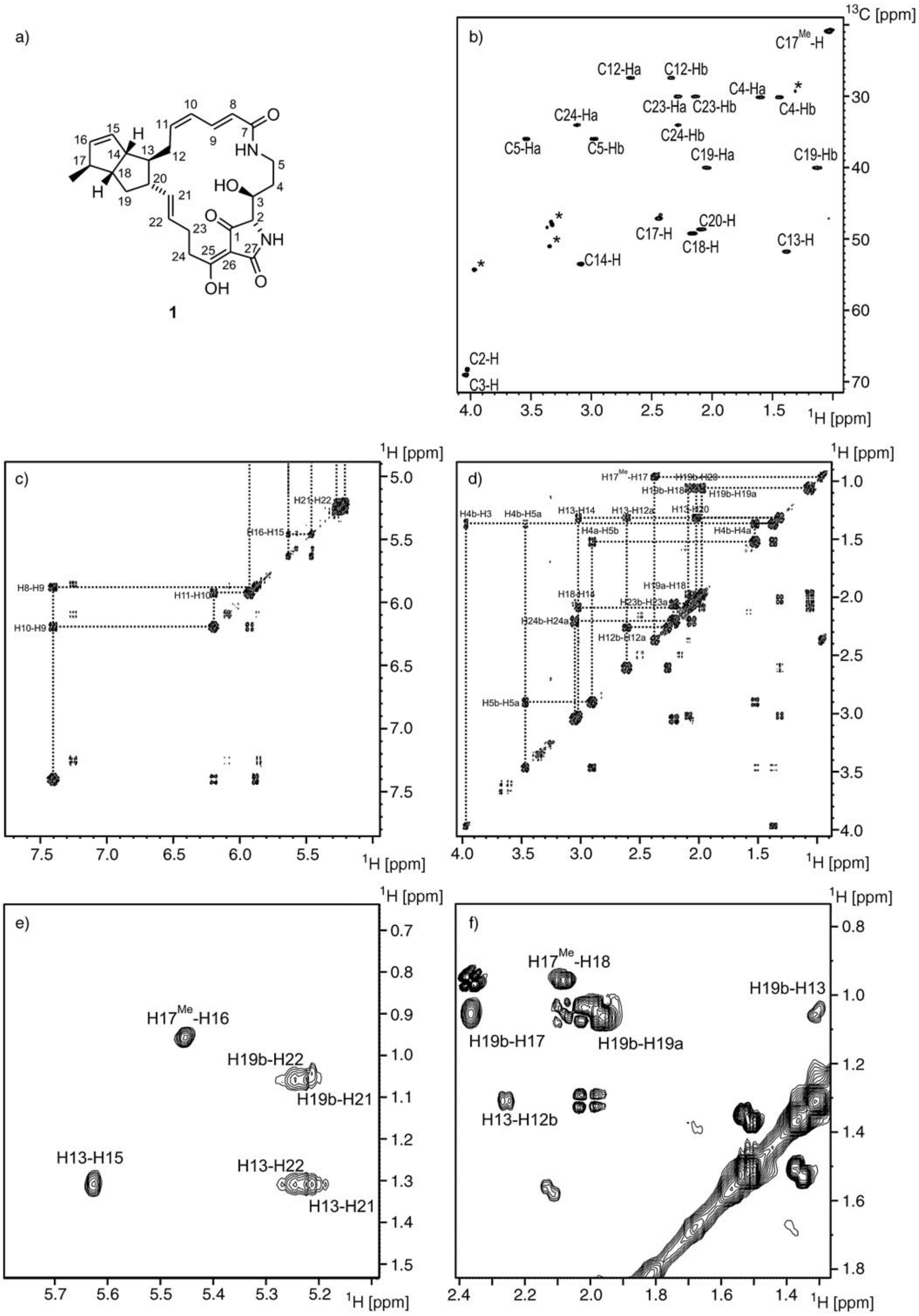


Figure 4. a) Constitution and configuration of cylindramide. b) Aliphatic region of the $\{^1H\}^{13}C$ HSQC spectrum obtained at 600 MHz. The signals from cylindramide are assigned and the signals due to impurities are indicated with a star. c) and d) show two regions in the $\{^1H\}^1H$ DQF-COSY spectrum. The connectivity walk is indicated by lines. e) and f) show selected regions in the $\{^1H\}^1H$ ROESY spectrum recorded at 600 MHz from cylindramide by using a mixing time of 400 ms.

Table 2). Figure 5 shows two lowest-energy structures from two different structure calculations of cylindramide.[55] Both structures differ mainly in the orientation of the amide bond. The amide proton could not be observed due to fast exchange with the solvent. In addition, the five-membered lactam ring has a slightly different orientation in the structures. The proton-rich region around the bicyclo[3.3.0]octane unit occurs in both structures in good agreement. While a structure refinement will be performed in the future using residual dipolar couplings, we can at this point

Table 2. NMR data of cylindramide (**1**) in MeOD (previous investigations by Fusetani and co-workers[2] used MeOD/$CDCl_3$ 1:1 as solvent).

Group	δ ^{13}C [ppm]	δ ^{1}H [ppm]	COSY correlations	HMBC correlations	ROESY correlations
1	194.1	–	–	–	–
2	69.3	3.96	–	1, 4, 27	–
3	69.9	3.97	4a, 4b	5	4a, 5b
4a	31.0	1.51	3, 4b, 5a, 5b	5	3, 4b, 5a
4b		1.36	3, 4a, 5a, 5b	–	4a, 5a, 5b
5a	36.8	3.48	4a, 4b, 5b	3	4b, 5b, 8
5b		2.89	4a, 4b, 5a	3, 4, 7	3, 4a, 4b
6	–	–	–	–	–
7	168.5	–	–	–	–
8	123.8	5.88	9	7, 10	5b, 9, 10
9	136.7	7.41	8, 10	7, 8, 10	8, 10, 12a
10	128.7	6.20	9, 11	8, 9, 12	9, 11
11	136.4	5.93	10, 12a, 12b	9, 12, 13	8, 10, 12a, 12b, 14, 10, 20
12a	28.2	2.63	11, 13, 12b	10, 11, 13, 14	9, 11, 12b, 13, 14
12b		2.24	11, 13, 12a	9, 10, 13, 20	11, 12a, 13, 14, 15
13	52.6	1.32	12a, 12b, 14, 20	–	12a, 12b, 15, 19b
14	54.3	3.03	13, 15, 17, 18	12, 13, 15, 16, 18, 19	11, 12a, 15, 16, 18
15	132.9	5.64	14, 16, 17	14, 15, 16, 17, 17^{Me}, 18	12b, 13, 14, 16, 17
16	135.2	5.46	15, 17	14, 15, 17, 17^{Me}, 18	14, 15, 17, 17^{Me}
17	48.0	2.37	14, 16, 17^{Me}, 18	15, 16, 17^{Me}, 19	15, 16, 17^{Me}, 18, 19a, 19b
17^{Me}	21.8	0.96	17	16, 17, 18	16, 17
18	50.1	2.09	14, 17, 19a, 19b	12, 15, 16, 17^{Me}	14, 17
19a	40.9	1.97	17, 18, 19b, 20	13, 14, 20	17, 19b
19b		1.05	17, 18, 19a, 20	17, 18, 20	13, 17, 19a, 20, 21, 22
20	49.5	2.01	13, 19a, 19b, 21	13, 14, 21	11, 19b, 21, 22
21	133.8	5.21	20, 22	13, 19, 20, 23	19b, 20, 22
22	131.6	5.24	21, 23a, 23b	20, 23	19b, 20, 21, 23a, 23b
23a	31.1	2.20	22, 23b, 24b	25, 22	22, 23b, 24a, 24b
23b		2.05	22, 23a, 24a	25, 22	22, 23a, 24a, 24b
24a	34.9	3.05	23b	21, 23, 26	23a, 23b, 24b
24b		2.18	24a	25, 26	23a, 23b, 24a
25	190.0	–	–	–	–
26	101.0	–	–	–	–
27	177.0	–	–	–	–

conclude that the stereochemistry also fulfils all the experimental restraints.

Conclusion

A highly convergent approach to the cytotoxic tetramic acid lactam cylindramide (**1**) has been developed and the overall yield from our previous total synthesis could be improved from 1.0 to 2.1 % (starting from ketone **37**). In addition, the C_2-symmetric bicyclo[3.3.0]octa-3,7-diene-2,6-dione **11** was prepared on a gram-quantity scale in an enantiomerically pure form. Although compound **11** seemed to be an attractive building block for further functionalization towards cylindramide and related natural products, the high tendency to undergo polymerization and sluggish reactivity with cuprates or other nucleophiles prevented its further use in synthesis.

Detailed NMR investigations proved the structural identity of the synthesized compound **1** to be comparable to that of the natural product isolated by Fusetani. ROESY data were consistent with two lowest-energy conformations that differ in the orientations of the amide bond and the tetramic acid moiety. Further investigations as to how the conformation might effect biological properties are currently being performed.

Experimental Section

General methods: Column chromatography was carried out on silica gel 60 (grain size 0.04–0.063 mm, Fluka) with hexanes (PE, b.p. 40–60 °C) and ethyl acetate (EtOAc) as eluents. HPLC was performed by using a Nucleosil C-18 AB column (250 × 21 mm, grain size 7 µm) (Macherey–Nagel); MPLC was performed on Nucleosil 1525 CN (grain size 10–15 µm) (Macherey–Nagel). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC250 (250 MHz and 62.5 MHz, respectively), a Bruker ARX300 (300 MHz and 75 MHz, respectively), a Bruker ARX500 (500 MHz and 125 MHz, respectively), and a Bruker Avance 900 (900 MHz and 225 MHz, respectively) spectrometer. ^{13}C NMR multiplicities were determined with DEPT experiments. FTIR spectra were recorded on a Bruker Vektor 22 spectrometer. Mass spectra were measured on a Finnigan MAT 95 (CH_4, chemical ionization) and a Varian MAT 711 (EI, 70 eV). Optical rotations were measured on a Perkin–Elmer Polarimeter 241.

Compounds **12**,[59] **19**,[17] (*S,S*)-**28**,[25–27] [(1-ethoxyvinyl)oxy]trimethylsilane,[60] IBX,[61] and MPO = 4-methoxypyridin-*N*-oxide[62] were prepared according to literature procedures.

Methyl (2*E*)-5-[(*tert*-butoxycarbonyl)amino]pent-2-enoate (13): Methyl triphenylphosphoranylacetate (25.0 g, 74.0 mmol) was added to a solution of freshly prepared compound **12** (12.3 g, 71.2 mmol) in CH_2Cl_2 (230 mL) at 0 °C and the reaction mixture was stirred for 4 h at 0 °C, and for a further 16 h at RT. The solvent was removed under vacuum, the residue taken up in cold Et_2O, and crystalline triphenylphosphine oxide was separated. The residue was purified by chromatography ($R_f = 0.38$, PE/EtOAc 4:1) to give compound **13** (14.17 g, 87 %, 98 % GC purity) as a viscous colorless oil. The spectroscopic data corresponded with those in the literature.[59]

Methyl (2*R*,3*S*)-5-[(*tert*-butoxycarbonyl)amino]-2,3-dihydroxypentanoate (15): Compound **13** (3.20 g, 14.0 mmol) was added to an ice-cold solution of AD-mix-α (19.8 g) and methanesulfonamide (1.4 g, 14 mmol) in *t*BuOH/H_2O 1:1 (140 mL) and the biphasic mixture was stirred for 24 h. Then Na_2SO_3 (21 g, 170 mmol) was added and, after stirring for 30 min, the organic layer was separated. The aqueous layer was extracted with EtOAc (4 × 70 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was taken up in some cold Et_2O and solid methanesulfonamide was separated to give compound **15** (3.58 g, 96 % *ee*, 95 %, 94 % purity as indicated by NMR spectroscopy) as a colorless resin that was used without further purification. $R_f = 0.20$ (PE/EtOAc 1:1); $[\alpha]_D^{20} = -15.8$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.41$ (s, 9H; $(CH_3)_3C$), 1.63–1.73 (m, 1H; H4), 1.77–1.87 (m, 1H; H4), 3.16–3.25 (m, 1H; H5), 3.30–3.45 (m, 1H; H5), 3.62 (br, 1H; NH), 3.79 (s, 3H; CO_2Me), 3.95 (d, $J = 9.7$ Hz,

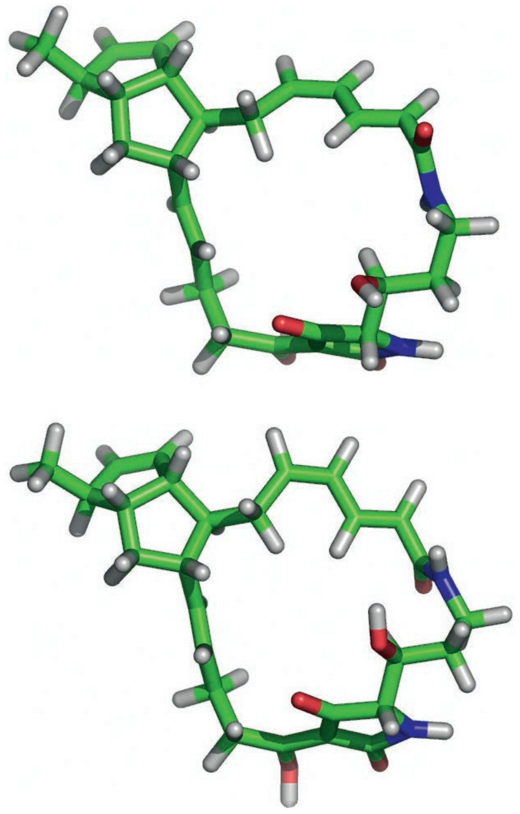


Figure 5. Lowest-energy structures for two different structure calculations of cylindramide (**1**). The rmsd (root-mean-square deviation) value of each run was 0.2 Å.

1H; H3), 4.08 (d, $J=1.9$ Hz, 1H; H2), 4.95 (br, 1H; OH), 5.24 ppm (br, 1H; OH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=28.3$ ($(CH_3)_3C$), 33.9 (C4), 37.1 (C5), 52.6 (CO_2Me), 69.8 (C3), 73.7 (C3), 79.6 ($(CH_3)_3C$), 156.9 (NCO_2), 173.5 ppm (C1); FTIR (ATR): $\tilde{\nu}=3343$ (s), 3224 (m), 2948 (m), 1747 (vs), 1679 (vs), 1518 (vs), 1454 (s), 1439 (s), 1384 (m), 1364 cm^{-1} (s); MS (EI): *m*/*z* (%): 263 (0.5) $[M]^+$, 128 (30), 118 (69), 90 (14), 74 (20), 57 (100); elemental analysis calcd (%) for $C_{11}H_{21}NO_6$: C 50.18, H 8.04, N 5.32; found: C 50.22, H 8.01, N 5.15; GC: Astec GTA (30 m×0.25 mm), H_2 (flow 6 mL min^{-1}), 1 min at 60°C, then 10°C min^{-1} gradient, $t_R(2R,3S)$-**15**: 15.11 min, 96% *ee*, $t_R(2S,3R)$-**15**: 15.43 min.

Methyl (2*R*,3*S*)-5-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-2-*O*-[(4-nitrophenyl)sulfonyl]pentanoate (17): NEt_3 (10 mL, 72.0 mmol) and 4-nitrobenzenesulfonyl chloride (7.98 g, 36.0 mmol) were added to a solution of compound **15** (9.50 g, 36.0 mmol) in dry CH_2Cl_2 (325 mL) at 4°C and the reaction mixture was stirred for 16 h at 4°C. The solvent was removed under vacuum, the residue was dissolved in EtOAc (450 mL) and was successively washed with 0.5 M HCl, satd $NaHCO_3$ solution, and brine (72 mL each). The organic layer was dried ($MgSO_4$), concentrated, and the residue washed with some cold Et_2O to give compound **17** (10.5 g, 65%, 95% NMR purity) as a white solid. M.p. 140°C; $[\alpha]_D^{20}=-14.2$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.43$ (s, 9H; $(CH_3)_3C$), 1.55–1.65 (m, 1H; H4), 1.77 (ddt, $J=14.2$, 10.5, 4.2 Hz, 1H; H4), 3.10–3.20 (m, 1H; H5), 3.42–3.54 (m, 1H; H5), 3.70 (s, 3H; CO_2Me), 3.95 (d, $J=4.6$ Hz, 1H; H3), 4.12–4.20 (m, 1H; O*H*), 4.77 (br, 1H; N*H*), 5.04 (d, $J=3.3$ Hz, 1H; H2), 8.18 (d, $J=8.7$ Hz, 2H; Ar), 8.38 ppm (d, $J=8.7$ Hz, 2H; Ar); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=28.2$ ($(CH_3)_3C$), 33.9 (C4), 36.4 (C5), 52.8 (CO_2Me), 68.2 (C3), 80.3 ($(CH_3)_3C$), 81.1 (C2), 124.1 (Ar), 129.5 (Ar), 142.0 (Ar), 150.8 (Ar), 157.5 (NCO_2), 167.0 ppm (C1); FTIR (ATR): $\tilde{\nu}=3342$ (m), 3296 (w), 3109 (w), 2975 (w), 1756 (s), 1608 (w), 1531 (s), 1447 (m), 1405 (w), 1370 (s), 1350 (s), 1279 (s), 1243 (m), 1188 (vs), 994 (s), 850 (s), 738 (s), 618 cm^{-1} (s); MS (FAB, NBA): *m*/*z* (%): 471 (10) $[M+Na]^+$, 449 (55) $[M+H]^+$, 393 (100), 349 (85); elemental analysis calcd (%) for $C_{17}H_{24}N_2O_{10}S$: C 45.53, H 5.39, N 6.25, S 7.15; found: C 45.60, H 5.42, N 6.22, S 7.19.

Methyl (2*S*,3*S*)-5-ammonium-2-azido-3-(*tert*-butyldimethylsilyloxy)pentanoate trifluoroacetate (18): a) Powdered sodium azide (16.3 g, 251 mmol) was added to a solution of compound **17** (16.7 g, 37.2 mmol) in DMF (420 mL) and the suspension stirred for 16 h at 50°C. The solvent was removed under high vacuum and the residue taken up in H_2O (150 mL) and EtOAc (400 mL). The organic layer was dried ($MgSO_4$) and concentrated. The pale-yellow resinous methyl (2*S*,3*S*)-2-azido-5-[(*tert*-butoxycarbonyl)amino]-3-hydroxypentanoate (**16**) (95% NMR purity) was used without further purification. $[\alpha]_D^{20}=-26.7$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.42$ (s, 9H; $(CH_3)_3C$), 1.62–1.72 (m, 2H; H4), 3.10–3.20 (m, 1H; H5), 3.39–3.55 (m, 1H; H5), 3.80 (s, 3H; CO_2Me), 3.95–4.01 (m, 2H; H2, H3), 4.11 (br, 1H; O*H*), 4.90 ppm (br, 1H; N*H*); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=28.2$ ($(CH_3)_3C$), 33.5 (C4), 36.7 (C5), 52.6 (CO_2Me), 66.1 (C2), 69.1 (C3), 79.9 ($(CH_3)_3C$), 157.2 (NCO_2), 169.2 ppm (CO_2Me); FTIR (ATR): $\tilde{\nu}=3388$ (s), 2978 (m), 2110 (vs), 1744 (s), 1685 (vs), 1518 (s), 1367 (s), 1438 (m), 1364 cm^{-1} (s); MS (DCI, NH_3): *m*/*z* (%): 594 (25) $[2M+NH_4]^+$, 577 (30) $[2M+H]^+$, 306 (85) $[M+NH_4]^+$, 289 (100) $[M+H]^+$, 250 (75), 233 (25), 189 (15), 135 (15); HRMS (DCI): calcd for $C_{11}H_{21}N_4O_5$: 289.1506; found: 289.1499 $[M+H]^+$.

b) A solution of compound **16** (see above), TBSCl (9.00 g, 58.6 mmol), imidazole (8.20 g, 120 mmol), and DMAP (300 mg, 2.40 mmol) in dry DMF (24 mL) was stirred for 1 d at RT. After addition of H_2O (50 mL) and EtOAc (100 mL), the layers were separated and the organic layer was washed with brine, dried by using $MgSO_4$, and concentrated. The residue was purified by chromatography (PE/EtOAc 3:1) to give methyl (2*S*,3*S*)-2-azido-5-[(*tert*-butoxycarbonyl)amino]-3-(*tert*-butyldimethylsiloxy)-pentanoate (14.85 g, 99% over two steps, >95% NMR purity) as a pale yellow oil. $R_f=0.33$ (PE/Et_2O 6:1); $[\alpha]_D^{20}=+2.3$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.11$ (s, 3H; Me_2Si), 0.12 (s, 3H; Me_2Si), 0.90 (s, 9H; $(CH_3)_3CSi$), 1.44 (s, 9H; $(CH_3)_3C$), 1.62–1.76 (m, 1H; H4), 1.87 (ddt, $J=13.6$, 7.7, 7.6 Hz, 1H; H4), 3.21 (dd, $J=12.6$, 6.4 Hz, 2H; H5), 3.79 (s, 3H; CO_2Me), 4.09 (d, $J=4.8$ Hz, 1H; H2), 4.18 (dt, $J=6.9$, 4.4 Hz, 1H; H3), 4.69 ppm (br, 1H; N*H*); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.7$ (Me_2Si), -4.6 (Me_2Si), 17.8 (Me_3CSi), 25.6 (Me_3CSi), 28.3 ($(CH_3)_3C$), 32.8 (C4), 36.9 (C5), 52.6 (CO_2Me), 66.5 (C2), 71.5 (C3), 79.1 ($(CH_3)_3C$), 155.7 (NCO_2), 168.5 ppm (C1); FTIR (ATR): $\tilde{\nu}=3368$ (m), 2955 (m), 2931 (m), 2888 (m), 2858 (m), 2108 (vs), 1744 (s), 1702 (vs), 1473 (s), 1463 (m), 1437 (m), 1391 (m), 1365 cm^{-1} (s); MS (CI, NH_3): *m*/*z* (%): 420 (6) $[M+NH_4]^+$, 403 (28) $[M+H]^+$, 347 (16), 303 (24), 289 (100) $[M+H-TBS]^+$, 232 (30), 200 (28), 171 (30), 73 (25), 57 (23); HRMS (DCI): calcd for $C_{17}H_{35}N_4O_5Si$: 403.2371; found: 403.2370 $[M+H]^+$.

c) TFA (24 mL) was added dropwise over 15 min to an ice-cold solution of methyl (2*S*,3*S*)-2-azido-5-[(*tert*-butoxycarbonyl)amino]-3-(*tert*-butyldimethylsiloxy)pentanoate (1.60 g, 4.00 mmol) in dry CH_2Cl_2 (24 mL). After stirring for 2 h at 0°C, the solvent was removed under vacuum at 0°C. The residue was treated with dry benzene (2×15 mL), concentrated under vacuum at 0°C, and dried for 3 h under high vacuum to give compound **18** (99%, >95% NMR purity) as a colorless, highly hygroscopic solid. ^{1}H NMR (500 MHz, CD_2Cl_2): $\delta=0.14$ (s, 3H; Me_2Si), 0.16 (s, 3H; Me_2Si), 0.90 (s, 9H; Me_3CSi), 1.92–1.98 (m, 2H; H4), 3.21–3.35 (m, 2H; H5), 3.79 (s, 3H; CO_2Me), 4.31 (d, $J=4.1$ Hz, 1H; H2), 4.36 (td, $J=4.7$, 4.1 Hz, 1H; H3), 7.58 ppm (br, 3H; NH_3); ^{13}C NMR (125 MHz, CD_2Cl_2): $\delta=-5.4$ (Me_2Si), -5.2 (Me_2Si), 17.6 (Me_3CSi), 25.2 (Me_3CSi), 29.8 (C4), 36.8 (C5), 52.9 (CO_2Me), 67.1 (C2), 70.1 (C3), 115.3 (q, $J=288$ Hz; $CF_3CO_2^-$), 160.6 (q, $J=40$ Hz; $CF_3CO_2^-$), 168.4 ppm (C1).

Methyl (2*S*,3*S*)-2-azido-3-(*tert*-butyldimethylsilyloxy)-5-[(*E*-3-iodoprop-2-enoyl]amino)pentanoate (7): DEPC (200 µL, 1.20 mmol) was added to an ice-cold solution of compounds **18** (416 mg, 1.00 mmol) and **19** (198 mg, 1.00 mmol) in dry DMF (5 mL) followed by addition of NEt_3 (320 µL, 2.28 mmol) after 15 min. After stirring for 16 h at 0°C, EtOAc (25 mL) was added and the reaction mixture was washed successively with a cold solution of $KHSO_4$ (1 M), satd $NaHCO_3$, and brine (15 mL each). The organic layer was dried ($MgSO_4$) and concentrated. The residue was subjected to chromatography ($R_f=0.37$, PE/EtOAc 3:1) to give compound **7** (364 mg, 83%, >95% NMR purity) as a viscous colorless oil. $[\alpha]_D^{20}=+10.8$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=$

0.12 (s, 6H; Me_2Si), 0.90 (s, 9H; Me_3CSi), 1.71–1.81 (m, 1H; H4), 1.85–1.93 (m, 1H; H4), 3.30–3.39 (m, 1H; H5), 3.41–3.49 (m, 1H; H5), 3.79 (s, 3H; CO_2Me), 4.10 (d, $J=4.9$ Hz, 1H; H2), 4.18–4.23 (m, 1H; H3), 5.83 (br, 1H; N*H*), 6.78 (d, $J=14.5$ Hz, 1H; H8), 7.67 ppm (d, $J=14.5$ Hz, 1H; H8); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.7$ (Me_2Si), −4.6 (Me_2Si), 17.9 (Me_3*C*Si), 25.6 (Me_3CSi), 32.2 (C4), 35.8 (C5), 52.7 (CO_2Me), 66.4 (C2), 71.5 (C3), 94.5 (C8), 138.5 (C7), 163.7 (C6), 168.5 ppm (C1); FTIR (ATR): $\tilde{\nu}=3287$ (m), 2952 (s), 2929 (s), 2885 (m), 2856 (m), 2107 (vs), 1740 (vs), 1641 (vs), 1588 (s), 1546 (vs), 1252 (vs), 1110 (vs), 941 (s), 835 (vs), 776 cm^{-1} (vs); MS (DCI, NH_3): *m/z* (%): 500 (20) [*M*+NH_4]$^+$, 483 (100) [*M*+H]$^+$, 425 (20), 368 (15), 200 (15); HRMS (DCI): calcd for $C_{15}H_{28}IN_4O_4Si$: 483.0919; found: 483.0931 [*M*+H]$^+$.

6-(3-Hydroxypropyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (24): a) 1,3-Dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone (DMPU) (7 mL) was added to a freshly prepared solution of LDA (45.0 mmol, prepared from dry diisopropylamine (7.30 mL) and BuLi (28.3 mL, 1.6 M in hexane), 15 min at 0°C) in dry THF (30 mL). After 15 min, compound **22** (7.10 g, 46.0 mmol) was slowly added and the reaction cooled from 0 to −40°C after 20 min. Then compound **23** (5.50 mL, 60.0 mmol) was added dropwise and the mixture was allowed to warm to RT (16 h). The reaction was quenched with cold HCl (75 mL, 1 N), Et_2O (150 mL) was added, and the layers were separated. The organic layer was washed with brine, dried by using $MgSO_4$, and concentrated. The residue was purified by chromatography (PE/EtOAc 2:1; $R_f=0.20$, PE/Et_2O 3:1) to separate nonpolar byproducts. 6-(But-3-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (6.00 g, approximately 50%, about 70% NMR purity) was obtained as a pale-yellow oil that was used directly without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.68$ (s, 6H; H9), 2.29–2.33 (m, 4H; H4, H5), 5.04 (dd, $J=10.8$, 0.9 Hz, 1H; H7), 5.07 (d, $J=15.5$ Hz, 1H; H7), 5.24 (s, 1H; H2), 5.73–5.83 ppm (m, 1H; H6); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=24.9$ (C9), 29.5 (C5), 32.7 (C4), 93.3 (C2), 106.2 (C8), 116.0 (C7), 135.8 (C6), 161.0 (C3), 170.8 ppm (C1); FTIR (ATR): $\tilde{\nu}=1722$ (vs), 1632 (vs), 1373 (vs), 1269 (vs), 1250 (s), 1200 (vs), 1104 (m), 1011 (vs), 899 (s), 803 cm^{-1} (s); MS (CI): *m/z* (%): 365 (90) [2*M*+H]$^+$, 183 (100) [*M*+H]$^+$, 125 (50), 124 (30), 96 (15), 87 (20); HRMS (CI): calcd for $C_{10}H_{15}O_3$: 183.1016; found: 183.1021 [*M*+H]$^+$.

b) A slow stream of O_3 was passed through a solution of 6-(but-3-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (182 mg, 1.00 mmol) in MeOH/CH_2Cl_2/pyridine 4:4:1 (9 mL) at −78°C until a light-blue color was visible. Then N_2 gas was passed through for 1 min, $NaBH_4$ (109 mg, 2.80 mmol) was added, and the reaction mixture was allowed to warm to 10°C. After quenching with a satd solution of NH_4Cl (15 mL), the reaction mixture was extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography ($R_f=0.4$, PE/EtOAc 1:2) to give compound **24** (119 mg, 64%, >95% NMR purity) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.60$ (br, 1H; O*H*), 1.69 (s, 6H; H8), 1.76–1.84 (m, 2H; H5), 2.32–2.37 (m, 2H; H4), 3.69 (t, $J=6.0$ Hz, 2H; H6), 5.26 ppm (s, 1H; H2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=25.0$ (C8), 28.6 (C5), 30.0 (C4), 61.4 (C6), 93.3 (C2), 106.3 (C8), 161.2 (C3), 171.4 ppm (C1); FTIR (ATR): $\tilde{\nu}=3426$ (s), 2998 (m), 2942 (m), 2877 (m), 1705 (vs), 1628 (vs), 1389 (vs), 1374 (vs), 1271 (vs), 1253 (s), 1200 (vs), 1055 (vs), 1010 (vs), 902 (s), 805 cm^{-1} (s); MS (CI, CH_4): *m/z* (%): 187 (60) [*M*+H]$^+$, 129 (100), 128 (40), 111 (20), 87 (30); HRMS (CI): calcd for $C_9H_{15}O_4$: 187.0965; found: 187.0966 [*M*+H]$^+$.

2,2-Dimethyl-6-{3-[(1-phenyl-1*H*-tetrazol-5-yl)thio]propyl}-4*H*-1,3-dioxin-4-one (25): A solution of compound **24** (1.86 g, 10.0 mmol) in dry THF (5 mL) was added to a solution of 1-phenyl-1*H*-tetrazole-5-thiol (2.67 g, 15.0 mmol), diethyl azodicarboxylate (DEAD) (40% in toluene, 4.12 mL, 15 mmol), and triphenylphosphine (3.92 g, 15.0 mmol) in dry THF (60 mL) at 0°C, and the mixture was stirred for 1 h. Then a satd solution of $NaHCO_3$ (100 mL) was added and the mixture extracted with CH_2Cl_2 (2×150 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography ($R_f=0.5$, PE/EtOAc 1:1) and was recrystallized from CH_2Cl_2/diisopropyl ether to give compound **25** (2.49 g, 72%, >95% NMR purity) as colorless crystals. M.p. 73–75°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.69$ (s, 6H; H8), 2.11–2.18 (m, 2H; H5), 2.39–2.43 (m, 2H; H4), 3.40–3.44 (m, 2H; H6), 5.27 (s, 1H; H2), 7.53–7.59 ppm (m, 5H; Ar); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=25.0$ (C8), 25.5 (C5), 32.2 (C6), 32.3 (C4), 93.9 (C2), 106.6 (C7), 123.7 (Ar), 129.8 (Ar), 130.2 (Ar), 133.5 (Ar), 153.7 (Ar), 160.8 (C3), 169.8 ppm (C1); FTIR (ATR): $\tilde{\nu}=1713$ (vs), 1638 (vs), 1596 (m), 1498 (s), 1373 (vs), 1275 (vs), 1236 (vs), 1200 (vs), 1011 (vs), 760 (vs), 688 cm^{-1} (vs); MS (DCI, NH_3): *m/z* (%): 364 (30) [*M*+NH_4]$^+$, 347 (5) [*M*+H]$^+$, 289 (100) [*M*+H−acetone]$^+$; elemental analysis calcd (%) for $C_{16}H_{18}N_4O_5S$: C 55.48, H 5.24, N 16.17; found: C 55.42, H 5.25, N 16.37.

2,2-Dimethyl-6-{3-[(1-phenyl-1*H*-tetrazol-5-yl)sulfonyl]propyl}-4*H*-1,3-dioxin-4-one (8): A solution of compound **25** (1.56 g, 4.50 mmol) in EtOH (50 mL) was added to an ice-cold solution of ammonium heptamolybdate (12.2 g, 0.98 mmol) and 30% H_2O_2 (40.5 mL). After stirring for 1 h at 0°C, the mixture was warmed to RT within 3 h and the suspension was filtered through Celite. A satd solution of NH_4Cl (100 mL) was added to the filtrate that was then extracted with CH_2Cl_2 (2×150 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography ($R_f=0.5$, PE/EtOAc 1:1) to give compound **8** (1.585 g, 93%, >95% NMR purity) as a colorless solid. M.p. 79–81°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.70$ (s, 6H; H8), 2.24–2.32 (m, 2H; H5), 2.48 (t, $J=7.4$ Hz, 2H; H4), 3.77–3.82 (m, 2H; H6), 5.30 (s, 1H; H2), 7.59–7.71 ppm (m, 5H; Ar); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=18.8$ (C5), 25.0 (C8), 31.7 (C4), 54.8 (C6), 94.4 (C2), 106.8 (C7), 124.9 (Ar), 129.7 (Ar), 131.5 (Ar), 132.8 (Ar), 153.2 (Ar), 160.5 (C3), 168.4 ppm (C1); FTIR (ATR): $\tilde{\nu}=1718$ (vs), 1632 (vs), 1497 (s), 1390 (s), 1376 (s), 1338 (vs), 1201 (vs), 1152 (vs), 1010 cm^{-1} (vs); MS (DCI, NH_3): *m/z* (%): 396 (100) [*M*+NH_4]$^+$, 379 (5) [*M*+H]$^+$, 338 (30), 321 (20), 295 (10), 218 (10), 210 (10), 76 (18); elemental analysis calcd (%) for $C_{16}H_{18}N_4O_5S$: C 50.78, H 4.79, N 14.81; found: C 50.56, H 4.80, N 14.69.

(3a*R*,6a*R*)-Hexahydropentalene-1,4-dione (29): A solution of DMSO (123 mL, 1.74 mol) in CH_2Cl_2 (40 mL) was slowly added to a solution of oxalyl chloride (73.4 mL, 778 mmol) in CH_2Cl_2 (750 mL) at −60°C followed by addition of a solution of (*S*,*S*)-**28** (51.5 g, 362 mmol) in dry CH_2Cl_2 (160 mL). The temperature was not allowed to exceed −60°C. After stirring for 20 min, NEt_3 (515 mL, 4.25 mol) was added dropwise over 35 min, the mixture was stirred for a further 10 min and was then allowed to warm to RT. The reaction was quenched with H_2O (400 mL) and the layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was distilled under vacuum to give compound **29** (44.9 g, 90%, 97% GC purity) as a pale-yellow oil. B.p. 62–64°C (0.07 Torr); $[\alpha]_D^{20}=-412$ ($c=1.00$ in $CHCl_3$); ref. [28c]: −457 ($c=1$ in CH_2Cl_2); GC: GTA (20 m×0.25 mm), carrier gas H_2 (flow: 5 mL min^{-1}), 80°C, then 5°C min^{-1} gradient, $t_{R1}=17.13$ min, $t_{R2}=18.68$ min, 98% *ee*. The spectroscopic data agreed with those in the literature.[28]

(2′*R*,3a′*R*,5′*R*,6a′*R*)-2,5-Dibromohexahydrodispiro[1,3-dioxolane-2,1′-pentalene-4′,2′′-[1,3]dioxolane] (30): A solution of compound **29** (3.45 g, 25 mmol) and $PhNMe_3Br_3$ (24.3 g, 65 mmol) in THF/ethylene glycol 1:1 (120 mL) was stirred for 2 d at 30°C. The reaction was quenched with a bisulfite and a satd $NaHCO_3$ solution and extracted with Et_2O (2×250 mL). The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The crude product was recrystallized from boiling MeOH to give compound **30** (8.04 g, 84%, >95% NMR purity) as colorless crystals. M.p. 118–120°C; $[\alpha]_D^{20}=-106.3$ ($c=1.00$ in $CHCl_3$). The spectroscopic data agreed with those in the literature.[30]

(3a′*R*,6a′*R*)-Dihydrodispiro[1,3-dioxolane-2,1′-pentalene-4′,2′′-[1,3]dioxolane] (31): Compound **30** (5.73 g, 14.92 mmol) was added to a solution of NaOMe (4.82 g, 89.2 mmol) in DMSO (27 mL), whereby the temperature did not exceed 60°C, and the mixture was heated for 2 h at 70°C. Then H_2O (200 mL) was added and the mixture extracted with Et_2O (3×150 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give compound **31** (3.29 g, 99%, >95% NMR purity) as colorless crystals. M.p. 100–102°C; $[\alpha]_D^{20}=-217$ ($c=1.00$ in $CHCl_3$). The spectroscopic data agreed with those in the literature.[30]

(3a*R*,6a*R*)-Dihydropentalene-1,4-dione (11): A solution of compound **31** (3.29 g, 14.8 mmol) and PPTS (2.22 g, 8.80 mmol) in acetone/3% H_2O (300 mL) was heated for 3 h at reflux. The solvent was removed under vacuum, the residue was taken up in Et_2O (200 mL), and was washed with brine. The organic layer was dried ($MgSO_4$) and concentrated to give compound **11** (1.68 g, 84%, 99% GC purity) as a colorless solid. M.p. 72–74 °C; $[\alpha]_D^{20}=-1493$ ($c=1.00$ in $CHCl_3$); GC: Bondex un α (20 m × 0.25 mm), carrier gas: H_2 (0.4 bar), 3 min at 40 °C, then 2.5 °C min^{-1} gradient, $t_{R1}=35.43$ min, $t_{R2}=37.29$ min, 99.4% *ee*. The spectroscopic data agreed with those in the literature.[30]

Dimethyl (3a′*R*,4*R*,5*R*,6a′*R*)-4′-oxo-4′,6a′-dihydro-3a′*H*-spiro[1,3-dioxolane-2,1′-pentalene]-4,5-dicarboxylate (34): $BF_3\cdot OEt_2$ (180 µL, 4.80 mmol) was added to a solution of compound **11** (264 mg, 2.00 mmol) and (*R*,*R*)-dimethyl tartrate (1.07 g, 6.00 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C, and the mixture was stirred for 20 h at RT. After quenching with a solution of satd $NaHCO_3$, the reaction mixture was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography (PE/EtOAc 1:1; $R_f=0.23$, PE/EtOAc 2:1) to give compound **34** (176 mg, 30%, >95% NMR purity) as a colorless resin together with compound **11** (174 mg, 66%). $[\alpha]_D^{20}=-327$ ($c=1.00$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=3.43$–3.46 (m, 1H; H4), 3.77 (s, 3H; CO_2Me), 3.83 (s, 3H; CO_2Me), 3.87–3.90 (m, 1H; H8), 4.89 (d, $J=3.3$ Hz; H2′), 4.90 (d, $J=3.3$ Hz; H3′), 5.68 (dd, $J=5.6$, 2.3 Hz, 1H; H7), 5.95 (dd, $J=5.7$, 2.0 Hz, 1H; H2), 6.14 (dd, $J=5.6$, 2.7 Hz, 1H; H6), 7.53 ppm (dd, $J=5.7$, 3.0 Hz, 1H; H3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=52.7$ (CO_2Me), 53.1 (C4), 55.2 (C8), 77.3, 77.7 (C2′, C3′), 121.9 (C5), 131.3 (C2), 131.5 (C7), 135.5 (C6), 161.3 (C3), 169.3, 169.7 (C1′, C4′), 207.0 ppm (C1); FTIR (ATR): $\tilde{\nu}=2956$ (m), 1756 (vs), 1707 (vs), 1437 (s), 1343 (s), 1228 (vs), 1177 (s), 1151 (vs), 1097 (vs), 1004 (s), 968 (s), 887 (m), 827 (m), 762 (m), 676 cm^{-1} (m); MS (EI): *m*/*z* (%): 294 (100) $[M]^+$, 266 (10), 235 (20), 175 (15), 106 (20), 84 (35), 78 (35); HRMS (EI): calcd for $C_{14}H_{14}O_7$: 294.0740; found: 294.0738 $[M]^+$.

Dimethyl (3a′*R*,4*R*,5*R*,5′*R*,6*R*,6a′*R*)-5′-[(benzyloxy)methyl]-6′-(2-ethoxy-2-oxoethyl)-4′-oxo-4′,5′,6′,6a′-tetrahydro-3a′*H*-spiro[1,3-dioxolane-2,1′-pentalene]-4,5-dicarboxylate (35a): [(1-Ethoxyvinyl)oxy]trimethylsilane (75 mg, 467 µmol) was added to a solution of compound **34** (55 mg, 187 µmol) and scandium triflate (15 mg, 30.5 µmol) in dry CH_2Cl_2 (1.5 mL) at −70 °C. After stirring for 30 min, the mixture was added through a cannula to a stirred mixture of 2,6-di-*tert*-butylpyridine (45 µL, 200 µmol), TMSOTf (36 µL, 200 µmol), and formaldehyde dibenzylacetal (200 mg, 1.00 mmol) in CH_2Cl_2 (2 mL) at 0 °C, and the reaction mixture stirred for 1 h at 0 °C, and for a further 3 h at RT. After quenching with a satd solution of $NaHCO_3$, the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography ($R_f=0.22$, PE/EtOAc 2:1) to give compound **35a** (79 mg, 84%, >95% NMR purity) as a viscous colorless oil. $[\alpha]_D^{20}=-209$ ($c=1.00$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=1.23$ (t, $J=7.2$ Hz, 3H; CH_3CH_2O), 2.59–2.69 (m, 3H; H3, H9), 2.73–2.79 (m, 1H; H2), 3.18 (t, $J=8.5$ Hz, 1H; H4), 3.59–3.60 (m, 3H; H8, H10), 3.83 (s, 3H; CO_2Me), 3.85 (s, 3H; CO_2Me), 4.04–4.16 (m, 2H; CH_3CH_2O), 4.43 (d, $J=12.2$ Hz, 1H; $PhCH_2$), 4.46 (d, $J=12.2$ Hz, 1H; $PhCH_2$), 4.89 (d, $J=2.9$ Hz, 1H; H2′), 4.99 (d, $J=2.9$ Hz, 1H; H3′), 5.83 (dd, $J=5.5$, 3.0 Hz, 1H; H7), 6.04 (dd, $J=5.5$, 2.4 Hz, 1H; H6), 7.23–7.35 ppm (m, 5H; Ar); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=14.1$ (CH_3CH_2O), 35.7 (C3), 36.5 (C9), 48.9 (C4), 52.7 (CO_2Me), 55.2 (C2), 58.2 (C8), 60.1 (CH_3CH_2O), 67.4 (C10), 73.0 ($PhCH_2$), 77.1, 77.6 (C2′, C3′), 125.0 (C5), 127.3 (Ar), 127.3 (Ar), 128.1 (Ar), 132.2 (C6), 134.2 (C7), 138.2 (Ar), 169.5, 169.8, 172.0 (CO_2Me, C1′, C2′), 212.5 ppm (C1); FTIR (ATR): $\tilde{\nu}=2955$ (m), 1759 (vs), 1737 (vs), 1437 (m), 1354 (m), 1221 (s), 1148 (vs), 1095 (vs), 1020 (s), 984 (s), 741 (m), 700 cm^{-1} (m); MS (DCI, NH_3): *m*/*z* (%): 502 (2) $[M]^+$, 457 (2), 394 (30), 349 (10), 307 (5), 233 (10), 108 (100), 91 (50), 79 (75); HRMS (EI): calcd for $C_{26}H_{30}O_{10}$: 502.1839; found: 502.1840 $[M]^+$.

(3a*R*,6a*R*)-Hexahydro-4′*H*-spiro[1,3-dioxolane-2,1′-pentalen]-4′-one (37): a) A solution of compound **29** (25.6 g, 190 mmol), toluenesulfonic acid monohydrate (2.50 g, 13.0 mmol), and ethylene glycol (12.7 mL, 228 mmol) in dry toluene (1 L) was heated for 8 h at reflux (water trap). Then the mixture was washed with a satd solution of $NaHCO_3$ and brine (250 mL each), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography (PE/EtOAc 3:1) to give a first fraction containing compound **36** ($R_f=0.40$, 5.58 g, 13%) and a second fraction containing compound **37** ($R_f=0.25$, 27.66 g, 80%, 95% GC purity) and compound **29** (1.27 g, 5%) as pale-yellow oils.

b) HCl (25 mL, 1 N) was added to a solution of compound **36** (9.26 g, 41.0 mmol) in THF/MeOH/acetone 6:1:1 (250 mL) and the reaction mixture was stirred for 1 h. After quenching with a satd solution of $NaHCO_3$, the mixture was extracted with EtOAc (300 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (PE/EtOAc 2:1) to give compound **37** (6.34 g, 85%, 97% GC purity) and compound **36** (0.62 g, 11%). The spectroscopic data of compound **37** agreed with those in the literature.[27]

Bisacetal 36: $[\alpha]_D^{20}=-60.3$ ($c=1.00$ in $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): $\delta=1.62$–1.83 (m, 8H; H2, H3), 2.43–2.53 (m, 2H; H4), 3.89–3.92 ppm (m, 8H; OCH_2CH_2O); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta=23.7$ (C3), 34.5 (C2), 47.7 (C4), 63.9 (OCH_2CH_2O), 64.9 (OCH_2CH_2O), 118.9 ppm (C1).

Monoacetal 37: $[\alpha]_D^{20}=-175$ ($c=1.00$ in $CHCl_3$); ref. [27]: −160 ($c=1.35$ in $CHCl_3$).

(3a′*R*,6a′*R*)-2′,3′,3a′,6a′-Tetrahydro-4′*H*-spiro[1,3-dioxolane-2,1′-pentalen]-4′-one (38): A solution of compound **37** (1.12 g, 6.16 mmol) in THF (10 mL) was added to a freshly prepared solution of LDA (7.40 mmol) in dry THF (15 mL) at −78 °C followed by addition of TMSCl (1.17 mL, 12.7 mmol) after 30 min. The mixture was allowed to warm to 10 °C within 3 h and then ice-cold pentane (100 mL) was added. The mixture was washed successively with a satd solution of NH_4Cl, H_2O, and brine (30 mL each). The organic layer was dried ($MgSO_4$) and concentrated. The obtained intermediate was dissolved in CH_2Cl_2 (5 mL) and added in the absence of light to a solution of IBX (2.58 g, 9.24 mmol) and 4-methoxypyridin-*N*-oxide monohydrate (1.32 g, 9.24 mmol) in DMSO (24 mL). After stirring for 30 min, the mixture was poured into a mixture of ice-cold satd $NaHCO_3$ solution and Et_2O (150 mL), and was then filtered through Celite. The filtrate was extracted with Et_2O (3 × 70 mL) and the combined organic layers were washed with brine (70 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography ($R_f=0.35$, PE/EtOAc 2:1) to give compound **38** (700 mg, 63%, 95% NMR purity) as a colorless oil. $[\alpha]_D^{20}=-290$ ($c=1.00$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=1.56$ (ddd, $J=13.1$, 13.0, 7.7 Hz, 1H; H6), 1.62 (dd, $J=13.0$, 7.0 Hz, 1H; H6), 1.84 (ddt, $J=13.1$, 7.7, 1.2 Hz, 1H; H7), 1.92–2.01 (m, 1H; H7), 2.76 (dd, $J=9.4$, 5.6 Hz, 1H; H8), 3.17–3.22 (m, 1H; H4), 3.86–4.06 (m, 4H; OCH_2CH_2O), 6.24 (dd, $J=5.6$, 1.9 Hz, 1H; H2), 7.62 ppm (dd, $J=5.6$, 2.9 Hz, 1H; H3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=24.5$ (C7), 31.8 (C6), 47.0 (C4), 53.5 (C8), 63.9 (OCH_2), 65.2 (OCH_2), 116.1 (C5), 135.6 (C2), 163.8 (C3), 212.3 ppm (C1); FTIR (ATR): $\tilde{\nu}=2951$ (s), 2881 (s), 1701 (vs), 1585 (m), 1456 (m), 1439 (m), 1323 (s), 1270 (s), 1232 (s), 1172 (vs), 1102 (vs), 1015 (vs), 998 (vs), 923 (s), 873 (s), 840 (vs), 768 (s), 643 cm^{-1} (s); MS (EI): *m*/*z* (%): 180 (15) $[M]^+$, 99 (100), 94 (12), 86 (22), 79 (10), 66 (20); HRMS (EI): calcd for $C_{10}H_{12}O_3$: 180.0786; found: 180.0783 $[M]^+$.

(3a′*R*,6′S,6a′*R*)-6′-Methyl-3′,3a′,6′,6a′-tetrahydro-2′*H*-spiro[1,3-dioxolane-2,1′-pentalen]-4′-yltrifluoromethanesulfonate (40): Methyllithium (68 mL, 1.6 M in Et_2O) was added dropwise to a suspension of copper iodide (10.5 g, 55.0 mmol) in dry THF (150 mL) at 0 °C. After formation of a clear solution, the mixture was cooled to −78 °C and a solution of compound **38** (5.76 g, 32.0 mmol) in THF (20 mL) was added followed by a solution of compound **39** (21.8 g, 56.0 mmol) in THF (100 mL) after 30 min. The mixture was allowed to warm to 0 °C within 5 h. After quenching with a solution of satd NH_4Cl (100 mL), Et_2O (250 mL) and a satd solution of EDTA (150 mL) were added, the layers were separated and the aqueous layer was extracted with Et_2O (250 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography (PE/EtOAc 2:1) to give a first fraction containing compound **41** ($R_f=0.55$, 2.47 g, 39%, 95% GC purity) and a second fraction containing compound **40** ($R_f=0.47$, 4.99 g, 47%, 95% NMR purity) as colorless oils. Compound **40**: $[\alpha]_D^{20}=+41$ ($c=1.00$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=1.11$ (d, $J=7.1$ Hz, 3H; 3-Me), 1.69–1.87 (m, 4H; H6, H7), 2.17 (ddd, $J=8.5$, 3.2, 1.0 Hz, 1H; H4), 2.88 (qq, $J=7.1$, 2.9 Hz, 1H; H8), 3.38 (tdt, $J=8.5$, 3.4, 1.6 Hz, 1H; H3), 3.84–3.97 (m, 4H; OCH_2CH_2O), 5.53 ppm (t, $J=1.9$ Hz, 1H; H2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=22.1$ (*Me*-C3), 25.4

(C7), 32.5 (C6), 37.4 (C3), 45.8 (C8), 54.2 (C4), 63.8 (O*C*H_2), 65.2 (O*C*H_2), 117.7 (C5), 118.6 (q, $J=320$ Hz; *C*F_3), 121.6 (C2), 148.3 ppm (C1); FTIR (ATR): $\tilde{\nu}=2960$ (m), 2879 (m), 1660 (m), 1419 (vs), 1342 (m), 1300 (w), 1248 (s), 1203 (vs), 1138 (vs), 1108 (vs), 1040 (s), 1017 (vs), 942 (vs), 840 (vs), 749 (m), 609 (vs), 579 cm^{-1} (vs); MS (CI): *m*/*z* (%): 329 (100) $[M+H]^+$, 284 (20), 195 (8), 179 (11), 99 (5); HRMS (CI): calcd for $C_{12}H_{16}F_3O_5S$: 329.0665; found: 329.0672 $[M+H]^+$.

(3a′*R*,6′*S*,6a′*R*)-6′-Methylhexahydro-4′*H*-spiro[1,3-dioxolane-2,1′-pentalen]-4′-one (41): $[\alpha]_D^{20}=-79.5$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.16$ (d, $J=6.8$ Hz, 3H; Me), 1.68–1.73 (m, 2H; H3, H6), 1.79–1.86 (m, 1H; H7), 1.91–2.06 (m, 2H; H2), 2.15–2.24 (m, 1H; H8), 2.28 (dd, $J=9.6$, 6.1 Hz, 1H; H3), 2.45 (dd, $J=17.5$, 7.7 Hz, 1H; H6), 2.79 (t, $J=10.2$ Hz, 1H; H4), 3.87–4.02 ppm (m, 4H; OCH_2CH_2O); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=21.8$ (Me), 24.5 (C3), 30.8 (C7), 34.2 (C2), 47.1 (C6), 49.6 (C4), 54.5 (C8), 64.2 (O$CH_2$$CH_2$O), 65.1 (O$CH_2CH_2$O), 118.7 (C1), 211.8 ppm (C5); FTIR (ATR): $\tilde{\nu}=2957$ (s), 2879 (s), 1735 (vs), 1459 (m), 1332 (m), 1199 (s), 1119 (s), 1017 (m), 946 (m), 845 cm^{-1} (m); MS (EI): *m*/*z* (%): 196 (10) $[M]^+$, 126 (8), 125 (10), 123 (6), 113 (5), 100 (60), 99 (100), 86 (40); HRMS (EI): calcd for $C_{11}H_{16}O_3$: 196.1099; found: 196.1087 $[M]^+$.

(3a′*S*,6′*S*,6a′*R*)-6′-Methyl-3′,3a′,6′,6a′-tetrahydro-2′*H*-spiro[1,3-dioxolane-2,1′-pentalene] (42): Triethylsilane (0.40 mL, 2.50 mmol) was added to a solution of compound **40** (285 mg, 0.87 mmol) and [$PdCl_2$(dppf)] (16 mg, 0.02 mmol) in DMF (5 mL) at 60 °C, and the mixture was heated at 60 °C for 1 h. Then Et_2O (25 mL) and H_2O (15 mL) were added, the layers were separated, and the aqueous layer was extracted with Et_2O (25 mL). The combined organic layers were washed with a satd solution of $NaHCO_3$ and brine (25 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography (PE/Et_2O 5:1; $R_f=0.74$, PE/Et_2O 3:1) to give compound **42** (141 mg, 90%, >95% NMR purity) as a colorless liquid. $[\alpha]_D^{20}=+133$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.04$ (d, $J=7.1$ Hz, 3H; 3-Me), 1.41–1.46 (m, 1H; H7), 1.59–1.69 (m, 2H; H6), 1.79–1.86 (m, 1H; H7), 2.06 (ddd, $J=8.3$, 3.7, 0.6 Hz, 1H; H4), 2.80–2.87 (m, 1H; H3), 3.27–3.29 (m, 1H; H8), 3.87–3.97 (m, 4H; OCH_2CH_2O), 5.46 (dt, $J=5.5$, 2.2 Hz, 1H; H1), 5.53 ppm (dt, $J=5.5$, 2.1 Hz, 1H; H2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=22.4$ (*Me*-C3), 28.0 (C7), 32.7 (C6), 42.9 (C3), 48.0 (C8), 55.7 (C4), 63.6 (O*C*H_2), 65.0 (O*C*H_2), 118.7 (C5), 132.2 (C1), 135.7 ppm (C2); FTIR (ATR): $\tilde{\nu}=3042$ (m), 2952 (s), 2868 (s), 1454 (m), 1436 (m), 1371 (m), 1339 (m), 1318 (m), 1261 (m), 1195 (s), 1151 (s), 1109 (vs), 1100 (vs), 1037 (vs), 1013 (vs), 943 (vs), 853 (s), 739 cm^{-1} (s); MS (CI): *m*/*z* (%): 181 (100) $[M+H]^+$, 179 (30), 165 (20), 137 (55), 119 (20), 99 (40), 83 (30); HRMS (EI): calcd for $C_{11}H_{16}O_2$: 180.1150; found: 180.1143 $[M]^+$.

(3a*R*,6*S*,6a*R*)-6-Methyl-6,6a-dihydropentalen-1(3a*H*)-one (10): a) A solution of compound **42** (1.99 g, 11.0 mmol) and pyridinium tosylate (753 mg, 3.00 mmol) in acetone/H_2O 95:5 (150 mL) was heated at reflux for 4 h. After removal of the solvent under reduced pressure (400 mbar, 40 °C bath temperature), the residue was taken up in Et_2O (150 mL), washed with H_2O and brine (75 mL each), and dried ($MgSO_4$). The solvent was removed under reduced pressure (800 mbar) and the residue was filtered through a short pad of silica gel (pentane/Et_2O 4:1). The filtrate was concentrated to 3–4 mL at 800 mbar pressure to give (3a*S*,6*S*,6a*R*)-6-methyl-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (quantified by NMR integration). The volatile product can be stored at −28 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.08$ (d, $J=7.0$ Hz, 3H; 3-Me), 1.93–2.26 (m, 4H; H7, H8), 2.29 (d, $J=7.3$ Hz, 1H; H2), 2.86–2.92 (m, 1H; H3), 3.57 (tt, $J=7.5$, 2.2 Hz, 1H; H6), 5.55 (dt, $J=5.6$, 1.6 Hz, 1H; H4), 5.69 ppm (dt, $J=5.6$, 2.4 Hz, 1H; H5); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=21.2$ (*Me*-C3), 25.2 (C7), 36.3 (C8), 45.5 (C6), 46.4 (C3), 57.5 (C2), 132.2 (C5), 137.2 (C4), 211.8 ppm (C1); FTIR (ATR): $\tilde{\nu}=3045$ (m), 2955 (m), 2900 (m), 2868 (m), 1732 (vs), 1454 (m), 1406 (m), 1372 (m), 1350 (m), 1307 (m), 1255 (m), 1226 (m), 1195 (m), 1151 (s), 1110 (m), 1093 (s), 943 (m), 918 (m), 877 (s), 807 (m), 738 (vs), 722 cm^{-1} (vs); MS (EI): *m*/*z* (%): 136 (70) $[M]^+$, 121 (25), 108 (50), 94 (20), 93 (20), 92 (20), 91 (20), 80 (90), 79 (100).

b) A solution of 6-methyl-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (approximately 11.0 mmol) in THF (10 mL) was added to a freshly prepared solution of LDA (15.0 mmol) in dry THF (40 mL) at −78 °C followed by slow addition of TMSCl (2.55 mL, 20.0 mmol) after 45 min. The mixture was allowed to warm to −20 °C within 2 h. Then ice-cold pentane (250 mL) was added and the mixture washed successively with a satd solution of NH_4Cl, H_2O, and brine (100 mL each). The organic layer was dried ($MgSO_4$) and carefully concentrated under vacuum (maximum 100 mbar, 40 °C bath temperature). The resultant silyl enol ether was dissolved in CH_2Cl_2 (10 mL) and added in the absence of light to a solution of IBX (5.23 g, 18.7 mmol) and MPO (2.67 g, 18.7 mmol) in DMSO (47 mL). After stirring for 35 min, the mixture was poured into a solution of ice-cold satd $NaHCO_3$ and Et_2O (300 mL) and filtered through Celite. The filtrate was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), and concentrated under 800 mbar pressure. After chromatography (pentane/Et_2O 3:1; $R_f=0.23$, PE/Et_2O 4:1), the filtrate was concentrated to an approximately 30% solution in Et_2O due to the volatility of compound **10** (87% by NMR integration). Compound **10** can be stored for the short-term at −28 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.21$ (d, $J=7.0$ Hz, 3H; 3-*Me*), 2.57 (dd, $J=5.7$, 3.2 Hz, 1H; H2), 2.85–2.93 (m, 1H; H3), 4.00–4.04 (m, 1H; H6), 5.57 (dt, $J=5.6$, 2.1 Hz, 1H; H4), 5.69 (dt, $J=5.6$, 2.1 Hz, 1H; H5), 6.02 (dd, $J=5.6$, 1.6 Hz, 1H; H8), 7.72 ppm (dd, $J=5.6$, 2.8 Hz, 1H; H7); MS (EI): *m*/*z* (%): 134 (100) $[M]^+$, 119 (60), 105 (25), 91 (75), 79 (20), 78 (16), 77 (20); HRMS (EI): calcd for $C_9H_{10}O$: 134.0732; found: 134.0723 $[M]^+$.

(2*R*,3*R*,3a*R*,6*S*,6a*R*)-2-(Dimethoxymethyl)-6-methyl-3-[3-(trimethylsilyl)prop-2-ynyl]-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (43): *tert*-Butyllithium (34.8 mL, 1.6 M in pentane) was added to a solution of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (8.6 mL, 57 mmol) and 1-trimethylsilylpropyne (8.2 mL, 55 mmol) in dry THF (90 mL) at −78 °C. After stirring for 1 h, this solution was added through a cannula to a suspension of copper iodide (5.29 g, 27.8 mmol) in THF (30 mL) at −40 °C. The mixture was warmed to 0 °C and, after clearing, immediately cooled to −78 °C. A solution of compound **10** (around 18.6 mmol) in THF (10 mL) was slowly added dropwise followed by addition of TMSCl (5.4 mL, 42.0 mmol) and the reaction mixture was warmed to −40 °C within 2 h. After quenching with a solution of satd NH_4Cl/EDTA (200 mL), the mixture was extracted with pentane (2 × 250 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was taken up in dry CH_2Cl_2 (50 mL), cooled to −20 °C, and trimethyl formate (13.1 mL, 120.0 mmol) and $BF_3 \cdot OEt_2$ (12.0 mL, 94.6 mmol) were successively added slowly. After 1 h, the reaction was quenched with a satd solution of $NaHCO_3$ (100 mL). The mixture was extracted with CH_2Cl_2 (2 × 150 mL), the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography (PE/Et_2O 5:1; $R_f=0.39$, PE/Et_2O 4:1) to give compound **43** (3.73 g, 63%, >95% NMR purity) as a colorless oil. $[\alpha]_D^{20}=+43$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.12$ (s, 9H; Si(CH_3)$_3$), 1.12 (d, $J=7.0$ Hz, 3H; 3-*Me*), 2.33–2.44 (m, 1H; H7), 2.46 (dd, $J=16.5$, 6.4 Hz, 1H; H9), 2.57 (dd, $J=16.5$, 4.5 Hz, 1H; H9), 2.58 (ddd, $J=8.9$, 3.7, 1.2 Hz, 1H; H2), 2.68 (ddd, $J=7.5$, 4.0, 1.6 Hz, 1H; H8), 2.90–2.97 (m, 1H; H3), 3.27–3.31 (m, 1H; H6), 3.34 (s, 3H; OMe), 3.36 (s, 3H; OMe), 4.55 (d, $J=4.0$ Hz, 1H; C*H*(OMe)$_2$), 5.56 (dt, $J=5.6$, 1.9 Hz, 1H; H4), 5.72 ppm (dt, $J=5.6$, 1.9 Hz, 1H; H5); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=0.0$ (Si*Me*$_3$), 21.2 (*Me*-C3), 26.0 (C9), 39.9 (C7), 43.5 (C3), 50.9 (C6), 55.1 (O*Me*), 56.2 (O*Me*), 57.2 (C8), 59.3 (C2), 86.5 (C11), 104.6 (*C*(OMe)$_2$), 105.0 (C10), 132.5 (C5), 135.6 (C4), 218.4 ppm (C1); FTIR (ATR): $\tilde{\nu}=3046$ (m), 2956 (s), 2927 (s), 2900 (s), 2870 (m), 2832 (m), 2172 (m), 1966 (w), 1732 (vs), 1453 (m), 1350 (m), 1308 (w), 1249 (s), 1218 (m), 1190 (m), 1132 (m), 1095 (s), 1069 (vs), 1036 (m), 1005 (m), 942 (m), 838 (vs), 758 (vs), 743 (vs), 697 cm^{-1} (s); MS (DCI, CH_4): *m*/*z* (%): 319 (3) $[M-H]^+$, 305 (10), 289 (25), 288 (20), 273 (16), 245 (4), 217 (5), 209 (10), 207 (15), 199 (8), 184 (18), 181 (15), 177 (10), 169 (5), 156 (10), 149 (4), 89 (10), 75 (100); HRMS (EI): calcd for $C_{18}H_{27}O_3Si$: 319.1729; found: 319.1748 $[M+H]^+$.

(2*S*,3*R*,3a*R*,6*S*,6a*R*)-2-(Dimethoxymethyl)-6-methyl-3-[3-(trimethylsilyl)prop-2-ynyl]-1,2,3,3a,6,6a-hexahydropentalen-1-ol (44): A solution of compound **43** (965 mg, 3.01 mmol) in dry MeOH (5 mL) was added to a solution of $NaBH_4$ (171 mg, 4.50 mmol) in dry MeOH (15 mL) at 0 °C. After stirring for 30 min at 0 °C, the reaction was quenched by careful addition of a satd solution of NH_4Cl (25 mL). The mixture was extracted with EtOAc (3×50 mL) and the combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), and concentrated. The residue was filtered through silica gel (PE/EtOAc 2:1; $R_f=0.24$, PE/Et_2O 3:1) to give compound **44** (967 mg, 99 %, >95 % NMR purity) as a colorless oil in a diastereomeric ratio 1:1. ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.15$ (s, 9H; $Si(CH_3)_3$), 0.16 (s, 9H; $Si(CH_3)_3$*), 1.04 (d, *J*=7.0 Hz, 3H; 3-*Me**), 1.05 (d, *J*=7.0 Hz, 3H; 3-*Me*), 1.50–1.70 (m, 2H; OH, OH*), 1.93–2.12 (m, 5H), 2.17–2.37 (m, 3H), 2.52–2.76 (m, 3H), 2.85–2.93 (m, 1H), 3.03–3.20 (m, 2H), 3.33 (s, 3H; OMe*), 3.36 (s, 3H; OMe*), 3.39 (s, 3H; OMe), 3.41 (s, 3H; OMe), 3.63 (t, *J*=9.0 Hz, 1H; H1*), 4.22–4.27 (m, 1H; H1), 4.34 (d, *J*=7.2 Hz, 1H; C*H*($OMe)_2$*), 4.53 (d, *J*=6.4 Hz, 1H; C*H*($OMe)_2$), 5.54 (dt, *J*=5.5, 2.2 Hz, 1H; H4*), 5.63 (dt, *J*=5.5, 1.8 Hz, 1H; H5*), 5.67 (dt, *J*=5.5, 2.2 Hz, 1H; H4), 5.77 ppm (dt, *J*=5.5, 1.8 Hz, 1H; H5); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=0.0$ (SiMe_3*), 0.1 (SiMe_3), 21.3 (*Me*-C3*), 21.4 (*Me*-C3), 24.2 (C9*), 24.4 (C9), 38.7 (C7*), 42.7 (C7), 43.8 (C3*), 44.9 (C3), 51.7 (OMe*), 51.9 (C2*), 52.4 (OMe*), 52.5 (C2), 53.6 (OMe), 53.8 (C6*), 54.0 (C6), 54.9 (C8*), 55.5 (OMe), 55.6 (C8), 75.1 (C1*), 79.8 (C1), 85.4 (C11*), 85.6 (C11), 105.8 (*C**($OMe)_2$), 105.9 (C10*), 106.3 (C10), 108.1 (*C*($OMe)_2$), 133.2 (C5*), 133.7 (C5), 134.9 (C4*), 136.5 ppm (C4) (* signals of the second diastereomer); FTIR (ATR): $\tilde{\nu}=3501$ (m), 3041 (m), 2954 (s), 2922 (s), 2832 (m), 2172 (m), 1454 (m), 1371 (m), 1249 (s), 1189 (m), 1142 (m), 1124 (s), 1094 (s), 1052 (vs), 959 (m), 895 (m), 842 (vs), 792 (m), 759 cm^{-1} (s); MS (DCI, CH_4): *m*/*z* (%): 323 (2) $[M+H]^+$, 322 (2) $[M]^+$, 321 (4) $[M-H]^+$, 307 (5), 305 (5), 291 (35), 290 (20), 275 (40), 273 (20), 243 (20), 219 (10), 204 (25), 186 (20), 169 (35), 89 (20), 87 (20), 75 (100), 73 (40); HRMS (EI): calcd for $C_{18}H_{30}O_3Si$: 322.1964; found: 322.1958 $[M]^+$.

{3-[(1*R*,2*R*,3a*R*,4*S*,6a*S*)-2-(Dimethoxymethyl)-4-methyl-1,2,3,3a,4,6a-hexahydropentalen-1-yl]prop-1-ynyl}trimethylsilane (45): A solution of compound **44** (65 mg, 0.20 mmol), thiocarbonyldiimidazole (178 mg, 1.00 mmol), and DMAP (122 mg, 1.00 mmol) in CH_2Cl_2 (4 mL) was heated at reflux for 16 h. The mixture was then filtered through silica gel with Et_2O to give a yellow oil (79 mg, 91 %), that was dissolved in dry toluene (8 mL). After addition of Bu_3SnH (250 µL, 0.93 mmol) and AIBN (5 mg, 30.5 µmol), a slow stream of dry Ar gas was passed through for 10 min and the mixture was heated at 110 °C for 30 min. The solvent was removed under vacuum and the residue purified by chromatography with PE followed by PE/Et_2O 9:1 ($R_f=0.50$) to give compound **45** (35 mg, 57 %, 94 % NMR purity) as a colorless oil. $[\alpha]_D^{20}=+89.5$ (*c*=1.00 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.15$ (s, 9H; $Si(CH_3)_3$), 0.99 (d, *J*=7.0 Hz, 3H; 3-*Me*), 1.44–1.56 (m, 1H; H1), 1.04–1.26 (m, 1H; H1), 1.79–2.04 (m, 3H; H2, H7, H8), 2.09 (dd, *J*=16.9, 8.2 Hz, 1H; H9), 2.20–2.31 (m, 1H; H6), 2.45 (dd, *J*=16.9, 4.4 Hz, 1H; H9), 2.85–2.93 (m, 1H; H3), 3.15 (s, 3H; OMe), 3.17 (s, 3H; OMe), 4.16 (d, *J*=6.9 Hz, 1H; C*H*($OMe)_2$), 5.47 (dt, *J*=5.5, 2.2 Hz, 1H; H4), 5.65 ppm (dt, *J*=5.5, 1.8 Hz, 1H; H5); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=0.1$ (SiMe_3), 21.4 (*Me*-C3), 24.9 (C9), 35.5 (C1), 46.1 (C7), 46.7 (C3), 47.2 (C8), 48.6 (C2), 52.8 (O*Me*), 53.7 (O*Me*), 56.4 (C6), 84.9 (C11), 106.9 (C10), 108.0 (*C*($OMe)_2$), 133.5 (C5), 134.2 ppm (C4); FTIR (ATR): $\tilde{\nu}=3041$ (m), 2954 (s), 2921 (s), 2868 (m), 2829 (m), 2173 (s), 1493 (m), 1452 (m), 1373 (w), 1305 (w), 1248 (s), 1184 (s), 1138 (s), 1116 (s), 1054 (s), 957 (s), 841 (vs), 759 (s), 642 cm^{-1} (m); MS (DCI, CH_4): *m*/*z* (%): 307 (2) $[M+H]^+$, 306 (4) $[M]^+$, 305 (4) $[M-H]^+$, 291 (18), 275 (90), 274 (60), 259 (20), 244 (20), 243 (35), 242 (25), 229 (10), 203 (20), 195 (25), 171 (15), 163 (35), 162 (20), 161 (25), 155 (10), 131 (15), 89 (10), 75 (100), 73 (20); HRMS (EI): calcd for $C_{18}H_{30}O_2Si$: 306.2015; found: 306.2007 $[M]^+$.

(1*R*,2*R*,3a*R*,4*S*,6a*S*)-2-(Dimethoxymethyl)-4-methyl-1-prop-2-ynyl-1,2,3,3a,4,6a-hexahydropentalene (9): Finely powdered potassium carbonate (420 mg, 3.04 mmol) was added to a solution of compound **45** (830 mg, 2.71 mmol) in MeOH (14 mL) and the suspension was stirred for 20 h at RT. After addition of H_2O (10 mL), the reaction mixture was extracted with EtOAc (2×50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give compound **9** (630 mg, 99 %, >95 % NMR purity) as a colorless oil. $[\alpha]_D^{20}=+149$ (*c*=1.00 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=0.99$ (d, *J*=7.0 Hz, 3H; 3-*Me*), 1.11–1.22 (m, 1H; H1), 1.64 (tdd, *J*=8.4, 6.2, 4.1 Hz, 1H; H7), 1.95 (t, *J*=2.6 Hz, 1H; H11), 1.98–2.07 (m, 2H; H1, H8), 2.16 (qt, *J*=8.2, 1.8 Hz, 1H; H2), 2.27 (ddd, *J*=16.7, 8.0, 2.6 Hz, 1H; H9), 2.41 (qq, *J*=7.0, 2.2 Hz, 1H; H3), 2.56 (ddd, *J*=16.7, 4.2, 2.6 Hz, 1H; H9), 3.06 (ddq, *J*=8.6, 6.3, 2.4 Hz, 1H; H6), 3.30 (s, 3H; OMe), 3.33 (s, 3H; OMe), 4.15 (d, *J*=7.0 Hz, 1H; C*H*($OMe)_2$), 5.49 (dt, *J*=5.5, 2.3 Hz, 1H; H4), 5.65 ppm (dt, *J*=5.5, 1.9 Hz, 1H; H5); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=21.4$ (*Me*-C3), 23.3 (C9), 35.6 (C1), 45.9 (C7), 46.7 (C3), 47.0 (C8), 48.6 (C2), 52.7 (O*Me*), 54.0 (O*Me*), 56.1 (C6), 68.7 (C11), 83.8 (C10), 108.1 (*C*($OMe)_2$), 133.2 (C5), 134.4 ppm (C4); FTIR (ATR): $\tilde{\nu}=3305$ (s), 3040 (m), 2952 (vs), 2921 (vs), 2867 (s), 2830 (s), 2115 (m), 1451 (m), 1372 (m), 1248 (m), 1188 (s), 1138 (vs), 1116 (vs), 1053 (vs), 957 (vs), 908 (m), 770 (m), 735 (m), 628 cm^{-1} (s); MS (CI, NH_3): *m*/*z* (%): 234 (4) $[M]^+$, 220 (10), 204 (15), 203 (100), 202 (60), 195 (20), 188 (12), 171 (40), 163 (40), 155 (5), 131 (15), 75 (75); HRMS (EI): calcd for $C_{15}H_{22}O_2$: 234.1620; found: 234.1620 $[M]^+$.

Methyl (2*S*,3*S*)-2-azido-3-*O*-[*tert*-butyl(dimethyl)silyl]-5-(2*E*)-6-[(1*R*,2*R*,3a*R*,4*S*,6a*S*)-(dimethoxymethyl)-4-methyl-1,2,3,3a,4,6a-hexahydropentalen-1-yl]hex-2-en-4-ynylamidopentanoate (46): Under Ar gas a solution of compound **7** (630 mg, 1.30 mmol) and compound **9** (276 mg, 1.18 mmol) in dry THF (1.6 mL) was added to a stirred suspension of $[Pd(PPh_3)_4]$ (19 mg, 16.0 µmol) and copper iodide (9 mg, 47.0 µmol) in NEt_3 (2.8 mL). After 1 h, the solvent was removed under vacuum and the residue was purified by chromatography ($R_f=0.32$, PE/EtOAc 3:1) to give compound **46** (630 mg, 91 %, >95 % NMR purity) as a yellow resin. $[\alpha]_D^{20}=-41$ (*c*=1.00 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=0.13$ (s, 6H; $(CH_3)_2$Si*t*Bu), 0.90 (s, 9H; ($Me_2SiC(CH_3)_3$), 0.99 (d, *J*=7.0 Hz, 3H; 3-*Me*), 1.15 (t, *J*=11.0 Hz, 1H; H1), 1.63–1.70 (m, 1H; H7), 1.71–1.79 (m, 1H; H16), 1.85–1.94 (m, 1H; H16), 1.95–2.07 (m, 2H; H8, H1), 2.11–2.18 (m, 1H; H2), 2.37–2.45 (m, 2H; H9), 2.73 (ddd, *J*=17.0, 4.0, 2.2 Hz, 1H; H3), 3.02 (ddq, *J*=8.6, 6.2, 2.3 Hz, 1H; H6), 3.30 (s, 3H; OMe), 3.32 (s, 3H; OMe), 3.31–3.41 (m, 1H; H15), 3.41–3.51 (m, 1H; H15), 3.78 (s, 3H; CO_2CH_3), 4.09 (d, *J*=4.8 Hz, 1H; H18), 4.15 (d, *J*=7.0 Hz, 1H; C*H*($OMe)_2$), 4.17–4.27 (m, 1H; H17), 5.49 (dt, *J*=5.1, 2.3 Hz, 1H; H4), 5.61 (dt, *J*=5.1, 1.9 Hz, 1H; H5), 5.78 (br, 1H; N*H*), 6.09 (d, *J*=15.3 Hz, 1H; H13), 6.71 ppm (dt, *J*=15.3, 1.8 Hz, 1H; H12); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.7$, -4.5 (2×Me_2Si*t*Bu), 17.9 (Si*C*($CH_3)_3$), 21.4 (*Me*-C3), 24.7 (C9), 25.6 ($SiC(CH_3)_3$), 32.4 (C16), 35.6 (C1), 35.9 (C15), 46.1 (C7), 46.8 (C3), 47.3 (C8), 48.6 (C2), 52.6 (CO_2Me), 52.8 (O*Me*), 54.1 (O*Me*), 56.4 (C6), 66.5 (C18), 71.5 (C17), 78.7 (C11), 98.1 (C10), 108.1 (*C*($OMe)_2$), 122.5 (C12), 131.3 (C13), 133.0 (C5), 134.6 (C4), 164.8 (C14), 168.5 ppm (C19); FTIR (ATR): $\tilde{\nu}=3286$ (m), 3042 (m), 2953 (s), 2928 (s), 2899 (m), 2859 (m), 2831 (m), 2214 (m), 2109 (vs), 1750 (vs), 1646 (vs), 1614 (vs), 1548 (vs), 1471 (s), 1462 (s), 1450 (s), 1437 (s), 1360 (m), 1329 (m), 1257 (s), 1205 (s), 1115 (s), 1053 (s), 1005 (m), 958 (m), 839 (s), 779 cm^{-1} (s); MS (FAB): *m*/*z* (%): 611 (4) $[M+Na]^+$, 587 (4) $[M-H]^+$, 557 (100), 531 (30), 474 (4), 394 (3), 303 (3), 255 (20), 216 (10), 171 (30), 163 (20), 131 (20), 74 (80), 73 (95), 71 (20); HRMS (FAB): calcd for $C_{30}H_{48}N_4NaO_6Si$: 611.3235; found: 611.3226 $[M+Na]^+$.

Methyl (2*S*,3*S*)-2-azido-3-*O*-[*tert*-butyl(dimethyl)silyl]-5-(2*E*)-6-{(1*S*,2*S*,3a*R*,4*S*,6a*S*)-2-[(1*E*)-4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)but-1-enyl]-4-methyl-1,2,3,3a,4,6a-hexahydropentalen-1-yl}hex-2-en-4-ynylamidopentanoate (48): a) A solution of compound **46** (1.06 g, 1.80 mmol) and PPTS (150 mg, 0.60 mmol) in acetone/5 % H_2O (30 mL) was heated at reflux for 3 h. The solvent was removed under vacuum, the residue was taken up in EtOAc and washed with a satd solution of $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated to give compound **47** as a colorless oil that was reacted without further purification. ^1H NMR (500 MHz, $CDCl_3$): $\delta=0.12$ (s, 6H; Me_2Si), 0.89 (s, 9H; Me_3CSi), 1.02 (d, *J*=7.0 Hz, 3H; 3-Me), 1.56–1.62 (m, 1H; H1), 1.71–1.79 (m, 1H; H16) 1.85–1.93 (m, 1H; H16), 2.16–2.22 (m, 2H; H2, H7), 2.29–2.35 (m, 1H; H1), 2.46–2.56 (m, 4H; H3, H8, H9), 3.02–3.07 (m, 1H; H6), 3.35–3.42 (m, 1H; H15), 3.43–3.49 (m, 1H; H15), 3.79 (s, 3H; CO_2Me), 4.10 (d, *J*=4.7 Hz, 1H; H18), 4.21 (dt, *J*=6.5, 4.7 Hz, 1H; H17), 5.56 (dt, *J*=5.5, 2.3 Hz, 1H; H5), 5.61 (dt, *J*=5.5, 1.9 Hz, 1H; H4), 5.71 (br, 1H; N*H*), 6.11 (d, *J*=15.4 Hz, 1H; H13), 6.69 (dt, *J*=15.4, 2.3 Hz, 1H; H12), 9.57 ppm (d, *J*=3.0 Hz, 1H; H20).

b) A solution of NaHMDS in dimethoxyethane (DME) (6 mL, 1.0 M) was slowly added to a solution of compound **8** (2.27 g, 6.00 mmol) in dry DME (20 mL) at −55 °C, and the mixture was stirred for 1 h. Then a solution of the intermediate **47** in dry DME (5 mL) was slowly added and after stirring for 1 h at −55 °C, the mixture was allowed to warm to RT

(16 h). After quenching with a satd solution of NH$_4$Cl, the mixture was extracted with EtOAc (2×250 mL). The combined organic layers were washed with brine, dried (MgSO$_4$), and concentrated. The residue was filtered through a short pad of SiO$_2$ with EtOAc, and the crude product was purified by MPLC on a CN phase (PE/EtOAc 3:1) to give compound **48** (660 mg, 53 %, >95 % NMR purity) as a viscous colorless oil. $[\alpha]_D^{20}=+39.5$ ($c=1.00$ in CHCl$_3$); $R_f=0.22$ (PE/EtOAc 2:1); ^{1}H NMR (500 MHz, CDCl$_3$): $\delta=0.12$ (s, 6H; *Me*$_2$Si), 0.91 (s, 9H; *Me*$_3$CSi), 1.01 (d, $J=7.0$ Hz, 3H; 3-*Me*), 1.12 (q, $J=11.7$ Hz, 1H; H1), 1.36 (dtd, $J=11.4$, 7.7, 3.9 Hz, 1H; H8), 1.67 (s, 6H; H28), 1.73–1.81 (m, 1H; H23), 1.87–1.94 (m, 1H; H23), 2.04–2.09 (m, 1H; H1), 2.10–2.20 (m, 1H; H7), 2.21–2.31 (m, 5H; H9, H16, H22), 2.38–2.45 (m, 1H; H3), 2.55 (ddd, $J=16.4$, 3.8, 2.2 Hz, 1H; H9), 2.95–3.01 (m, 1H; H6), 3.35–3.43 (m, 1H; H15), 3.43–3.50 (m, 1H; H15), 3.78 (s, 3H; CO$_2$*Me*), 4.10 (d, $J=6.7$ Hz, 1H; H18), 4.21 (dt, $J=6.7$, 4.5 Hz, 1H; H17), 5.23 (s, 1H; H25), 5.29 (dd, $J=15.0$, 8.1 Hz, 1H; H20), 5.40 (dt, $J=15.0$, 6.0 Hz, 1H; H21), 5.51 (dt, $J=5.5$, 2.0 Hz, 1H; H5), 5.66 (dt, $J=5.5$, 1.7 Hz, 1H; H4), 5.85 (t, $J=5.4$ Hz, 1H; N*H*), 6.11 (d, $J=15.4$ Hz, 1H; H13), 6.71 ppm (dt, $J=15.4$, 2.2 Hz, 1H; H12); ^{13}C NMR (125 MHz, CDCl$_3$): $\delta=-4.7$, -4.5 (2×*Me*$_2$Si), 17.9 (Me$_3$CSi), 21.7 (C3-*Me*), 22.7 (C9), 25.0 (C27A), 25.1 (C27B), 25.6 (*Me*$_3$CSi), 28.5 (C22), 32.5 (C23), 33.6 (C16), 35.9 (C15), 40.4 (C1), 46.8 (C3), 49.1 (C7), 49.4 (C8), 50.2 (C2), 52.6 (CO$_2$*Me*), 55.7 (C6), 66.5 (C18), 71.5 (C17), 79.0 (C11), 93.5 (C25), 97.1 (C10), 106.3 (C27), 122.3 (C13), 128.0 (C20), 131.5 (C4), 132.5 (C5), 134.3 (C12), 134.8 (C21), 161.2 (C24), 164.8 (C14), 168.5 (C19), 171.2 ppm (C26); FTIR (ATR): $\tilde{\nu}=3303$ (s), 3041 (w), 2951 (s), 2927 (s), 2896 (s), 2857 (s), 2211 (m), 2108 (vs), 1731 (vs), 1647 (vs), 1633 (vs), 1614 (vs), 1543 (s), 1461 (m), 1436 (s), 1389 (s), 1375 (s), 1327 (s), 1271 (vs), 1253 (vs), 1202 (vs), 1114 (s), 1012 (vs), 837 (vs), 777 (vs), 736 cm^{-1} (s); MS (FAB): *m*/*z* (%): 717 (10) $[M+Na]^+$, 695 (100) $[M+H]^+$, 637 (60), 580 (10), 171 (20), 73 (65); HRMS (FAB): calcd for C$_{37}$H$_{55}$N$_4$O$_7$Si: 695.3835; found: 695.3832 $[M+H]^+$.

Methyl (10*S*,11*S*,19a*S*,20a*R*,21*S*,23a*S*,23b*S*)-10-{[*tert*-butyl(dimethyl)silyl]oxy}-21-methyl-6,13,15-trioxo-2,3-didehydro-6,7,8,9,10,11,12,13,14,15,16,17,19a,20,20a,21,23a,23b-octadecahydro-1*H*-pentaleno[1,2-*m*,1,6]diazacyclohenicosine-11-carboxylate (49): A solution of triphenylphosphine (140 mg, 0.53 mmol) and compound **48** (320 mg, 0.46 mmol) in THF (3 mL) was stirred for 3 h at RT. After addition of H$_2$O (100 µL), the mixture was stirred for a further 18 h. The solvent was removed under vacuum, the residue was dried azeotropically with toluene and then heated at reflux for 7 h in dry toluene (1.9 L) under N$_2$ gas. The solvent was removed under vacuum and the residue purified by MPLC ($R_f=0.75$, PE/EtOAc 1:1) to give compound **49** (231 mg, 82 %, >95 % NMR purity) as a viscous colorless resin. $[\alpha]_D^{20}=+139$ ($c=1.00$ in CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): $\delta=-0.02$ (s, 3H; *Me*$_2$Si), -0.01 (s, 3H; *Me*$_2$Si), 0.82 (s, 9H; *Me*$_3$CSi), 1.00 (d, $J=7.0$ Hz, 3H; *Me*-C3), 1.19 (td, $J=12.1$, 9.8 Hz, 1H; H1), 1.42–1.49 (m, 1H; H8), 1.83–1.90 (m, 1H; H16), 1.95–2.02 (m, 1H; H16), 2.02–2.10 (m, 1H; H1), 2.10–2.17 (m, 1H; H7), 2.21–2.35 (m, 4H; H2, H9, H23), 2.39–2.40 (m, 1H; H3), 2.62–2.81 (m, 4H; H6, H22, H23), 3.16 (ddt, $J=14.9$, 10.8, 4.1 Hz, 1H; H15), 3.32 (d, $J=13.3$ Hz, 1H; H25), 3.52 (d, $J=13.3$ Hz, 1H; H25), 3.79 (s, 3H; CO$_2$*Me*), 3.90 (ddd, $J=10.3$, 4.5, 1.2 Hz, 1H; H17), 3.92–3.97 (m, 1H; H15), 4.60 (dd, $J=6.5$, 1.2 Hz, 1H; H18), 5.47–5.50 (m, 2H; H21, H22), 5.52 (dt, $J=5.4$, 2.0 Hz, 1H; H4), 5.62 (dd, $J=5.4$, 1.9 Hz, 1H; H5), 6.23 (d, $J=15.6$ Hz, 1H; H13), 6.59 (dt, $J=15.6$, 2.2 Hz, 1H; H12), 6.97 (d, $J=6.4$ Hz, 1H; N*H*), 7.54 ppm (dd, $J=8.3$, 4.3 Hz, 1H; N*H*); ^{13}C NMR (125 MHz, CDCl$_3$): $\delta=-5.1$, -4.6 (2×*Me*$_2$Si), 17.7 (Me$_3$CSi), 21.7 (*Me*-C3), 23.7 (C23), 25.5 (*Me*$_3$CSi), 26.3 (C9), 33.5 (C16), 35.5 (C15), 40.9 (C1), 43.5 (C22), 47.2 (C3), 48.6 (C7), 50.3 (C8), 50.7 (C2), 50.7 (C25), 52.5 (CO$_2$*Me*), 56.1 (C18), 56.9 (C6), 73.4 (C17), 79.4 (C11), 96.7 (C10), 121.0 (C12), 127.8 (C21), 131.5 (C4), 133.1 (C20), 133.6 (C13), 135.3 (C5), 165.0 (C14), 166.4 (C26), 169.0 (C19), 203.0 ppm (C24); FTIR (ATR): $\tilde{\nu}=3289$ (s), 3038 (m), 2952 (s), 2928 (s), 2898 (s), 2858 (s), 2213 (w), 1747 (vs), 1720 (vs), 1646 (vs), 1616 (vs), 1541 (vs), 1437 (s), 1361 (s), 1328 (s), 1253 (s), 1205 (s), 1112 (vs), 960 (vs), 910 (s), 837 (vs), 778 cm^{-1} (vs); MS (FAB): *m*/*z* (%): 633 (30) $[M+Na]^+$, 611 (45) $[M+H]^+$, 595 (5), 553 (20), 479 (20), 171 (35), 128 (35), 73 (100); HRMS (FAB): calcd for C$_{34}$H$_{51}$N$_2$O$_6$Si: 611.3511; found: 611.3502 $[M+H]^+$.

Methyl (10*S*,11*S*,19a*S*,20a*R*,21*S*,23a*S*,23b*S*)-10-hydroxy-21-methyl-6,13,15-trioxo-6,7,8,9,10,11,12,13,14,15,16,17,19a,20,20a,21,23a,23b-octadecahydro-1*H*-pentaleno[1,2-*m*,1,6]diazacyclohenicosine-11-carboxylate (51): a) Pd/BaSO$_4$ (35 mg, 5 % Pd) was briefly heated, dry MeOH (3 mL) was added, and the mixture ultrasonificated. Synthetic quinoline (6 µL, 50.6 µmol) was added followed by a solution of compound **49** (328 mg, 537 µmol) in dry MeOH (5 mL) and the mixture was vigorously stirred under H$_2$ atmosphere (1 atm) for 25 min. Then Celite was added and the mixture filtered through Celite. The filtrate was concentrated under vacuum and the residue purified by MPLC on a CN phase (PE/EtOAc 3:1) to give a first fraction containing compound **49** (160 mg, 49 %), a second fraction ($R_f=0.40$, PE/EtOAc 3:1) containing compound **50** (135 mg, 80 % based on conversion, >95 % NMR purity), and a third fraction ($R_f=0.27$, PE/EtOAc 3:1) containing the overreduced compound (11 % based on conversion) as colorless viscous resins.

Compound 50: $[\alpha]_D^{20}=+68$ ($c=1.00$ in CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): $\delta=0.01$ (s, 3H; *Me*$_2$Si), 0.04 (s, 3H; *Me*$_2$Si), 0.84 (s, 9H; *Me*$_3$CSi), 0.99 (d, $J=7.0$ Hz, 3H; 3-*Me*), 1.03–1.12 (m, 1H; H1), 1.19–1.28 (m, 1H; H8), 1.82–1.92 (m, 2H; H16), 1.94–2.10 (m, 3H; H1, H2, H23), 2.11–2.17 (m, 1H; H7), 2.17–2.25 (m, 1H; H9), 2.29–2.37 (m, 1H; H9), 2.37–2.42 (m, 1H; H3), 2.62–2.69 (m, 1H; H23), 2.73 (td, $J=7.1$, 3.2 Hz, 2H; H22), 2.87–2.92 (m, 1H; H6), 3.29–3.80 (m, 1H; H15), 3.45 (d, $J=15.3$ Hz, 1H; H25), 3.53 (d, $J=15.3$ Hz, 1H; H25), 3.57–3.66 (m, 1H; H15), 3.74 (s, 3H; CO$_2$*Me*), 4.10 (dt, $J=7.3$, 4.4 Hz, 1H; H17), 4.68 (dd, $J=7.4$, 4.8 Hz, 1H; H18), 5.25 (dd, $J=15.1$, 8.0 Hz, 1H; H20), 5.38 (ddd, $J=15.1$, 8.0, 5.1 Hz, 1H; H21), 5.49 (dt, $J=5.6$, 1.8 Hz, 1H; H4), 5.59 (dt, $J=5.6$, 1.5 Hz, 1H; H5), 5.84 (d, $J=15.1$ Hz, 1H; H14), 5.90 (ddd, $J=11.5$, 10.5, 6.7 Hz, 1H; H10), 6.08 (t, $J=11.5$ Hz, 1H; H11), 6.43 (t, $J=6.2$ Hz, 1H; N*H*), 7.42 (dd, $J=15.1$, 11.5 Hz, 1H; H12), 7.99 ppm (d, $J=7.5$ Hz, 1H; N*H*); ^{13}C NMR (125 MHz, CDCl$_3$): $\delta=-5.1$ (*Me*$_2$Si), -4.6 (*Me*$_2$Si), 17.8 (Me$_3$CSi), 21.7 (*Me*-C3), 25.5 (*Me*$_3$CSi), 26.1 (C9), 31.8 (C23), 34.0 (C16), 35.6 (C15), 40.7 (C1), 43.1 (C22), 46.6 (C3), 49.3 (C7), 50.2 (C8), 50.8 (C2), 51.8 (C25), 52.2 (CO$_2$*Me*), 56.0 (C6), 56.9 (C18), 71.4 (C17), 124.2 (C12), 127.1 (C21), 128.5 (C11), 132.7 (C5), 134.2 (C20), 134.6 (C4), 135.4 (C13), 138.1 (C10), 166.0 (C14), 166.9 (C26), 170.4 (C19), 204.3 ppm (C24); FTIR (ATR): $\tilde{\nu}=3298$ (s), 3039 (s), 2951 (vs), 2927 (vs), 2857 (vs), 1742 (vs), 1721 (vs), 1651 (vs), 1617 (vs), 1543 (vs), 1436 (s), 1409 (m), 1361 (s), 1335 (s), 1256 (vs), 1201 (s), 1179 (m), 1118 (vs), 1034 (m), 1004 (m), 967 (m), 910 (m), 837 (vs), 732 cm^{-1} (vs); MS (FAB): *m*/*z* (%): 613 (40) $[M+H]^+$, 555 (10), 436 (8), 419 (100), 391 (5), 310 (5), 394 (20), 279 (20), 161 (5); HRMS (FAB): calcd for C$_{34}$H$_{53}$N$_2$O$_6$Si: 613.3667; found: 613.3669 $[M+H]^+$.

b) A solution of compound **50** (120 mg, 197 µmol) in MeCN (2 mL) was added to a solution of MeCN (6 mL) and HF/H$_2$O (48 %, 1.3 mL) in a Teflon vessel. After stirring for 2 h at RT, brine (15 mL) was added and the mixture extracted with chloroform (2×35 mL). The combined organic layers were dried (MgSO$_4$) and concentrated. The residue was purified by MPLC on a CN phase (CHCl$_3$/MeOH 99:1; $R_f=0.4$, PE/EtOAc/CH$_2$Cl$_2$ 2:2:1) to give compound **51** (98 mg, 96 %, >95 % NMR purity) as a colorless amorphous solid. M.p. 184 °C (decomp); $[\alpha]_D^{20}=+107$ ($c=1.00$ in CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): $\delta=0.99$ (d, $J=7.0$ Hz, 3H; 3-*Me*), 1.01–1.10 (m, 1H; H1), 1.13–1.20 (m, 1H; H8), 1.22 (br, 1H; OH), 1.64–1.72 (m, 1H; H16), 1.83 (ddt, $J=14.3$, 9.9, 4.1 Hz, 1H; H16), 1.95 (ddd, $J=14.8$, 9.5, 6.5 Hz, 1H; H23), 1.97–2.07 (m, 2H; H1, H2), 2.16 (qq, $J=9.2$, 1.9 Hz, 1H; H7), 2.20–2.28 (m, 1H; H9), 2.28–2.34 (m, 1H; H9), 2.37–2.43 (m, 1H; H3), 2.52–2.68 (m, 2H; H22), 2.73 (ddd, $J=14.5$, 10.8, 4.1 Hz, 1H; H23), 2.91 (qq, $J=9.6$, 2.2 Hz, 1H; H6), 3.15 (dq, $J=14.2$, 4.8 Hz, 1H; H15), 3.38 (d, $J=14.8$ Hz, 1H; H25), 3.45 (d, $J=14.8$ Hz, 1H; H25), 3.75–3.82 (m, 1H; H15), 3.77 (s, 3H; CO$_2$*Me*), 3.84 (dt, $J=10.3$, 3.6 Hz, 1H; H17), 4.59 (dd, $J=8.3$, 3.9 Hz, 1H; H18), 5.26 (dd, $J=15.4$, 7.5 Hz, 1H; H20), 5.42 (dt, $J=15.4$, 6.1 Hz, 1H; H21), 5.49 (dt, $J=5.5$, 2.1 Hz, 1H; H4), 5.59 (dt, $J=5.5$, 1.8 Hz, 1H; H5), 5.82 (d, $J=14.9$ Hz, 1H; H13), 5.90–5.95 (m, 1H; H10), 5.97 (dd, $J=10.5$, 5.6 Hz, 1H; N*H*), 6.08 (dd, $J=11.5$, 10.5 Hz, 1H; H11), 7.29 (d, $J=8.3$ Hz, 1H; N*H*), 7.49 ppm (dd, $J=14.9$, 11.5 Hz, 1H; H12); ^{13}C NMR (125 MHz, CDCl$_3$): $\delta=21.6$ (*Me*-C3), 25.9 (C9), 32.3 (C23), 34.2 (C16), 36.0 (C15), 40.5 (C1), 42.5 (C22), 46.5 (C3), 49.3 (C7), 50.6 (C8), 50.8 (C2), 51.5 (C25), 52.5 (CO$_2$*Me*), 56.5 (C6), 56.5 (C18), 69.4 (C17), 122.8 (C12), 126.3 (C21), 128.1 (C11), 132.8 (C5), 133.4 (C20), 134.7 (C4), 136.8

(C13), 139.4 (C10), 165.3 (C14), 168.2 (C26), 169.9 (C19), 204.1 ppm (C24); FTIR (ATR): $\tilde{\nu}=3282$ (s), 3038 (m), 2950 (s), 2925 (s), 2889 (s), 2863 (s), 1744 (vs), 1716 (vs), 1646 (vs), 1619 (vs), 1537 (vs), 1436 (s), 1331 (s), 1256 (s), 1204 (s), 1130 (m), 1098 (s), 1019 (m), 958 (vs), 870 (s), 731 cm^{-1} (vs); MS (FAB, NBA): m/z (%): 521 (40) $[M+Na]^+$, 499 (100) $[M+H]^+$, 481 (20) $[M-H_2O+H]^+$, 419 (10); HRMS (FAB): calcd for $C_{28}H_{39}N_2O_6$: 499.2803; found: 499.2797 $[M+H]^+$.

Cylindramide (1) and 2-*epi*-cylindramide (2-*epi*-1): A freshly prepared 1.45 M solution of NaOMe (275 μL, 0.40 mmol) was added to a briefly ultrasonificated suspension of compound **51** (46 mg, 92.3 μmol) in freshly distilled dry MeOH (5 mL) and the mixture was heated at 55 °C for 1.5 h. H_2O (20 mL) was added, the mixture was adjusted to pH 2.0 with 1 N HCl and extracted with *n*-butanol (2×25 mL). The combined organic layers were washed with H_2O (10 mL) and the solvent removed. The residue was dissolved in MeOH (4.5 mL) and purified (aliquots of 600 μL each) by preparative HPLC on Nucleosil C-18 AB (250×21 mm) with CH_3CN/H_2O 55:45, 0.05 % TFA, 6 mg Titriplex II per 2.5 L eluent (flow 50 mL min^{-1}) to give a first fraction containing *epi*-**1** (11.3 mg, 26 %, 97 % HPLC purity) and a second fraction containing **1** (23.0 mg, 53 %, 96 % HPLC purity) as amorphous beige solids.

Cylindramide (1): HPLC: 17.33 min (CH_3CN/H_2O 50:50, 0.05 % TFA; 1.0 mL min^{-1}, 263 nm); $[\alpha]_D^{20}=+171$ ($c=0.32$ in MeOH); FTIR (ATR): $\tilde{\nu}=3318$ (s), 2951 (m), 2923 (m), 2864 (m), 1714 (m), 1654 (vs), 1604 (vs), 1536 (m), 1479 (m), 1329 (m), 1281 (m), 1208 (m), 1122 (m), 1088 (m), 1014 (m), 993 (m), 964 (m), 867 cm^{-1} (m); ref. [2]: (KBr): $\tilde{\nu}=3330$, 2940, 1660, 1610, 1520, 1440, 1330, 1280, 1210, 960, 860 cm^{-1}; UV (MeOH): λ_{max} $(\varepsilon)=264$ nm (19800 $mol^{-1} dm^3 cm^{-1}$). MS (FAB): m/z (%): 529 (63) $[M+Cu]^+$, 511 (12) $[M-H+2Na]^+$, 505 (15) $[M+K]^+$, 489 (50) $[M+Na]^+$, 467 (100) $[M+H]^+$, 449 (20) $[M-H_2O]^+$; HRMS (FAB): calcd for $C_{27}H_{35}N_2O_5$: 467.2540; found: 467.2565 $[M+H]^+$.

***epi*-Cylindramide (2-*epi*-1)**: HPLC: 16.01 min (CH_3CN/H_2O 50:50, 0.05 % TFA; 1.0 mL min^{-1}, 263 nm); $[\alpha]_D^{20}=+21$ ($c=0.50$ in MeOH); ^1H NMR (500 MHz, MeOD/$CDCl_3$ 1:1): $\delta=0.97$ (d, $J=6.9$ Hz, 3H; 17-*Me*), 1.09 (q, $J=13.1$ Hz, 1H; H19), 1.20–1.32 (m, 2H; H4, H13), 1.63–1.74 (m, 1H; H4), 1.92–2.04 (m, 2H; H19, H20), 2.07–2.20 (m, 3H; H12, H18, H23), 2.29–2.36 (m, 2H; H23, H24), 2.36–2.44 (m, 1H; H17), 2.47–2.58 (m, 1H; H12), 2.87–2.96 (m, 1H; H14), 3.04–3.13 (m, 1H; H5), 3.33–3.40 (m, 1H; H24), 3.40–3.49 (m, 1H; H3), 3.60–3.67 (m, 1H; H5), 3.68–3.74 (m, 1H; H2), 5.15–5.37 (m, 2H; H21, H22), 5.47 (d, $J=5.1$ Hz, 1H; H15), 5.57 (d, $J=5.1$ Hz, 1H; H16), 5.82–5.92 (m, 1H; H11), 5.86 (d, $J=15.2$ Hz, 1H; H8), 6.10 (t, $J=11.0$ Hz, 1H; H10), 7.23 ppm (dd, $J=15.2$, 11.0 Hz, 1H; H9); ^{13}C NMR (125 MHz, MeOD/$CDCl_3$ 1:1): $\delta=$ 21.9 (C17-*Me*), 29.4 (C12), 31.6 (C4), 32.7 (C23), 34.9 (C24), 36.3 (C5), 40.9 (C19), 47.3 (C17), 50.0 (C20), 50.2 (C18), 52.0 (C13), 56.0 (C14), 66.5 (C2), 70.6 (C3), 102.1 (C26), 125.2 (C8), 127.9 (C22), 128.2 (C10), 133.4 (C15), 135.2 (C21), 135.3 (C16), 135.3 (C9), 138.1 (C11), 169.3 (C7), 175.9 (C27), 190.7 (C25), 195.1 ppm (C1); FTIR (ATR): $\tilde{\nu}=3311$ (s), 3043 (m), 2951 (s), 2918 (s), 2861 (s), 1716 (s), 1658 (vs), 1603 (vs), 1545 (vs), 1439 (vs), 1348 (s), 1262 (s), 1225 (s), 1192 (s), 1112 (m), 1009 (s), 975 (s), 963 (s), 910 (m), 831 (m), 763 (s), 733 (s), 647 cm^{-1} (s); MS (FAB): m/z (%): 589 (8) $[M+Na]^+$, 467 (100) $[M+H]^+$, 449 (8) $[M-H_2O]^+$, 299 (10), 247 (14), 155 (50); HRMS (FAB): calcd for $C_{27}H_{35}N_2O_5$: 467.2540; found: 467.2544 $[M+H]^+$.

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