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Total Synthesis of (−)-Hymenosetin

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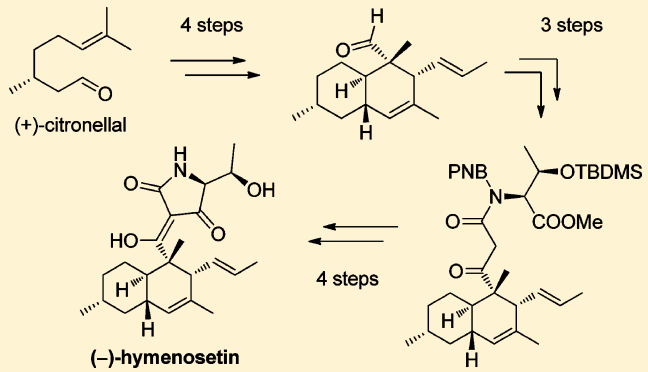
Supporting Information

ABSTRACT: The 3-decalinoyltetramic acid (−)-hymenosetin and its *N*-methyl analogue were prepared in 11 and 8 steps, respectively, from (+)-citronellal using an intramolecular Diels−Alder reaction as the key step. This method represents the first example for the synthesis of a 3-decalinoyltetramic acid with a free NH moiety. The stereochemistry of the title compound, an unnatural diastereomer, and of a decalin building block was studied in detail using circular dichroism spectroscopy in the IR and UV/VIS freqeuncy range. This allowed to determine the absolute configuration of the natural product and to plan the synthetic route.



INTRODUCTION

In 2014, Stadler and co-workers reported the isolation of the new fungal metabolite hymenosetin (**1**) from *Hymenoscyphus pseudoalbidus* (recently renamed to *H. fraxineus*), an invasive species causing severe dieback of the European ash.[1,2] Besides antifungal and moderate cytotoxic effects against the mouse fibroblast cell line L929, the compound was found to show promising biological activities against Gram-positive bacteria, including strong bacteriostatic inhibition of methicillin-resistant *Staphylococcus aureus* (MRSA), the growing resistance of which to most common antibiotics necessitates the discovery and development of new antibacterial agents.[1]

Hymenosetin belongs to the 3-decalinoyltetramic acids, a class in which equisetin (**2**) is the first discovered and best investigated member (Figure 1). This class of natural products can be subdivided based on the presence or absence of an *N*-methyl group.[3] Further examples for non-*N*-methylated 3-decalinoyltetramic acids are paecilosetin, altersetin, coniosetin, and *epi*-trichosetin.[4−6]

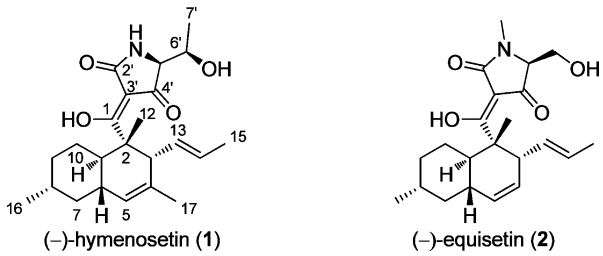


Figure 1. Structures of hymenosetin and equisetin.

The absolute and relative configurations of **1** have been determined based on comparison of its ECD (electronic circular dichroism) spectra with those of equisetin, phomasetin, and *epi*-trichosetin as well as by HSQC-HECADE-experiments and is the same as in equisetin.[1,7−9] HECADE is a 2D-NMR experiment suitable for the determination of heteronuclear long-range coupling constants which can be used for stereochemical assignment of acyclic structures.[7,10] Both the quaternary center of the decalin part (C-2) and the stereocenter in the tetramic acid part (C-5′) are S-configurated. In contrast to equisetin, hymenosetin bears an additional methyl group in the decalin part, an L-threonine-derived instead of L-serine-derived side chain, and a nonmethylated nitrogen in the tetramic acid moiety.

We aimed to develop an efficient synthetic strategy for the synthesis of 3-decalinoyltetramic acids with a free NH moiety to establish structure−activity relationships for this class of natural products and to prove the absolute configuration of hymenosetin through chemical synthesis. Furthermore, we report the isolation and structure elucidation of hymenosetin from the ascomycete IBWF-E99318 (*Phoma* sp.), which was used as a reference material in our subsequent studies. Here, we report the firm stereochemical assignment by CD spectroscopy at different wavelengths as well as the first total synthesis of (−)-hymenosetin.

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STRUCTURE ELUCIDATION

During a screening campaign for bioactive microbial natural products, a fungal secondary metabolite was obtained as a pale beige solid by extraction and purification of the culture filtrates of fungal strain IBWF-E99318 (unidentified ascomycete of the genus *Phoma*; see the Experimental Section for details). The $^{1}H/^{13}C$ NMR and HSQC spectra revealed the presence of five CH_3 groups [δ 1.41/13.7 (H-12/C-12), δ 1.56/18.1 (H-15/C-15), δ 1.32/19.7 (H-7′/C-7′), δ 1.60/22.3 (H-17/C-17), δ 0.92/22.6 (H-16/C-16)], three CH_2 groups [δ (1.05, 1.96)/28.4 (H-10/C-10), δ (1.11, 1.77)/35.9 (H-9/C-9), δ (0.88, 1.80)/42.7 (H-7/C-7)], nine CH groups including three olefinic ones [δ 1.51/33.7 (H-8/C-8), δ 1.83/39.2 (H-6/C-6), δ 1.67/39.8 (H-11/C-11), δ 3.10/49.5 (H-3/C-3), δ 3.70/65.4 (H-5′/C-5′), δ 4.04/68.0 (H-6′/C-6′), δ 5.16/125.7 (H-5/C-5), δ 5.25/127.8 (H-13/C-13), δ 5.14/130.7 (H-14/C-14)], and six quaternary carbons [δ 49.7 (C-2), 100.4 (C-3′), 132.1 (C-4), 179.5 (C-2′), 191.0 (C-4′), 200.7 (C-1)] (Table 1).

Table 1. NMR Data of (−)-Hymenosetin (1) ($CDCl_3$, ^{1}H, 600 MHz, ^{13}C, 150.9 MHz)

position	δ ^{1}H	δ ^{13}C
1, C_q		200.7
2, C_q		49.7
3, CH	3.10	49.5
4, C_q		132.1
5, CH	5.16	125.7
6, CH	1.83	39.2
7, CH_2	0.88, 1.80	42.7
8, CH	1.51	33.7
9, CH_2	1.11, 1.77	35.9
10, CH_2	1.05, 1.96	28.4
11, CH	1.67	39.8
12, CH_3	1.41	13.7
13, CH	5.25	127.8
14, CH	5.14	130.7
15, CH_3	1.56	18.1
16, CH_3	0.92	22.6
17, CH_3	1.60	22.3
2′, C_q		179.5
3′, C_q		100.4
4′, C_q		191.0
5′, CH	3.70	65.4
6′, CH	4.04	68.0
7′, CH_3	1.32	19.7

By analysis of 2D-NMR data (COSY; HSQC, HMBC, NOESY), the skeleton of hymenosetin (**1**) was identified, although the ^{1}H and ^{13}C chemical shifts revealed some minor differences from the previously reported data.[1] The relative configuration of the decalin part was suggested to be the same as for hymenosetin based on the NOESY correlations between protons H_{ax}-10, H-6, H-8, between H-11, H_{ax}-9, H_{ax}-7 as well as between the protons of methyl group H-12, H-6, H_{ax}-10, and H-3. (Figure 2).

However, the specific rotation of the natural product from *Phoma* strain IBWF-E99318 deviated significantly from the literature value reported for hymenosetin isolated from *Hymenoscyphus fraxineus* (vide infra).[1]

To elucidate the absolute configuration of the *trans*-decalin system by DFT-assisted VCD (vibrational circular dichroism) spectroscopy,[11−13] an oxidative cleavage of compound **1** to the decalinic acid **3** with subsequent O-methylation by diazomethane was performed (Scheme 1 and Figure 3).

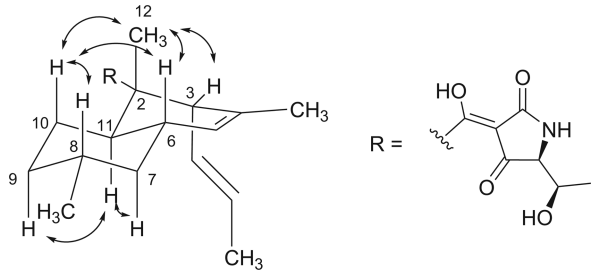
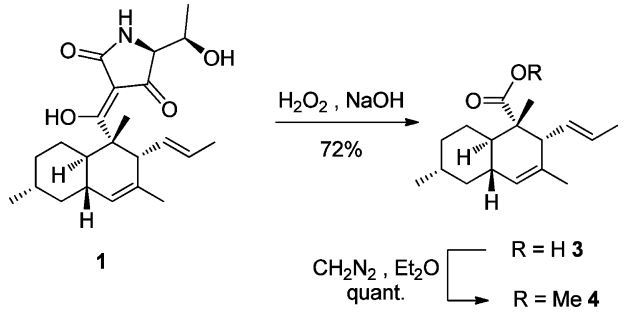


Figure 2. Selected NOESY correlations of (−)-hymenosetin (**1**).

Scheme 1. Oxidative Cleavage and Subsequent Esterification of Natural Product 1



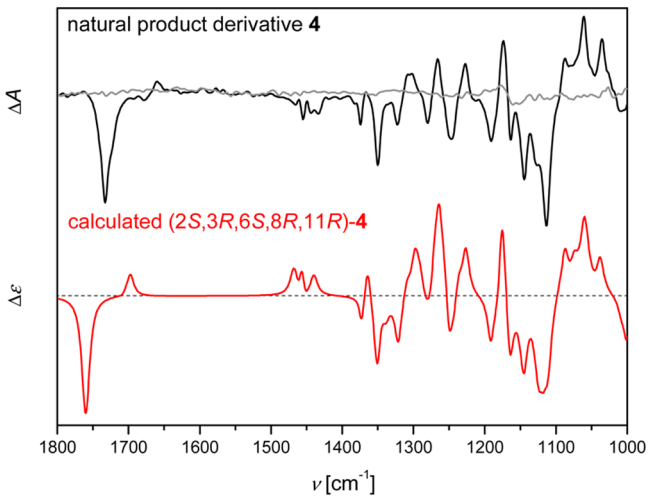


Figure 3. VCD spectrum of methyl ester **4** and calculated spectrum for (2*S*,3*R*,6*S*,8*R*,11*R*)-**4**.

The esterification was necessary to avoid the well-known discrepancies between experiment and predicted VCD spectra for carboxylic acids.[14−17] The VCD spectrum of the resulting methyl ester **4** was compared with the Boltzmann weighted average spectrum obtained from DFT calculations[18] at the B3PW91/6-311G(d,p) level of theory[19−23] (see Computational Methods for further details) for (2*S*,3*R*,6*S*,8*R*,11*R*)-**4** and shows a very good agreement between experiment and prediction over the complete spectral range. The enantiomeric similarity index (ESI) introduced by Bultinck et al.,[24] which indicates the similarity between the experimental and the theoretical spectra with SpecDis,[25,26] is very high (86.1%).

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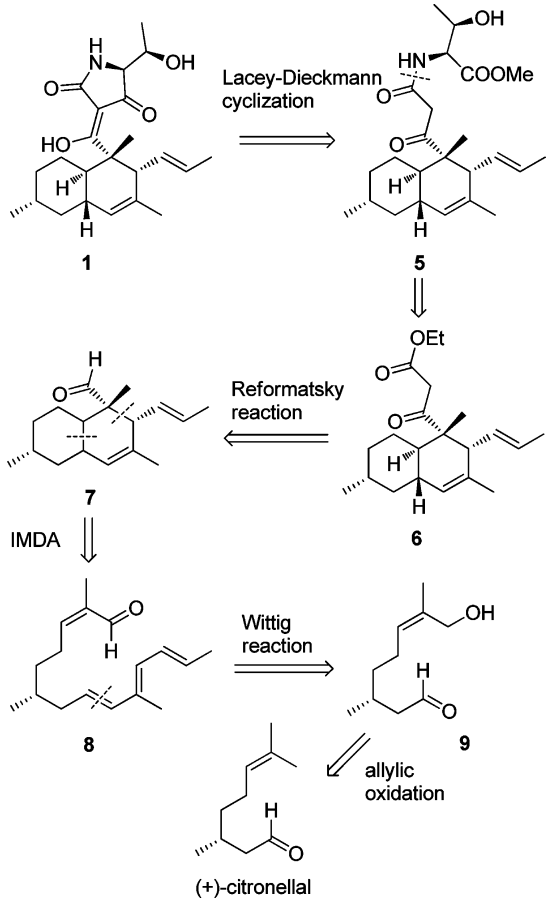
RETROSYNTHETIC ANALYSIS

The retrosynthetic analysis suggests (+)-citronellal to be a suitable starting material (Scheme 2). The chosen route, based

Scheme 2. Retrosynthetic Analysis of Hymenosetin



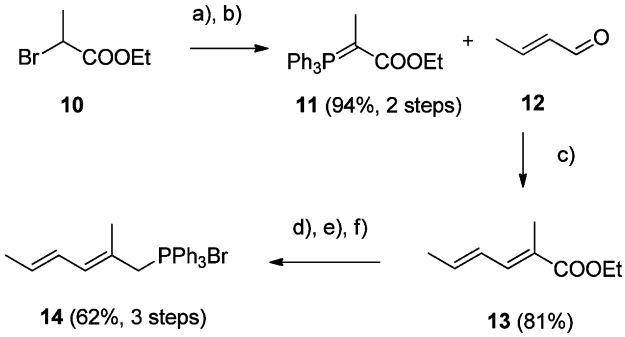
on this retrosynthetic analysis, is similar to the syntheses of equisetin by Gao, Ley, Theodorakis, and others.[14,27−29] Hymenosetin (**1**) should be prepared by ring closure of amide **5** via Lacey-Dieckmann condensation to the target tetramic acid. Amide **5** could be obtained by aminolysis of *β*-keto ester **6**, which should be prepared by Reformatsky reaction from decalinoyl aldehyde **7**. The *trans*-decalin system of aldehyde **7** should be established by an intramolecular Diels−Alder reaction (IMDA) of unsaturated aldehyde **8**, creating four stereogenic centers in a single step. Aldehyde **8** could be derived via a Wittig reaction from aldehyde **9**, which finally could be obtained from (+)-citronellal by allylic oxidation. A direct acylation of the tetramic acid part with decalinic acid **3** according to the synthesis strategy of Schobert proved to be unsuitable due to the steric hindrance imposed by the quaternary center at C-1 in the decalinic system.[30,31]

RESULTS AND DISCUSSION

The phosphonium bromide **14** required for the preparation of the *trans*-decalin system of hymenosetin was obtained using a known six-step procedure starting from ethyl 2-bromopropionate in high yield (Scheme 3).[29,32,33]

Allylic alcohol **9** was obtained by SeO_2-catalyzed allylic oxidation of (+)-citronellal in 52% yield along with 23% of the

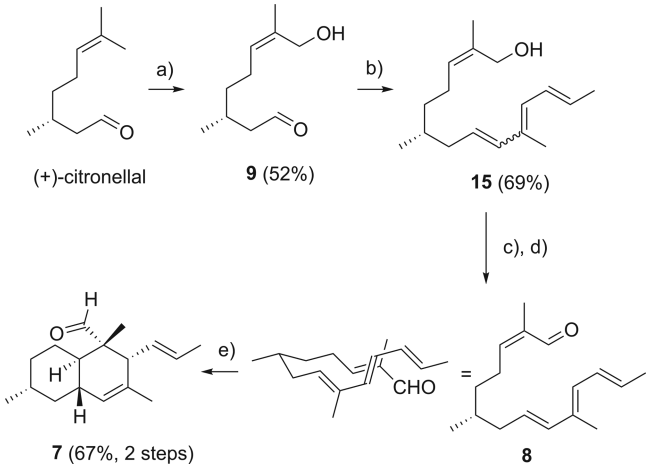
Scheme 3. Synthesis of Phosphonium Bromide 14[a]



[a](a) PPh_3, 50 °C, 10 h, 99%;[33] (b) 10% NaOH, CH_2Cl_2, 95%;[33] (c) CH_2Cl_2, reflux, 20 h, 81%;[32] (d) $LiAlH_4$, EtOH, Et_2O, 0 °C, 99%;[32] (e) PBr_3, CH_2Cl_2, −10 °C; (f) PPh_3, toluene, rt, 96 h, 63% over 2 steps.[29]

dialdehyde and 15% of unchanged starting material using a method reported by Theodorakis (Scheme 4).[28]

Scheme 4. Synthesis of the *trans*-Decalin Ring System[a]



[a](a) SeO_2, *t*BuOOH, salicylic acid, CH_2Cl_2, 36 h, rt; (b) **14**, 2 equiv *sec*-BuLi, THF, −78 °C; (c) oxalyl chloride, DMSO, NEt_3, CH_2Cl_2, −78 °C, (d) I_2, 500 W lamp, CH_2Cl_2, rt, quant.; (e) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C.

The subsequent Wittig reaction of the main product of the allylic oxidation (**9**) with **14** led to the desired triene alcohol **15** in 69% yield and moderate stereoselectivity (3:2 E/Z). Oxidation of the isomeric mixture of alcohols **15** according to the Swern protocol or with the Dess−Martin periodinane (DMP) led to aldehyde **8** (isomeric mixture).[14,27] The former method was used in our subsequent studies. The isomeric mixture was converted almost exclusively to the desired all-*trans* triene **8** by irradiation under a 500 W incandescent lamp in dichloromethane in the presence of 5 mol % I_2.[29] Without further purification, the IMDA was initiated by addition of $BF_3{\cdot}Et_2O$ at −78 °C to give the *trans*-decalin aldehyde **7** in 67% yield and high diastereoselectivity (>10:1 as judged by NMR spectroscopy).[14] To prove the absolute configuration of the synthetic *trans*-decalin system, aldehyde **7** was converted to acid **3** by Pinnick oxidation,[34] followed by esterification with CH_2N_2 (Scheme 5). A VCD spectrum of the obtained ester **4** was recorded under the same conditions as the natural product derivative. The results are

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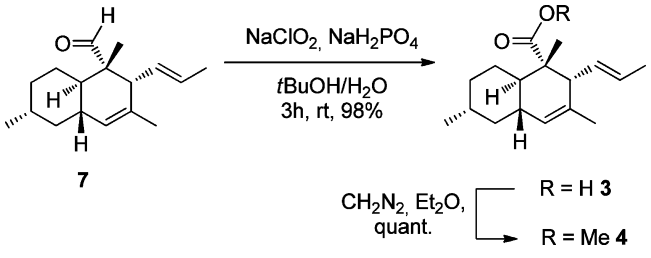
Scheme 5. Conversion of Aldehyde 7 to Ester 4



shown in Figure 4 and show perfect agreement, proving the previously assigned relative and absolute configuration of **4**.

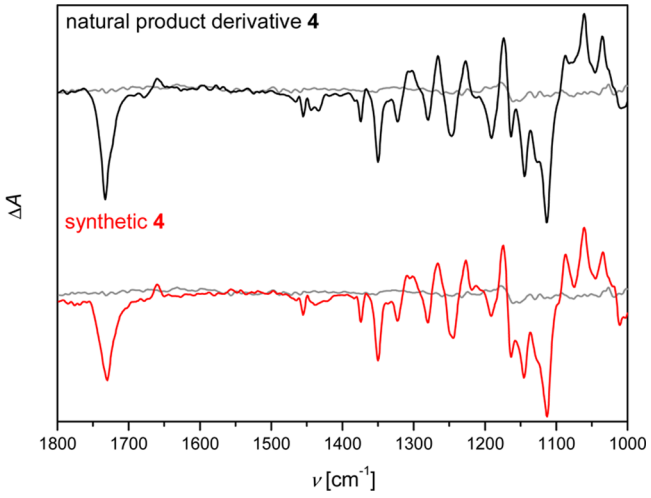


Figure 4. VCD spectra of natural and synthetic **4**.

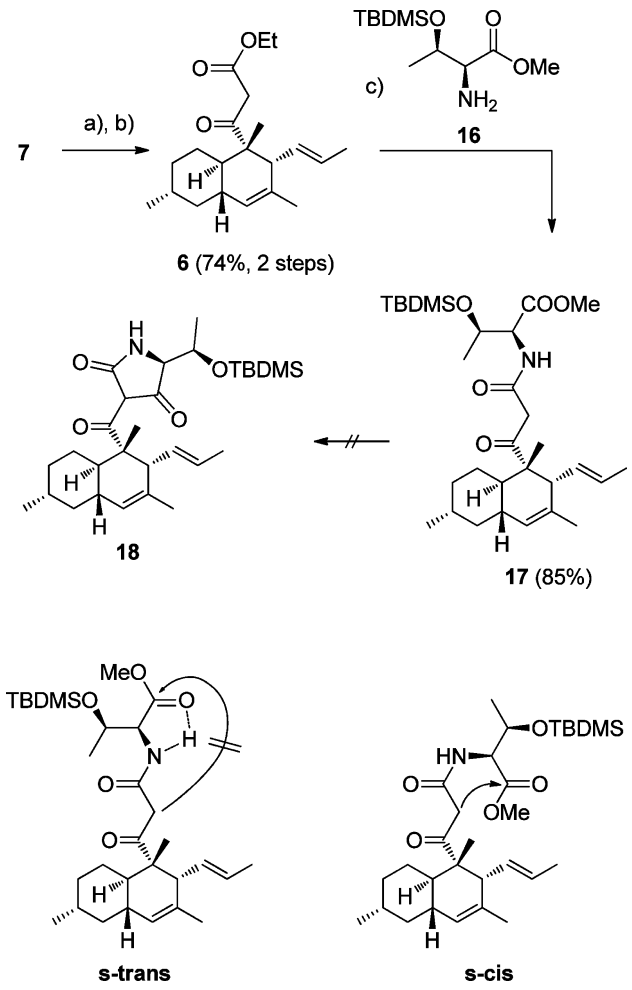
Initial studies for the synthesis of the tetramic acid part were discouraging (Scheme 6).

Decalinoyl aldehyde **7** was converted to the *β*-keto ester **6** by Reformatsky reaction and subsequent IBX oxidation. Aminolysis of compound **6** with TBDMS-protected L-threonine **16** in toluene at 80 °C in the presence of DMAP[14] produced amide **17** in 85% yield.[14,35,36] However, the following Lacey−Dieckmann cyclization failed to afford the desired tetramic acid **18** using NaOMe as the base under various conditions.[27,37] We attributed this to a distinct preference of the reactant for the s-*trans* conformation of the amide bond precluding the desired cyclization. A similar observation was previously reported by Pfaltz and Suzuki in their synthesis of macrocidin A.[30,38] To confirm the hypothesis that an additional substituent on nitrogen would make the s-*cis* conformer energetically accessible and should enable ring closure, we used the doubly protected N-methylated L-threonine derivative **19** (prepared according to a method by Schöllkopf)[15] for the synthesis of *N*-methylhymenosetin (**22**), in analogy to the synthesis of equisetin (Scheme 7).[28]

After aminolysis of *β*-keto ester **9** to amide **20**, the N-methylated derivative smoothly underwent Lacey−Dieckmann cyclization using KO*t*Bu (1 h at room temperature) to give the tetramic acid **21** in 89% yield. Subsequent removal of the TBDMS-group with HF/MeCN led to *N*-methylhymenosetin (**22**) in 91% yield.

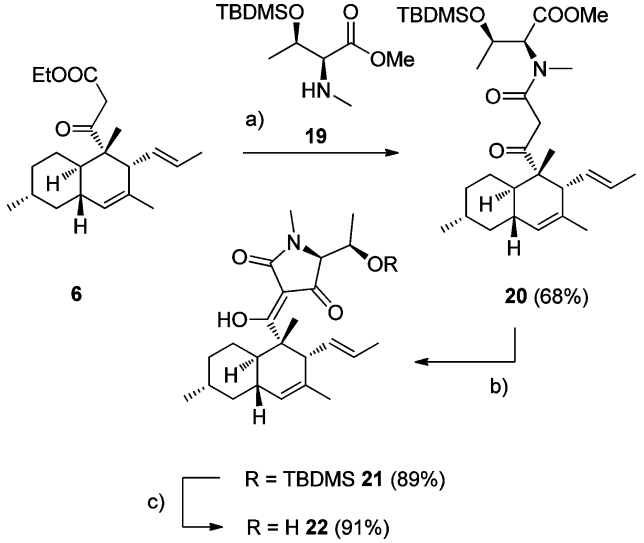
On the basis of these findings, PMB and 2,4-DMB (2,4-dimethoxybenzyl) were examined as protection of threonine's nitrogen. Indeed, the Lacey−Dieckmann cyclization was promoted; however, the removal of these protecting groups

Scheme 6. Synthesis of Amide 17 and Unsuccessful Lacey−Dieckmann Cyclization[a]



[a](a) ethyl 2-bromoacetate, activated Zn dust, PhH, 80 °C; (b) IBX, DMSO, 80 °C, 10 min; (c) **16**, DMAP, toluene, 80 °C.

Scheme 7. Synthesis of the *N*-Methyl Tetramic Acid 22[a]



[a](a) **19**, DMAP, toluene, 80 °C; (b) *t*BuOK, *t*BuOH, rt; (c) 48% HF, MeCN.

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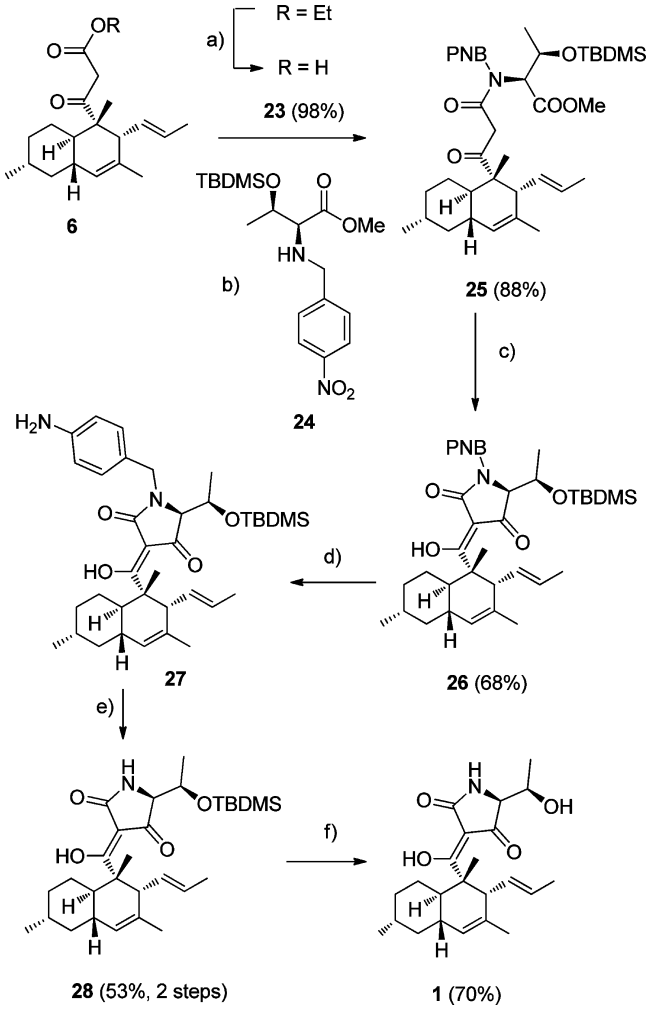
under oxidative (DDQ/CAN) or acidic conditions (TFA) resulted in complex mixtures. After these unsuccessful attempts, we found *para*-nitrobenzyl (PNB) to be a suitable protecting group for our purposes (Scheme 8).

Scheme 8. Synthesis of (−)-Hymenosetin 1[a]



[a](a) NaOH, EtOH/H_2O; (b) **24**, DCC, CH_2Cl_2; (c) NaOMe, MeOH, rt; (d) $Na_2S_2O_4$, $NaHCO_3$, EtOH/H_2O, rt, 30 min; (e) DDQ, DCM, 0 °C to rt, 1 h; (f) 48% HF, MeCN, rt.

The use of *para*-nitrobenzyl protected L-threonine **24** as the N-nucleophile afforded the aminolysis product **25** in 32% yield. The overall efficiency of the fragment coupling could be improved by careful saponification of the *β*-keto ester with NaOH/EtOH and subsequent DCC-mediated coupling to **24**, which led to the desired amide **25** in 88% yield. The Lacey−Dieckmann cyclization of the PNB-protected derivative using sodium methoxide was successful and produced the tetramic acid **26** in 68% yield.

Cleavage of the PNB-protecting group first required the sodium dithionite-induced reduction to the *para*-aminobenzyl derivative **27**, which could be debenzylated oxidatively by DDQ[38] in the presence of water to furnish the silyl-protected tetramic acid **28** in 53% yield. Removal of the TBDMS-group with 48% HF in acetonitrile finally led to hymenosetin (**1**) in 70% yield (3.9% overall from (+)-citronellal). The product is a mixture of two major keto−enol tautomers.[39] Physical properties (^{1}H and ^{13}C NMR, IR, mass spectra, CD spectra) were consistent with the reported data. However, the magnitude of the specific rotation exhibited a significant discrepancy to the reported value ($[\alpha]_D^{22} = -403$, $c = 0.1$, CH_2Cl_2; lit. $[\alpha]_D^{25} = -748$, $c = 0.1$, CH_2Cl_2),[1] whereas it matched the rotation of the compound isolated from fungal strain IBWF-E99318 ($[\alpha]_D^{22} = -417$, $c = 0.1$, CH_2Cl_2).

The correctness of the assignment of the relative configuration of the threonine portion was ensured by HECADE NMR experiments also employed by Halecker et al. for hymenosetin (Figure 5).[10]

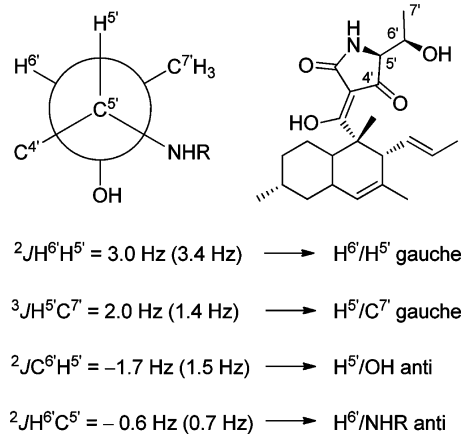


Figure 5. Assignment of the relative configuration of the tetramic acid side chain by HSQC-HECADE NMR based on the model of Matsumori[10] and matching the results of Stadler.[1] Literature values are given in brackets.

The corresponding data matched those previously reported, proving that the relative configuration of the threonine part of synthetic **1** and hymenosetin was identical. The compound was additionally analyzed by ECD spectroscopy, and again, the match between synthetic and natural hymenosetin was good (see the Supporting Information). As a final proof that the discrepancy in the specific rotation does not originate from a misassigned absolute configuration of the tetramic acid part, which was not included in the prior VCD analysis, a derivative of hymenosetin with the opposite absolute configuration of the threonine part was synthesized (Scheme 9).

Using PNB-protected D-threonine **29** as the coupling partner, we were able to obtain the 5′*R*, 6′*S*-configurated hymenosetin derivative **34** in a 1.5% overall yield under nonoptimized conditions. Physical properties (^{1}H, ^{13}C, and ECD spectra) were not consistent with the reported data and the isolated natural product. As additional evidence, the comparison of the VCD spectra (Figure 6) showed poor correlation for synthetic hymenosetin derivative **34** with the natural product **1**, whereas the latter showed perfect agreement with synthetic **1**, proving the correct absolute configuration of hymenosetin.

CONCLUSION

In summary, a general strategy for the synthesis of 3-decalinoyltetramic acids with a free NH moiety using the PNB-protecting group to enable the closure of the five-membered heterocycle was developed and was applied to an 11-step synthesis of hymenosetin. The proposed absolute configuration of this natural product was confirmed.

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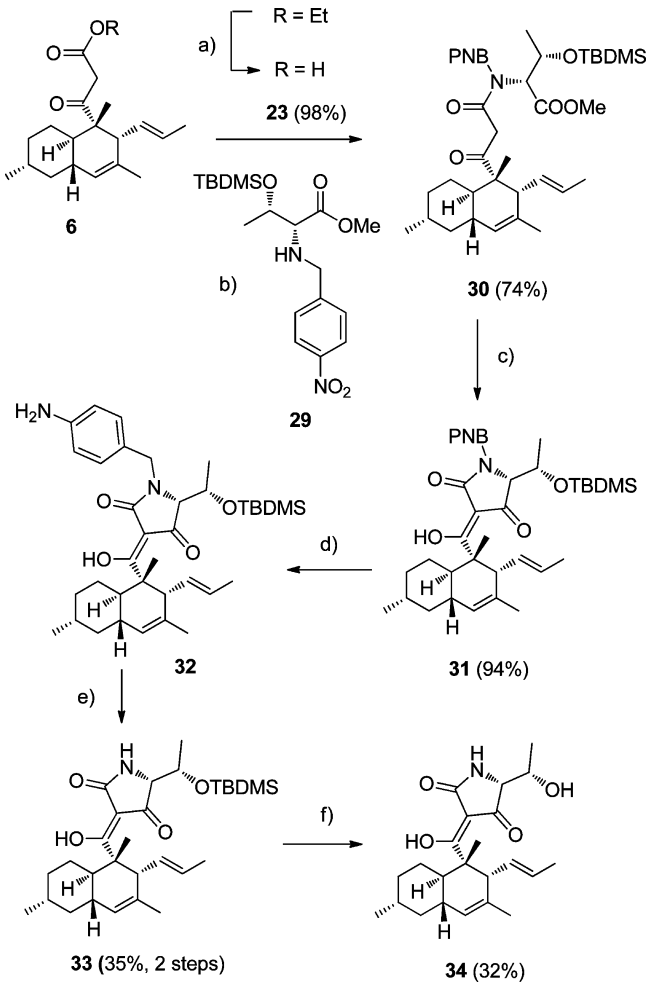
Scheme 9. Synthesis of the 5′*R*,6′*S*-Configurated Hymenosetin Derivative 34[a]



[a](a) NaOH, EtOH/H_2O; (b) **29**, DCC, CH_2Cl_2; (c) *t*BuOK, *t*BuOH, rt; (d) $Na_2S_2O_4$, EtOH/H_2O, 55 °C, 50 min, (e) DDQ, THF, 0 °C, 2 h; (f) 48% HF, MeCN, rt.

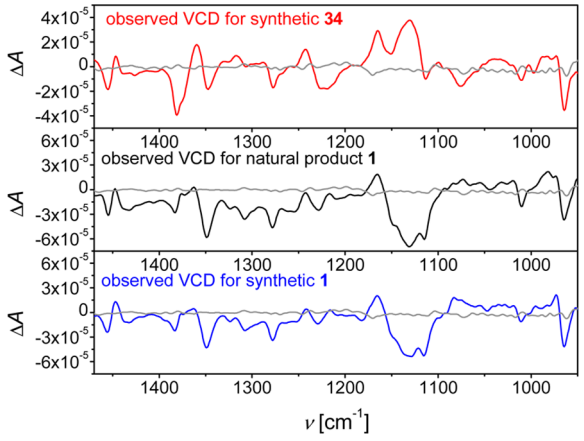


Figure 6. VCD spectra of synthetical compounds **1** and **34** compared to the spectra of the isolated natural product **1**.

EXPERIMENTAL SECTION

General Procedures. All reagents were reagent grade and used without further purification unless otherwise noted. All reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of argon in glassware that was oven-dried. Reaction temperatures refer to the temperature of the particular cooling/heating bath. Chromatography was performed using flash chromatography with the indicated solvent system on 35−70 μm silica gel unless otherwise noted. Alternatively, the purifications were performed on an automatic Flash Purification System with an integrated diode array detector. Preparative HPLC separation was carried out on an ACE 5 C18-PFP column, 30 mm × 150 mm at a flow rate of 37.5 mL/min using diode array detection. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300, 400, or 600 MHz spectrometer. Chemical shifts were referenced to the residual/deuterated solvent (e.g., for $CDCl_3$, δ = 7.26 and 77.16 ppm for ^{1}H and ^{13}C NMR, respectively) and reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ = 0.00 ppm). Coupling constants (J) are reported in Hz, and the splitting abbreviations used were: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates using an aqueous solution of $KMnO_4$ (1%) and $NaHCO_3$ (2%) and heat as developing agents. Specific reactions were monitored by LC-MS on a system with a binary pump and integrated diode array detector coupled to an LC/MSD-ion trap mass spectrometer. Ionization was achieved by an electron spray ionization source (ESI). High-resolution masses were recorded on an ESI/QTOF-Instrument and a suitable external calibrant. Infrared spectra were recorded as FT-IR spectra using a diamond ATR unit and are reported in terms of frequency of absorption (ν, cm^{-1}). Tetrahydrofuran, benzene, toluene, and diethyl ether were distilled under inert gas from sodium and benzophenone, dichloromethane from P_2O_5, and *t*BuOH from CaH_2. HSQC-HECADE was measured with a standard pulse-sequence (hsqcdietgpjcndsisp) using a d1-delay of 1.5 s, a mixing time (TOCSY) of 80 ms, and an assumed $^1J_{CH}$ coupling constant of 145 Hz.

Producing Strain, Fermentation, and Isolation of Hymenosetin. The producing strain IBWF-E99318 was isolated from a plant sample collected in northern Germany. The strain was determined as a *Phoma* species by morphology. IBWF-E99318 has been deposited in the culture collection of the Institut für Biotechnologie und Wirkstoff-Forschung gGmbH (IBWF gGmbH), Kaiserslautern, Germany. In this study, the fungus was maintained on HMG medium (yeast extract 4.0 g/L, malt extract 10 g/L, glucose 10 g/L; the pH value was adjusted to 5.5 before sterilization). In order to isolate hymenosetin, the fungus was grown in a submerged culture of 20 L of HMG medium. The temperature was set to 22 °C and aeration (3 L/min) and agitation (120 rpm) were maintained constant. For inoculation, a well-grown submerged culture (HMG medium, 250 mL) was used. During fermentation, the hymenosetin production was quantified by HPLC−MS. Eight days after inoculation, the highest amount of hymenosetin was determined and the fermentation was stopped. The culture fluid (15 L) was separated from the mycelium by filtration and discarded. The mycelium was lyophilized, and a portion of the dried material (168 g) was extracted with 2.5 L of MeOH. The solvent was evaporated, and the brown oily crude extract (16.4 g) was used for further workup. Solid-phase extraction with 100% MeOH generated fraction A (7.59 g), which was subjected to preparative HPLC of intermediate A (phenyl-RP silica, 5 μm, 21 × 250 mm, 21 mL/min, isocratic conditions: 60% acetonitrile/40% of 0.1% formic acid), finally resulting in the isolation of hymenosetin (381 mg, 2.27 mg/g dry weight, t_R 5.9 min).

*(3R,6E)-8-Hydroxy-3,7-dimethyloct-6-enal (**9**).* Using the method of Theodorakis[28] for the allylic oxidation, (+)-citronellal was oxidizied to allylic alcohol **9**. To a stirred solution of SeO_2 (540 mg, 4.86 mmol, 0.03 equiv) and salicylic acid (2.24 g, 16.2 mmol, 0.10 equiv) in DCM (50 mL) was added dropwise *t*BuOOH (89 mL, 70% in water, 0.64 mol, 4 equiv). After 15 min of vigorous stirring, (+)-citronellal (25.0 g, 0.16 mol, 1.00 equiv) was added dropwise, and the solution was stirred for 46 h at rt. DCM was evaporated, and the mixture was diluted with Et_2O (300 mL). The organic layer was washed with 10% NaOH (4 × 75 mL) and brine (1 × 150 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography (petrol ether/diethyl ether, gradient 0% to 100% diethyl ether, automatic flash purification system) to afford **9** (14.2 g, 51%) as a pale yellow oil along with the corresponding dialdehyde (6.25 g, 23%) and recovered

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citronellal (3.89 g, 16%). R_f = 0.09 (cyclohexane/ethyl acetate, 8:2); IR (ATR) ν (cm^{-1}) = 3398, 2955, 2919, 2871, 1722, 1458, 1380, 1098, 1014; $[\alpha]_D^{31}$ = +3.4 (c = 0.50, $CHCl_3$); ^1H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 9.74 (t, J = 2.3 Hz, 1H, H-1), 5.37 (tq, J = 7.1, 1.4 Hz, 1H, H-6), 3.98 (s, 2H, H-8), 2.40 (ddd, J = 16.2, 5.7, 2.1 Hz, 1H, H-2), 2.24 (ddd, J = 16.2, 7.8, 2.5 Hz, 1H, H-2), 2.11−1.98 (m, 3H, H-3, H-5), 1.77 (br s, 1H, OH), 1.64 (s, 3H, C7-Me), 1.44−1.21 (m, 2H, H-4), 0.96 (d, J = 6.7 Hz, 3H, C3-Me); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = δ 203.1 (C-1), 135.2 (C-7), 125.7 (C-6), 68.9 (C-8), 51.1 (C-2), 36.6 (C-4), 27.9 (C-3), 25.1 (C-5), 19.9 (C-3-Me), 13.8 (C-7-Me); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{18}O_2Na$ 193.1204; Found 193.1194. The data are in accordance with the literature.[28]

*[(2E,4E)-2-Methylhexa-2,4-dien-1-yl](triphenyl)phosphonium Bromide (**14**).* A solution of PBr_3 (4.69 g, 17.3 mmol, 0.34 equiv) in DCM (25 mL) was added slowly to a solution of (2*E*,4*E*)-2-methylhexadien-1-ol (5.00 g, 51.0 mmol, 1.00 equiv) in DCM (40 mL) at −8 °C. After stirring for 2 h at that temperature, the mixture was diluted with Et_2O (100 mL) and washed with cold 5% $NaHCO_3$ (50 mL) and brine. The aqueous layer was extracted with Et_2O (2 × 50 mL), and the combined organic extracts were dried over Na_2SO_4 and evaporated to give the crude (2*E*,4*E*)-2-methyl-hexadienbromide as a dark yellow oil (7.32 g, R_f = 0.63, cyclohexane/ethyl acetate 7:3). The crude bromide was dissolved in anhydrous toluene (50 mL), and PPh_3 (12.2 g, 46.3 mmol, 1.11 equiv) was added. After stirring for 96 h at room temperature, the crystalline solid was collected by suction filtration and washed with a small amount of toluene. After drying under high vacuum for 15 h, phosphonium salt **14** was obtained as beige crystalline solid (14.0 g, 63% over two steps): R_f = 0.18 (chloroform/MeOH, 5% MeOH); mp 78−80 °C; IR (ATR) ν (cm^{-1}) = 3053, 3007, 2853, 1438, 1111, 925, 721; ^1H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.82−7.73 (m, 9H, *p*-Ar-H, *o*-Ar-H), 7.68−7.60 (m, 6H, *m*-Ar-H), 6.08−5.97 (m, 1H, H-4), 5.74 (dd, J = 10.9, 5.6 Hz, 1H, H-3), 5.51−5.36 (m, 1H, H-5), 4.58 (d, J = 15.2 Hz, 2H, H-1), 1.69−1.62 (m, 3H, H-6), 1.52 (d, J = 4.2 Hz, 3H, C-2-*Me*); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 135.38 (d, $J_{C,P}$ = 11.9 Hz, C-3), 135.07 (d, $J_{C,P}$ = 3.0 Hz, Ar-C-4), 134.15 (d, $J_{C,P}$ = 9.8 Hz, Ar-C-2/6), 132.17 (d, $J_{C,P}$ = 5.2 Hz, C-5), 130.28 (d, $J_{C,P}$ = 12.5 Hz, Ar-C-3/5), 126.50 (d, $J_{C,P}$ = 5.6 Hz, C-4), 120.26 (d, $J_{C,P}$ = 12.2 Hz, C-2), 118.28 (d, $J_{C,P}$ = 84.6 Hz, Ar-C-1), 34.66 (d, $J_{C,P}$ = 46.1 Hz, C-1), 18.95 (d, $J_{C,P}$ = 2.5 Hz, C-2-*Me*), 18.45 (d, $J_{C,P}$ = 1.7 Hz, C-6); HRMS (ESI) m/z: $[M - Br]^+$ Calcd for $C_{25}H_{26}P$ 357.1772; Found 357.1773.

*(2E,6R,8E,10E,12E)-2,6,10-Trimethyltetradeca-2,8,10,12-tetraen-1-ol (**15**).* To a suspension of phosphonium bromide **14** (5.14 g, 11.75 mmol, 1.00 equiv) in THF (50 mL) was added dropwise *sec*-BuLi (16.8 mL, 1.4 M in cyclohexane, 23.49 mmol, 2.00 equiv) at −78 °C over 20 min. After stirring for an additional 10 min, a solution of compound **9** (2.04 g, 11.75 mmol, 1.00 equiv) in THF (30 mL) was slowly added. After stirring for 20 min at −78 °C, the mixture was allowed to come to room temperature overnight. Sat. NH_4Cl (15 mL) was added, and the mixture was stirred vigorously for 30 min. The layers were separated, and the aqueous layer was extracted with pentane/Et_2O (40 mL, 3:1). The combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash column chromatography (petrol ether/Et_2O, gradient 0% to 40% Et_2O, automatic flash purification system) to afford **15** (2.01 g, 8.10 mmol, 69%) as a light yellow viscous oil. The product was obtained as an inseparable mixture of E/Z-isomers (E/Z, 3:2): R_f = 0.44 (cyclohexane/ethyl acetate, 7:3); IR (ATR) ν (cm^{-1}) = 3312, 2956, 2913, 2869, 1440, 1377, 1012, 964; $[\alpha]_D^{22}$ = −23.2 (c = 1.00, $CHCl_3$); ^1H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 6.42−6.28 (m, 1H, *E*/*Z*-H-12), 6.05 (d, J = 15.5 Hz, 0.6H, *E*-H-9), 5.94 (d, J = 11.0 Hz, 1H, *E*/*Z*-H-11), 5.87 (d, J = 12.0 Hz, 0.4H, *Z*-H-9), 5.71 (dq, J = 6.9, 3.0 Hz, 1H, *E*/*Z*-H-13), 5.62 (dt, J = 15.2, 7.4 Hz, 0.6H, *E*-H-8), 5.42−5.36 (m, 1H, *E*/*Z*-H-3), 5.32 (dt, J = 11.9, 7.4 Hz, 0.4H, *Z*-H-8), 3.99 (s, 2H, *E*/*Z*-H-1), 2.28 (dddd, J = 15.1, 7.6, 5.8, 2.0 Hz, 0.4H, *Z*-H-7), 2.19−1.92 (m, 2.6H, *E*-H-7, *E*/*Z*-H-4), 1.89 (s, 1.2H, *Z*-C-10-Me), 1.83 (s, 1.8H, *E*-C-10-Me), 1.80 (d, J = 6.9 Hz, 3H, *E*/*Z*-H-14), 1.66 (s, 3H, *E*/*Z*-C-2-Me), 1.59−1.46 (m, 1H, *E*/*Z*-H-6), 1.44−1.33 (m, 1.4H, *Z*-H-7, *E*/*Z*-H-5), 1.24−1.13 (m, 1H, *E*/*Z*-H-5), 0.92−0.86 (m, 3H, *E*/*Z*-C-6-Me); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 136.2 (*E*-C-9), 134.7 (0.5 *E*/*Z*-C-2), 134.6 (0.5 *E*/*Z*-C-2), 133.6 (*Z*-C-9), 132.9 (*E*-C-10), 132.6 (*Z*-C-10), 130.0 (*Z*-C-11), 129.5 (*Z*-C-8), 129.40, 129.36 (*E*-C-11, *Z*-C-13), 129.26 (*E*-C-13), 128.27, 128.08 (2 × *E*/*Z*-C-12), 127.7 (*E*-C-8), 126.7 (*E*/*Z*-C-3), 69.2 (*E*/*Z*-C-1), 40.6 (*E*-C-7), 36.5 (*E*-C-5), 36.4 (*Z*-C-5), 36.2 (*Z*-C-7), 33.8 (*Z*-C-6), 33.2 (*E*-C-6), 25.3 (*E*/*Z*-C-4), 19.7 (*E*-C-6-Me), 19.6 (*Z*-C-6-Me), 18.7 (0.5 *E*/*Z*-C-14), 18.7 (0.5 *E*/*Z*-C-14), 17.2 (*Z*-C-10-Me), 13.8 (*E*/*Z*-C-2-Me), 12.8 (*E*-C-10-Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{29}O$ 249.2218; Found 249.2222.

*(2E,6R,8E,10E,12E)-2,6,10-Trimethyltetradeca-2,8,10,12-tetraenal (**8**).* DMSO (2.46 g, 31.44 mmol, 4.00 equiv) was added dropwise to a solution of oxalyl chloride (2.00 g, 15.72 mmol, 2.00 equiv) in DCM (80 mL). After stirring at this temperature for 30 min, a solution of compound **15** (1.95 g, 7.86 mmol, 1.00 equiv) in DCM (40 mL) was added dropwise. After stirring for 1 h, Et_3N (4.77 g, 47.17 mmol, 6.00 equiv) was added, and after stirring for an additional 10 min at −78 °C, the mixture was allowed to warm to room temperature. The reaction mixture was poured into water (250 mL), the layers were separated, and the aqueous layer was extracted with DCM (2 × 150 mL). The combined organic layers were washed with brine (75 mL) and dried over Na_2SO_4. After evaporation, the residue was dissolved in pentane/Et_2O (3:1) and filtered. The solvent was removed *in vacuo*, and the residue was kept under high vacuum for 3 h to give a yellow oil (1.92 g). The crude product was used for the next step without further purification.

Alternative Procedure. A solution of alcohol **15** (6.51 g, 26.28 mmol, 1.00 equiv) in DCM (150 mL) was added dropwise to a suspension of DMP (16.5 g, 29.45 mmol, 1.50 equiv) in DCM (75 mL), and the mixture was stirred for 20 min at rt. Water (706 μL, 1.50 equiv) was added and stirred for an additional 10 min, after which the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (300 mL) and stirred together with sat. $NaHCO_3$/10% $Na_2S_2O_3$ (150 mL) for 15 min. The layers were separated, and the organic layer was washed with sat. $NaHCO_3$ (3 × 100 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and evaporated to give a yellow oil (6.48 g), which was used for the next step without further purification. R_f = 0.45 (silica gel, pentane/Et_2O, 3:1); IR (ATR) ν (cm^{-1}) = 2957, 2926, 2872, 1720, 1685, 1456, 1378, 992.

*(1S,2R,4aS,6R,8aR)-1,3,6-Trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (**7**).* To a solution of compound **8** (6.48 g, 26.3 mmol, 1.00 equiv) in DCM (450 mL) was added dropwise a solution of I_2 (333 mg, 1.31 mmol, 0.05 equiv) in DCM (50 mL). The solution was irradiated for 5 min with a 500 W lamp (visible light). The mixture was then cooled down to −78 °C, and $BF_3{\cdot}Et_2O$ (11.20 g, 78.88 mmol, 3.00 equiv) was added slowly. After stirring the mixture for 14 h at that temperature, it was allowed to reach room temperature and was quenched by addition of 1:1 sat. $Na_2S_2O_3$/sat. $NaHCO_3$ (230 mL). The aqueous layer was extracted with DCM (3 × 100 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (petrol ether 9.5/0.5 Et_2O) to afford the decalin aldehyde (4.34 g, 67%) as a colorless oil (NMR shifts are assigned according to the numbering scheme given in Figure 1 to facilitate comparison with the literature): R_f = 0.52 (PE/Et_2O, 5% Et_2O); IR (ATR) ν (cm^{-1}) = 2947, 2917, 2856, 1723, 1454, 1374; $[\alpha]_D^{29}$ = −250.2 (c = 1.00, $CHCl_3$); ^1H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 9.48 (s, 1H, *CHO*), 5.45 (dq, J = 14.9, 5.9 Hz, 1H, H-14), 5.40−5.33 (m, 1H, H-13), 5.22 (s, 1H, H-5), 2.28 (d, J = 8.3 Hz, 1H, H-3), 1.85−1.68 (m, 4H, H-7, H-6, H-11, H-7), 1.67 (dd, J = 6.0, 1.1 Hz, 3H, H-15), 1.57 (t, J = 1.8 Hz, 3H, H-17), 1.53−1.43 (m, 1H, H-8), 1.43−1.37 (m, 1H, H-10), 1.11−0.98 (m, 2H, H-9, H-10), 0.96 (s, 3H, H-12), 0.92 (d, J = 6.6 Hz, 3H, H-16), 0.90−0.82 (m, 1H, H-7); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = δ 209.2 (*CHO*), 132.4 (C-4), 129.4 (C-13), 129.1 (C-24), 126.4 (C-5), 53.8 (C-3), 50.75 (C-2), 42.1 (C-7), 38.9 (C-11), 38.1 (C-6), 35.6 (C-9), 33.3 (C-8), 26.9 (C-10), 22.7 (C-16), 21.8 (C-17), 18.0 (C-15), 13.7 (C-12); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{27}O$ 247.2062; Found 247.2050.

*(1S,2R,4aS,6R,8aR)-1,3,6-Trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic Acid (**3**).* Aldehyde **7** (275 mg, 1.12 mmol, 1.00 equiv) was dissolved in *t*BuOH (30 mL), and 2-methyl-2-butene (955 mg, 13.6 mmol, 12.2 equiv) was added. A solution of $NaClO_4$ (80%) (770 mg, 6.81 mmol, 6.10 equiv)

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and NaH_2PO_4 (1.22 g, 10.2 mmol, 9.10 equiv) in water (30 mL) was added and stirred for 3 h at rt. Water (45 mL) was added, and the solution was extracted with DCM (4 × 50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give decalinic acid **3** (289 mg, 1.10 mmol, 99%) as a colorless solid (NMR shifts are assigned according to the numbering scheme of Figure 1): mp 158−162 °C; R_f = 0.26 (pentane/Et_2O, 8:2); IR (ATR) ν (cm^{-1}) = 3130, 2947, 2915, 2849, 1712, 1458, 1388, 1218, 1166, 968, 838; $[\alpha]_D^{22}$ = −157.0 (c = 0.47, $CHCl_3$); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 5.43 (dq, J = 15.3, 6.3 Hz, 1H, H-14), 5.26 (ddq, J = 15.1, 9.4, 1.6 Hz, 1H, H-13), 5.16 (s, 1H, H-5), 2.31 (d, 9.5 Hz, 1H, H-3), 1.83−1.65 (m, 4H, H-7, H-9, H-10, H-11), 1.63 (dd, J = 6.3, 1.6 Hz, 3H, H-15), 1.61−1.58 (m, 3H, H-17), 1.58−1.52 (m, 1H, H-6), 1.52−1.41 (m, 1H, H-8), 1.13 (s, 3H, H-12), 1.09−1.01 (m, 2H, H-9. H-10), 0.90 (d, J = 6.5 Hz, 3H, H-16), 0.88−0.73 (m, 1H, H-7); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 182.2 (COOH), 132.2 (C-4), 131.1 (C-13), 127.4 (C-14), 126.0 (C-5), 54.9 (C-3), 49.6 (C-2), 42.2 (C-7), 39.9 (C-11), 38.9 (C-6), 35.7 (C-9), 33.5 (C-8), 27.6 (C-10), 22.7 (C-16), 22.6 (C-17), 17.9 (C-15), 16.6 (C-12); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{26}O_2Na$ 285.1831; Found 285.1833.

*Methyl (1S,2R,4aS,6R,8aR)-1,3,6-Trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (**4**).* The esterification of decalinic acid **3** was performed with a diazomethane generator (flame polished glassware). EtOH (5 mL), H_2O (4 mL), and KOH (2.5 g) were added to the reaction vessel and warmed to 75 °C. Diazald (250 mg, 1.17 mmol) was dissolved in Et_2O (25 mL) and added dropwise. After addition of further Et_2O (10 mL), a solution of decalinic acid **3** (27.5 mg, 0.11 mmol) in Et_2O (3 mL) was added slowly. The reaction mixture was allowed to stand overnight at rt. Et_2O was evaporated to give methyl ester **4** (28.9 mg) as a yellow oil in quantitative yield (NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.65 (silica gel, pentane/Et_2O, 9:1); IR (ATR) ν (cm^{-1}) = 2947, 2916, 1729, 1450, 1376, 1254, 1236, 1145, 1120, 967; $[\alpha]_D^{36}$ = −149.3 (c = 1.00, $CHCl_3$); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 5.36 (dq, J = 15.0, 6.3 Hz, 1H, H-14), 5.21 (ddq, J = 15.0, 9.6, 1.5 Hz, 1H, H-13), 5.14 (s, 1H, H-5), 3.56 (s, 3H, COO*Me*), 2.27 (d, J = 9.3 Hz, 1H, H-3), 1.79−1.66 (m, 4H, H-5, H-9, H-10, H-6,), 1.62 (dd, J = 6.3, 1.5 Hz, 3H, H-15), 1.58−1.56 (m, 4H, H-11, H-17), 1.50−1.43 (m, 1H, H-8), 1.11 (s, 3H, H-12), 1.09−1.00 (m, 2H, H-7, H-10), 0.90 (d, J = 6.5 Hz, 3H, H-16), 0.88−0.73 (m, 1H, H-7); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 176.5 (COOMe), 132.3 (C-4), 131.6 (C-13), 126.9 (C-14), 126.0 (C-5), 55.3 (C-3), 51.1 (COO*Me*), 49.8 (C-2), 42.3 (C-7), 40.1 (C-11), 38.8 (C-6), 35.8 (C-9), 33.5 (C-8), 27.7 (C-10), 22.7 (C-16), 22.5 (C-17), 17.9 (C-15), 16.8 (C-12); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{28}O_2Na$ 299.1987; Found 299.1985.

*Ethyl 3-Oxo-3-{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}propanoate (**6**).* Zinc dust (404 mg, 6.18 mmol, 3.00 equiv) was activated by refluxing in benzene (3 mL) containing TMSCl (96 mg, 0.88 mmol) for 15 min. Ethyl 2-bromoacetate (413 mg, 2.47 mmol, 1.20 equiv) was added dropwise and was refluxed for a further 15 min. The reaction mixture was diluted with benzene (10 mL), and a solution of **7** (507 mg, 12.1 mmol, 1.00 equiv) was added dropwise. After refluxing for 1 h, the reaction mixture was allowed to cool down to room temperature, acidified with 1 N HCl, and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with $NaHCO_3$ (35 mL) and brine, dried over Na_2SO_4, and evaporated. The residue was resolved in DMSO (8 mL), IBX (1.15 g, 4.12 mmol, 2.00 equiv) was added, and the reaction mixture was heated to 80 °C for 15 min. After cooling to rt, the reaction was quenched with water (35 mL) and filtered, and the filtrate was extracted with diethyl ether (4 × 40 mL). The combined organic layers were washed with 10% NaOH (2 × 35 mL) and brine (1 × 35 mL), dried over Na_2SO_4, and evaporated. After purification by flash chromatography over silica gel (PE/Et_2O, 5% Et_2O), the product was obtained as a clear colorless oil (509 mg, 74%) beside recovered starting material (92 mg, 18%). NMR shows a mixture of keto/enol tautomers (NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.33 (pentane/Et_2O, 9:1); IR (ATR) ν (cm^{-1}) = 2946, 2913, 1745, 1708, 1614, 1449, 1376, 1308, 1263, 967, 805; $[\alpha]_D^{22}$ = −156.0 (c = 1.00, $CHCl_3$); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 12.41 (s, 0.11 H, enol-OH), 5.47−5.34 (m, 1H, H-14), 5.17 (s, 1H, H-5), 5.12−5.04 (m, 1.1H, H-13, C=C*H*-COOEt), 4.25−4.09 (m, 2H, OCH_2-CH_3), 3.49 (d, J = 15.8 Hz, 1H, CO-CH_2COOEt), 3.33 (d, J = 15.8 Hz, 1H, CO-CH_2COOEt), 2.27 (d, J = 9.5 Hz, 1H, H-3), 2.13 (d, J = 6.29 Hz, 0.12H, H-3 enol), 1.81−1.66 (m, 4H, H-7, H-6, H-9, H-10), 1.62 (dd, J = 6.4, 1.6 Hz, 3H, H-15), 1.61−1.58 (m, 4H, H-11, H-17), 1.52−1.40 (m, 1H, H-8), 1.26 (t, J = 7.1 Hz, 3H, OCH_2-CH_3), 1.13 (s, 3H, H-12), 1.10−1.04 (m, 1H, H-9), 0.94 (dd, J = 11.3, 2.4 Hz, 1H, H-10), 0.90 (dd, J = 6.5, 2.1 Hz, 3H, H-16), 0.87−0.78 (m, 1H, H-7); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 205.7 (C-1), 168.0 (COOEt), 131.5 (C-4), 130.2 (C-13), 127.8 (C-14), 126.4 (C-5), 89.0 (C=CH-COOEt enol), 61.2 (OCH_2CH$_3$), 60.0 (OCH_2CH$_3$ enol), 56.7 (C-3 enol), 54.2 (C-3), 54.1 (C-2), 46.6 (CO-CH_2COOEt), 42.3 (C-7), 39.6 (C-10), 39.1 (C-6), 35.7 (C-9), 33.6 (C-8), 27.2 (C-10), 22.6 (C-16), 22.4 (C-17), 17.9 (C-15), 16.8 (C-12), 14.3 (OCH_2CH_3); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{33}O_3$ 333.2430; Found 333.2420.

General Procedure for L- and D-Threonine TBDMS-Protection. Acetyl chloride (14 mL) was slowly added to a suspension of threonine (2.50 g, 21.0 mmol) in MeOH (75 mL) under cooling with an ice bath. After the addition was completed, the solution was heated to reflux for 24 h. The solvent was evaporated to give threonine methyl ester hydrochloride (3.55 g) as a colorless solid. Threonine methyl ester hydrochloride (3.55 g, 21.0 mmol, 1.00 equiv) was dispersed in DCM (70 mL), and imidazole (4.29 g, 63.0 mmol, 3.00 equiv) was added. The mixture was stirred for 30 min. TBDMSCl (3.48 g, 23.1 mmol, 1.10 equiv) was added, and the mixture was allowed to stir overnight at rt. The solvent was evaporated, and the residue was dissolved in water (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (5 × 40 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (ethyl acetate) to give the TBDMS-protected threonine methyl esters as a colorless liquid:

*Methyl O-[tert-Butyl(dimethyl)silyl]-L-threoninate (**16**).* 4.51 g, slightly yellowish oil, (19.6 mmol, 93%); R_f = 0.27 (silica gel, 100% ethyl acetate); IR (ATR) ν (cm^{-1}) = 3392, 2954, 2931, 2896, 2858, 1746, 1473, 1375, 1252, 1189, 1076, 836, 775; $[\alpha]_D^{31}$ = −17.9 (c = 1.00, $CHCl_3$); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 4.25 (qd, J = 6.3, 2.7 Hz, 1H, H-3), 3.66 (s, 2H, COO*Me*), 3.23 (d, J = 2.7 Hz, 1H, H-2), 1.57 (br s, 2H, NH_2), 1.20 (d, J = 6.3 Hz, 3H, 3 × H-4), 0.80 (s, 6H, C(CH_3)$_3$), 0.00 (s, 3H, Si-*Me*), −0.06 (s, 3H, Si-*Me*); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 175.0 (C-1), 69.5 (C-3), 60.8 (C-2), 51.9 (COO*Me*), 25.7 (C(CH_3)$_3$), 20.9 (C-4), 17.9 (*C*(CH$_3$)$_3$), −4.3 (Si-CH$_3$), −5.2 (Si-CH$_3$); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{26}NO_3Si$ 248.1682; Found 248.1690. The data are in accordance with the literature.[40]

*Methyl O-[tert-Butyl(dimethyl)silyl]-D-threoninate (ent-**16**).* 4.76 g, slightly yellowish oil, (20.6 mmol, 98%); R_f = 0.32 (silica gel, 100% ethyl acetate); IR (ATR) ν (cm^{-1}) = 2954, 2930, 2869, 2858, 1745, 1291, 1189, 1118, 967, 835, 774; $[\alpha]_D^{22}$ = +17.8 (c = 1.00, $CHCl_3$); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 4.28 (qd, J = 6.3, 2.7 Hz, 1H, H-3), 3.70 (s, 3H, COO*Me*), 3.27 (d, J = 2.7 Hz, 1H, H-2), 1.59 (br s, 2H, NH_2), 1.23 (d, J = 6.3 Hz, 3H, H-4), 0.83 (s, 9H, C(CH_3)$_3$), 0.03 (s, 3H, Si-*Me*), −0.03 (s, 3H, Si-*Me*); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 175.1 (C-1), 69.6 (C-3), 60.9 (C-2), 52.0 (COO*Me*), 25.8 (C(CH_3)$_3$), 21.0 (C-4), 18.0 (*C*(CH$_3$)$_3$), −4.2 (Si-CH$_3$), −5.1 (Si-CH$_3$); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{26}NO_3Si$ 248.1682; Found 248.1689. The data are in accordance with the literature.[40]

General Procedure for L- and D-Threonine PNB-Protection. TBDMS-protected threonine methyl ester (800 mg, 3.46 mmol, 1.00 equiv) was dissolved in MeOH (20 mL), and *p*-nitrobenzaldehyde (575 mg, 3.80 mmol, 1.10 equiv) and acetic acid (396 μL, 6.92 mmol, 2.00 equiv) were added. After stirring for 1 h at rt, $NaCNBH_3$ (400 mg, 6.06 mmol, 1.75 equiv) was added, and the mixture was allowed to stir for 24 h at rt. $NaHCO_3$ (870 mg, 10.4 mmol, 3.00 equiv) was added, and the solvent was removed *in vacuo*. Water (20 mL) and DCM (80 mL) were added, and the aqueous layer was extracted with DCM (2 × 80 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. After

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purification by flash column chromatography (cyclohexane/ethyl acetate, 5% ethyl acetate), the protected threonine was obtained as a yellow oil:

*Methyl O-[tert-Butyl(dimethyl)silyl]-N-(4-nitrobenzyl)-D-threoninate (**29**).* 1.28 g, slightly yellowish oil, (3.33 mmol, 96%); R_f = 0.41 (silica gel, cyclohexane/ethyl acetate, 8:1); IR (ATR) ν (cm^{-1}) = 2954, 2931, 2896, 2857, 1743, 1522, 1345, 1097, 837, 777; $[\alpha]_D^{22}$ = +57.1 (c = 1.00, $CHCl_3$); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.19−8.12 (m, 2H, *m*-Ar-H), 7.57−7.49 (m, 2H, *o*-Ar-H), 4.21 (qd, J = 6.2, 3.0 Hz, 1H, H-3), 4.10 (d, J = 14.7 Hz, 1H, Ar-CH_2), 3.74−3.66 (m, 4H, COO*Me*, Ar-CH_2), 3.05 (d, J = 3.0 Hz, 1H, H-2), 2.30 (br s, 1H NH), 1.27 (d, J = 6.2 Hz, 3H, H-4), 0.84 (s, 9H, C(CH_3)$_3$), 0.03 (s, 3H, Si-*Me*), −0.02 (s, 3H, Si-*Me*); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 173.8 (COOMe), 148.4 (Ar-C-1), 147.2 (Ar-C-4), 128.8 (Ar-C-2, Ar-C-6), 123.6 (Ar-C-3, Ar-C-5), 69.9 (C-3), 66.4 (C-2), 51.8 (COO*Me*), 51.3 (Ar-CH_2), 25.8 (C(CH_3)$_3$), 21.1 (C-4), 18.0 (C(CH_3)$_3$), −4.3 (Si-*Me*), −5.1 (Si-*Me*); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{31}N_2O_5Si$ 383.2002; Found 383.2019.

*Methyl O-[tert-Butyl(dimethyl)silyl]-N-(4-nitrobenzyl)-L-threoninate (**24**).* 1.28 g, slightly yellowish oil, (3.35 mmol, 97%); R_f = 0.41 (silica gel, cyclohexane/ethyl acetate, 8:1); IR (ATR) ν (cm^{-1}) = 2953, 2930, 2895, 2857, 1741, 1604, 1521, 1435, 1343, 1253, 1095, 828, 775; $[\alpha]_D^{22}$ = −55.1 (c = 1.00, $CHCl_3$); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.19−8.13 (m, 2H, 2 × *m*-Ar-H), 7.57−7.51 (m, 2H, 2 × *o*-Ar-H), 4.21 (qd, J = 6.2, 3.0 Hz, 1H, H-3), 4.10 (d, J = 14.7 Hz, 1H, Ar-CH_2), 3.72 (s, 3H, COO*Me*), 3.69 (d, J = 14.8 Hz, 1H, Ar-CH_2), 3.05 (d, J = 3.0 Hz, 1H, H-2), 2.15 (br s, 1H, NH), 1.27 (d, J = 6.2 Hz, 3H, 3 × H-4), 0.84 (s, 9H, *t*Bu), 0.03 (s, 3H, Si-Me), −0.02 (s, 3H, Si-Me); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 173.8 (C-1), 148.4 (Ar-C-1), 147.2 (Ar-C-4), 128.8 (Ar-C-2, Ar-C-6), 123.6 (Ar-C-3/C-5), 69.9 (C-3), 66.4 (C-2), 51.8 (COO*Me*), 51.4 (Ar-CH_2), 25.8 (C(CH_3)$_3$), 21.1 (C-4), 18.0 (C(CH_3)$_3$), −4.3 (Si-CH_3), −5.1 (Si-CH_3); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{31}N_2O_5Si$ 383.2002; Found 383.2013.

*Methyl O-[tert-Butyl(dimethyl)silyl]-N-methyl-L-threoninate (**19**).* Imidazole (182 mg, 2.67 mmol, 1.20 equiv) was added to a stirred solution of *N*-methyl threonine methylester (prepared according to Schöllkopf)[15] (327 mg, 2.22 mmol, 1.00 equiv) in DCM (5.5 mL). TBDMSCl (400 mg, 2.67 mmol, 1.20 equiv) was added, and the solution was stirred for 18 h at rt. The solvent was evaporated, and water (2 mL) and ethyl acetate (5 mL) were added. The aqueous layer was extracted with ethyl acetate (2 × 5 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (cyclohexane/ethyl acetate, 9:1) to afford compound **19** (465 mg, 1.78 mmol, 80%) as a colorless liquid: R_f = 0.29 (cyclohexane/ethyl acetate 9:1); IR (ATR) ν (cm^{-1}) = 2954, 2931, 2888, 2804, 1747, 1473, 1253, 1169, 1098, 1059, 836, 776; $[\alpha]_D^{22}$ = −27.5 (c = 1.00, $CHCl_3$); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 4.15 (qd, J = 6.2, 3.8 Hz, 1H, H-3), 3.72 (s, 3H, COO*Me*), 3.06 (d, J = 3.7 Hz, 1H, H-2), 2.41 (s, 3H, N-*Me*), 1.80 (s, 1H, NH), 1.23 (d, J = 6.2 Hz, 3H, 3 × H-4), 0.85 (s, 9H, C(CH_3)$_3$), 0.03 (s, 3H, Si-*Me*), 0.00 (s, 3H, Si-*Me*); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 173.8 (C-1), 69.7 (C-3), 69.4 (C-2), 51.8 (COO*Me*), 35.4 (N-*Me*), 25.8 (C(CH_3)$_3$), 20.9 (C-4), 18.1 (C(CH_3)$_3$), −4.3 (Si-*Me*), −5.0 (Si-*Me*); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{28}NO_3Si$ 262.1838; Found 262.1843.

*Methyl N-(3-Oxo-3-{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}-propanoyl)-O-(2,3,3-trimethylbutan-2-yl)-L-threoninate (**17**).* β-Keto ester **6** (80 mg, 0.2 mmol, 1.0 equiv), amino acid **16** (119 mg, 0.48 mmol, 2.0 equiv), and DMAP (59 mg, 0.48 mmol, 2.0 equiv) were dissolved in toluene (4 mL) and refluxed for 12 h. The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography (pentane/Et_2O 1:1) to give amide **17** (109 mg, 85%) as a clear, colorless oil (NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.19 (pentane/Et_2O, 1:1); IR (ATR) ν (cm^{-1}) = 3348, 2950, 2857, 1754, 1681, 1519, 1253, 1095, 836; $[\alpha]_D^{22}$ = −58.3 (c = 0.10, $CHCl_3$); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 13.76 (s, 0.1H, enol-OH), 7.73 (d, J = 8.8 Hz, 1H, NH), 7.58−7.53 (m, 0.15H, NH minor), 5.40 (dq, J = 15.2, 6.4 Hz, 1H, H-14), 5.17 (s, 1H, H-5), 5.08 (ddd, J = 15.1, 9.8, 1.6 Hz, 1H, H-13), 4.55−4.43 (m, 2H, H-2′, H-3′), 3.69 (s, 3H, COO*Me*), 3.49 (d, J = 16.4 Hz, 1H, CO-CH_2-CONHR), 3.30 (d, J = 16.4 Hz, 1H, CO-CH_2-CONHR), 2.31 (d, J = 9.7 Hz, 1H, H-3), 1.81−1.62 (m, 5H, H-7, H-6, H-9, H-10, H-11), 1.61−1.56 (m, 6H, H-17, H-15), 1.54−1.43 (m, 1H, H-8), 1.16 (d, J = 2.5 Hz, 3H, H-5), 1.14 (s, 3H, H-12), 1.12−1.05 (m, 1H, H-9), 0.99−0.94 (m, 1H, H-10), 0.91 (d, J = 6.5 Hz, 3H, H-16), 0.89−0.81 (m, 10H, C(CH_3)$_3$, H-10), 0.06 (s, 3H, Si-*Me*), −0.01 (s, 3H, Si-*Me*).; ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 209.54 (C-1), 171.02 (*C*OOMe), 166.60 (*C*ONHR), 131.52 (C-4), 130.46 (C-13), 127.91 (C-14), 126.43 (C-5), 68.68 (C-3′), 58.18 (C-2′), 54.40 (C-2), 54.12 (C-3), 52.30 (COO*Me*), 46.19 (CO-CH_2-CONHR), 42.41 (C-7), 39.61 (C-10), 39.14 (C-6), 35.72 (C-9), 33.51 (C-8), 27.41 (C-10), 25.65 (C(CH_3)$_3$), 22.64 (C-16), 22.22 (C-17), 21.11 (C-4′), 18.01 (C(CH_3)$_3$), 17.96 (C-15), 16.11 (C-12), −4.20 (Si-*Me*), −5.25 (Si-*Me*); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{30}H_{52}NO_5Si$ 534.3615; Found 534.3607.

*Methyl O-[tert-Butyl(dimethyl)silyl]-N-methyl-N-(3-oxo-3-{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}propanoyl)-L-threoninate (**20**).* Compound **6** (64 mg, 0.2 mmol, 1.0 equiv), amino acid **19** (60 mg, 0.2 mmol, 1.2 equiv), and DMAP (28 mg, 0.2 mmol, 1.2 equiv) were dissolved in toluene and refluxed for 18 h. The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography (pentane/Et_2O 8:2) to give amide **20** (71 mg, 68%) as a clear, colorless oil beside recovered compound **9** (9 mg, 14%) (NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.16 (pentane/Et_2O, 8:2); IR (ATR) ν (cm^{-1}) = 2952, 2927, 2856, 1752, 1711, 1655, 1459, 1062, 970, 837; $[\alpha]_D^{22}$ = −49.8 (c = 0.40, $CHCl_3$); ^{1}H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) = 14.95 (s, 0.02H, enol-OH), 14.85 (s, 0.04H, enol-OH), 14.80 (s, 0.3H, enol-OH), 5.46−5.40 (m, 0.6H, H-2‴ keto), 5.39 (d, J = 3.4 Hz, 0.6H, H-2′ keto), 5.34 (d, J = 3.6 Hz, 0.3H, H-2′ enol), 5.27−5.24 (m, 0.6H, H-13 enol, H-14 enol), 5.23 (s, 0.3H, C=C*H*-CONR$_2$ enol), 5.19−5.10 (m, 1.5H, H-5 keto, H-5 enol, H-13 keto), 4.66−4.60 (m, 1H, H-3′), 3.80 (d, J = 16.5 Hz, 0.6H, CO-CH_2-CONR$_2$ keto), 3.73 (s, 1H, N-*Me* enol), 3.71 (s, 2H, N-*Me* keto), 3.45 (d, J = 16.4 Hz, 0.6H, CO-CH_2-CONR$_2$ keto), 3.16 (s, 1H, COO*Me* enol), 3.14 (s, 2H, COO*Me* keto), 2.31 (d, J = 9.5 Hz, 0.6H, H-3 keto), 2.20 (d, J = 7.2 Hz, 0.3H, H-3 enol), 1.82−1.62 (m, 5H, H-7, H-9, H-10, H-6 keto, H-11 keto, H-6 enol), 1.62−1.57 (m, 6H, H-15, H-17), 1.56−1.52 (m, 0.3H, H-11 enol), 1.51−1.44 (m, 1H, H-8), 1.23 (d, J = 6.4 Hz, 2H, H-4′ keto), 1.17 (s, 2H, H-12 keto), 1.13−1.11 (m, 1.6H, H-4′ enol, H-9 keto), 1.06 (s, 1H, H-12 enol), 1.03−0.93 (m, 1.3H, H-10, H-9 enol), 0.92−0.88 (m, 3H, H-16), 0.88−0.85 (m, 1H, H-7), 0.85−0.81 (m, 9H, C(CH_3)$_3$), 0.08 (s, 2H, Si-*Me* keto), 0.07 (s, 1H, Si-*Me* enol), 0.03 (s, 1H, Si-*Me* enol), 0.03 (s, 2H, Si-*Me* keto); ^{13}C NMR, HSQC, HMBC (150.9 MHz, $CDCl_3$) δ (ppm) = 207.12 (C-1 keto), 183.31 (C-1 enol), 173.60 (*C*ONR$_2$ enol), 170.70 (*C*OOMe enol), 170.46 (*C*OOMe keto), 169.62 (*C*ONR$_2$ keto), 133.37 (C-4 enol), 131.81 (C-4 keto), 131.66 (C-13 enol), 130.60 (C-13 keto), 127.71 (C-14 keto), 126.32 (C-5 keto), 125.62 (C-5 enol), 125.39 (C-14 enol), 85.90 (C=*C*H-CONR$_2$ enol), 69.66 (C-3′ enol), 69.61 (C-3′ keto), 60.78 (C-2′ keto), 60.25 (C-2′ enol), 56.18 (C-3 enol), 54.23 (C-2 keto), 54.21 (C-3 keto), 52.11 (N-*Me* enol), 52.08 (N-*Me* keto), 46.69 (C-2 enol), 45.97 (CO-CH_2-CONR$_2$ keto), 42.48 (C-7 enol), 42.28 (C-7 keto), 39.77 (C-11 enol), 39.74 (C-11 keto), 39.41 (C-6 enol), 39.25 (C-6 keto), 35.87 (C-9 enol), 35.68 (C-9 keto), 34.83 (COO*Me* keto), 34.48 (COO*Me* enol), 33.57 (C-8), 27.44 (C-10 enol), 27.24 (C-10 keto), 25.78 (C(CH_3)$_3$), 22.84 (C-16 enol), 22.68 (C-17 enol), 22.66 (C-16 keto), 22.45 (C-17 keto), 20.66 (C-4′ enol), 20.59 (C-4′ keto), 17.97 (C-15 keto), 17.94 (C(CH_3)$_3$), 17.89 (C-15 enol), 16.94 (C-12 keto), 16.92 (C-12 enol), −4.08 (Si-*Me* keto), −4.14 (Si-*Me* enol), −5.25 (Si-*Me* enol), −5.32 (Si-*Me* keto). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{31}H_{54}NO_5Si$ 548.3771; Found 548.3762.

*(3Z,5S)-5-[(1R)-1-{[tert-Butyl(dimethyl)silyl]oxy}ethyl]-3-(hydroxy-{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}methylidene)-1-methylpyrrolidine-2,4-dione (**21**).* *t*BuOK (40.3 mg, 0.36 mmol, 1.2 equiv) was added to a stirred solution of **20** (164 mg, 0.30 mmol, 1.0 equiv) in *t*BuOH (1.6 mL). After stirring for 1 h at rt, the reaction

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mixture was partitioned between sat. NH_4Cl (3 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (4 × 25 mL), and the combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, and evaporated. Purification by flash column chromatography (pentane/ethyl acetate, 5% ethyl acetate) gave compound **21** (138 mg, 89%) as a colorless oil (NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.42 (pentane/ethyl acetate, 8:2); IR (ATR) ν (cm^{-1}) = 2951, 2927, 2857, 1695, 1661, 1567, 1495, 1377, 1256, 977, 835, 777; $[\alpha]_D^{22}$ = −156.6 (c = 1.00, $CHCl_3$); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 5.26−5.09 (m, 3H, H-14, H-13, H-5), 4.33−4.24 (m, 1H, H-6′), 3.37 (d, J = 2.2 Hz, 1H, H-5′), 3.11 (s, 3H, N-*Me*), 3.03 (d, J = 10.4 Hz, 1H, H-3), 1.98−1.89 (m, 1H, H-10), 1.86−1.71 (m, 3H, H-6, H-7, H-9), 1.71−1.64 (m, 1H, H-11), 1.61−1.52 (m, 6H, H-17, H-15), 1.52−1.48 (m, 1H, H-8), 1.43−1.37 (m, 6H, H-12, H-7′), 1.17−0.98 (m, 2H, H-9, H-10), 0.94−0.83 (m, 4H, H-16, H-7), 0.80 (s, 9H, $C(CH_3)_3$), 0.03 (s, 3H, Si-*Me*), −0.05 (s, 3H, Si-*Me*); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 197.8 (C-1), 190.9 (C-4′), 177.5 (C-2′), 132.3 (C-4), 130.9 (C-13), 127.5 (C-14), 125.7 (C-5), 100.4 (C-3′), 71.8 (C-5′), 68.0 (C-6′), 49.9 (C-3), 49.4 (C-2), 42.7 (C-7), 39.8 (C-11), 39.3 (C-6), 35.95 (C-9), 33.8 (C-8), 29.8 (N-*Me*), 28.3 (C-10), 25.8 ($C(CH_3)_3$), 23.2 (C-7′), 22.7 (C-16), 22.4 (C-17), 18.1 (C-15), 18.0 ($C(CH_3)_3$), 13.7 (C-12), −3.9 (Si-*Me*), −5.1 (Si-*Me*); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{30}H_{50}NO_4Si$ 516.3509; Found 516.3498.

*(3Z,5S)-5-[(1R)-1-Hydroxyethyl]-3-(hydroxy{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}methylidene)-1-methylpyrrolidine-2,4-dione (**22**).* HF (1.12 mL, 48 wt % in water) was added to a solution of silyl ether **21** (72 mg, 0.14 mmol, 1.0 equiv) in MeCN (2.8 mL). After stirring for 30 min at room temperature, solid $NaHCO_3$ (2.3 g) was added portionwise. The solvent was removed in vacuo, and the residue was partitioned between EtOAc (40 mL) and water (8 mL). After filtration, the aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was subjected to reversed phase flash chromatography (5% water/MeCN) to give pure *N*-methyl-hymenosetin (51 mg, 91%) as a colorless lyophylisate (mixture of enols, NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.37 (ethyl acetate/cyclohexane, 9:1); IR (ATR) ν (cm^{-1}) = 3428, 2947, 2919, 1752, 1702, 1657, 1579, 1451, 1377, 1236, 1055; $[\alpha]_D^{22}$ = −180.4 (c = 0.25, $CHCl_3$); ^{1}H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) = 5.31−5.19 (m, 1H, H-14), 5.18−5.08 (m, 2H, H-5, H-13), 4.22−4.16 (br m, 1H, H-6′), 4.04 (d, J = 4.1 Hz, 0.17H, H-5′ minor enol), 3.71 (d, J = 4.5 Hz, 1H, H-5′), 3.49 (br s, 1H, OH), 3.36 (d, J = 9.7 Hz, 0.17H, H-3 minor), 3.09−3.04 (d, J = 9.2 Hz, 1H, H-3), 2.99 (s, 3H, N-*Me*), 2.94 (s, 0.6H, N-*Me* minor), 2.00−1.93 (m, 1H, H-10), 1.87−1.72 (m, 3H, H-7, H-6, H-9), 1.70−1.64 (m, 1H, H-11), 1.59 (s, 3H, H-17), 1.55 (d, J = 6.3 Hz, 3H, H-15), 1.51−1.56 (m, 3H, H-8, H-12, H-15 minor), 1.39 (s, 3H, H-12), 1.11 (d, J = 6.4 Hz, 4H, H-9, H-7′), 1.07−1.00 (m, 2H, H-10, H-7′ minor), 0.92 (d, J = 6.5 Hz, 3H, H-16), 0.90−0.86 (m, 1H, H-7) ; ^{13}C NMR, HSQC, HMBC (150.9 MHz, $CDCl_3$) δ (ppm) = 203.9 (C-1 minor), 199.9 (C-1), 198.2 (C-4′ minor), 192.2 (C-4′), 177.4 (C-2′), 166.8 (C-2′ minor), 132.1 (C-4 minor), 132.0 (C-4), 131.1 (C-13 minor), 130.6 (C-13), 127.8 (C-14), 125.8 (C-5), 125.6 (C-5 minor), 107.1 (C-3′ minor), 100.5 (C-3′), 67.8 (C-5′), 66.7 (C-6′), 65.12 (C-5′ minor), 50.6 (C-2 minor), 50.0 (C-3 minor), 49.5 (C-2), 49.4 (C-3), 42.7 (C-7 minor), 42.6 (C-7), 40.1 (C-11 minor), 39.8 (C-11), 39.3 (C-6), 39.1 (C-6 minor), 35.9 (C-9), 33.7 (C-8), 28.4 (C-10), 28.2 (C-10 minor), 27.6 (N-*Me*), 22.7 (C-6″-*Me*), 22.3 (C-17), 22.2 (C-17 minor), 18.1 (C-15), 17.8 (C-15 minor), 17.7 (C-7′), 17.3 (C-7′ minor), 14.5 (C-12 minor), 13.7 (C-12); HRMS (ESI): calculated for $[C_{24}H_{35}NO_4+H]^+$: 402.2644, found: 402.2628 $[M + H]^+$.

*3-Oxo-3-{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}propanoic Acid (**23**).* Compound **6** (275 mg, 0.83 mmol, 1.00 equiv) was dissolved in EtOH (14 mL). A solution of NaOH (60 mg, 1.49 mmol, 1.80 equiv) in H_2O (1 mL) was added, and the solution was allowed to stir overnight at room temperature. The mixture was acidified carefully with 1 N HCl under cooling with an ice bath. The solution was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was removed *in vacuo*. The product was afforded as a crystalline solid (264 mg, 98%), which was used rapidly for the next step.

*Methyl O-[tert-Butyl(dimethyl)silyl]-N-(4-nitrobenzyl)-N-(3-oxo-3-{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}propanoyl)-L-threoninate (**25**).* Compounds **23** (233 mg, 0.77 mmol, 1.00 equiv) and **24** (440 mg, 1.15 mmol, 1.50 equiv) were dissolved in DCM (2 mL). A solution of DCC (174 mg, 0.84 mmol, 1.10 equiv) and DMAP (5 mg, 0.04 mmol, 0.05 equiv) in DCM (1 mL) was added dropwise under cooling with an ice bath. The solution was allowed to stir for 12 h at room temperature. The solution was filtered and evaporated, and the residue was resolved in acetone. The remaining urea was filtered off, and the solvent was removed in vacuo. The product was isolated after purification through reversed phase chromatography (acetonitrile/water, 5% to 95% acetonitrile, automatic flash purification system) as a colorless oil (450 mg, 88%). NMR spectra show a mixture of rotameres (R1/R2) and keto−enol tautomers (NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.23 (pentane/Et_2O, 9:1);IR (ATR) ν (cm^{-1}) = 2951, 2929, 2857, 1751, 1609, 1522, 1472, 1345, 1254, 944, 836; $[\alpha]_D^{22}$ = −73.1 (c = 1.00, $CHCl_3$); ^{1}H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) = 14.61 (s, 1H, enol-OH), 8.25−8.19 (m, 1H, *m*-Ar-H R2), 8.21−8.18 (m, 2H, *m*-Ar-H enol), 8.16−8.11 (m, 2H, *m*-Ar-H R1), 7.52 (d, J = 8.7 Hz, 1H, *o*-Ar-H R2), 7.50−7.45 (m, 2H, *o*-Ar-H R1/enol), 5.44 (dq, J = 15.1, 6.4 Hz, 2H, H-14 R1, H-2′ enol), 5.39−5.34 (m, 0.7H, H-2′ R2), 5.29 (d, J = 18.6 Hz, 0.7H Ar-CH_2 R2), 5.26−5.15 (m, 4H, Ar-CH_2 enol, H-14 R2, H-5 R1, H-14 enol), 5.14−5.10 (m, 2H, H-5 R2, H-13 R1), 5.09−4.95 (m, 4H, Ar-CH_2 R1, H-5 enol, H-13 enol, H-13 R2), 4.79 (d, J = 18.6 Hz, 0.7H, Ar-CH_2 R2), 4.74−4.63 (m, 4.7H, Ar-CH_2 R1/enol, H-3′ enol/R2, C=C*H*-CONR$_2$ enol), 4.40−4.33 (m, 1H, H-3′ R1), 4.06 (d, J = 6.9 Hz, 1H, H-2′ R1), 4.02 (d, J = 17.1 Hz, 1H, CO-CH_2-CONR$_2$ R1), 3.66 (s, 3H, COO*Me* enol), 3.65 (s, 2H, COO*Me* R2), 3.47 (s, 3H, COO*Me* R1), 3.46 (d, J = 17.1 Hz, 1H, CO-CH_2-CONR$_2$ R1), 3.36 (d, J = 16.3 Hz, 0.6H, CO-CH_2-CONR$_2$ R2), 3.28 (d, J = 16.3 Hz, 0.6H, CO-CH_2-CONR$_2$ R2), 2.31 (d, J = 9.6 Hz, 1H, H-3 R1), 2.12 (d, J = 9.4 Hz, 0.6H, H-3 R2), 2.03 (d, J = 9.0 Hz, 1H, H-3 enol), 1.82−1.62 (m, 12H, H-7 R1/R2/enol, H-6 R1/R2/enol, H-11 R1 or R2, H-9 R1/R2, H-10 R1/R2), 1.62−1.54 (m, 10H, H-11, H-17 R1, H-15 enol/R1), 1.54−1.45 (m, 7H, H-17 enol/R2, H-8 R1/R2), 1.42 (dd, J = 6.4, 1.6 Hz, 2H, H-15 R2), 1.37−1.30 (m, 4H, H-4′ R2, H-8 enol, H-9 enol), 1.24−1.15 (m, 10H, H-4′ enol/R1, H-12 R1, H-10 enol), 1.14−1.04 (m, 3H, H-9 R1/R2, H-11 enol), 1.00−0.93 (m, 1H, H-10 R1 or R2), 0.93−0.87 (m, 8H, H-12 R2, H-16 R1/R2, H-7 R1), 0.88−0.83 (m, 11H, H-12 enol, $C(CH_3)_3$), 0.83−0.80 (m, 14H, H-16 enol, H-7 R2, H-9, $C(CH_3)_3$), 0.79 (s, 9H, $C(CH_3)_3$), 0.78−0.74 (m, 1H, H-9 enol), 0.66 (q, J = 12.0 Hz, 1H, H-7 enol), 0.41 (q, J = 12.6 Hz, 1H, H-9 enol), 0.08 (s, 3H, Si-*Me*), 0.07−0.04 (m, 5H, Si-*Me*), 0.03 (s, 3H, Si-*Me*), 0.01−0.02 (m, 6H, Si-*Me*); ^{13}C NMR, HSQC, HMBC (150.9 MHz, $CDCl_3$) δ (ppm) = 207.2 (C-1 R2), 207.1 (C-1 R1), 184.0 (C-1 enol), 174.2 (CONR$_2$ enol), 170.6 (CONR$_2$ R2), 170.5 (COO*Me* R2), 170.3 (COO*Me* enol), 169.4 (COO*Me* R1), 169.2 (CONR$_2$ R1), 147.0 (Ar-C-4 R2), 146.9 (Ar-C-4 enol), 146.7, 146.6 (Ar-C-1 R2/enol), 146.5 (Ar-C-4 R1), 146.2 (Ar-C-1 R1), 132.8 (C-4 enol), 131.7 (C-4 R1), 131.6 (C-4 R2), 131.4 (C-13 enol), 130.3 (C-13 R1/R2), 128.0 (C-14 R1), 127.7 (C-14 R2), 127.5 (Ar-C-2/6 enol), 127.5 (Ar-C-2/6 R2), 127.3 (Ar-C-2/6 R1), 126.3 (C-5 R1/R2), 125.5 (C-5 enol, C-14 enol), 123.8 (Ar-C-3/5 R2), 123.6 (Ar-C-3/5 enol), 123.4 (Ar-C-3/5 R1), 87.8 (C=*C*H-CONR$_2$ enol), 70.3 (C-3′ enol), 70.2 (C-3′ R2), 67.9 (C-3′ R1), 66.8 (C-2′ R1), 62.1 (C-2′ R2), 61.43 (C-2′ enol), 55.5 (C-3 enol), 54.3 (C-3 R1), 54.3 (C-2 enol), 54.2 (C-2 R1), 53.9 (C-3 R2), 52.3 (COO*Me* enol), 52.2 (COO*Me* R1), 52.2 (COO*Me* R2), 51.1 (Ar-*C*H$_2$ enol and R2), 47.3 (Ar-*C*H$_2$ R1), 46.8 (CO-*C*H$_2$-CONR$_2$ R1), 46.6 (C-2 enol), 46.3 (CO-*C*H$_2$-CONR$_2$ R2), 42.3 (C-7 enol), 42.2, 42.2 (C-7 R1/R2), 39.6, 39.6, 39.5 (C-11 R1/R2/enol), 39.3 (C-6 enol), 39.2 (C-6 R2), 39.1 (C-6 R1), 35.9 (C-9 enol), 35.7, 35.6 (C-9 R1/R2), 33.5 (C-8), 33.5 (C-8), 33.3 (C-8 enol), 27.1, 27.1, 27.1 (C-10 R1/R2/enol), 25.8, 25.8, 25.7 ($C(CH_3)_3$ R1/R2/enol), 22.7, 22.6 (C-16 R1/R2), 22.6 (C-17 enol), 22.5 (C-16 enol), 22.4 (C-17 R1), 22.3 (C-17 R2), 21.2 (C-4′ R1), 21.1 (C-4′ R2/enol), 18.0 (C-15 enol/R1), 17.9, 17.9, 17.8 ($C(CH_3)_3$ R1/R2/enol), 17.7 (C-15 R2), 17.0 (C-12

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R1), 16.7 (C-12 R2), 16.5 (C-12 enol), −4.2 (Si-*Me*), −4.2 (Si-*Me*), −4.4 (Si-*Me*), −4.9 (Si-*Me*), −5.2 (Si-*Me*); HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{37}H_{57}N_2O_7Si$ 669.3930; Found 669.3928.

*(3Z,5S)-5-[(1R)-1-{[tert-Butyl(dimethyl)silyl]oxy}ethyl]-3-(hydroxy-{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}methylidene)-1-(4-nitrobenzyl)pyrrolidine-2,4-dione (**26**).* NaOMe (20.2 mg, 0.37 mmol, 2.00 equiv) was added to a stirred solution of **25** (125 mg, 0.19 mmol, 1.00 equiv) in MeOH (1 mL). After stirring for 20 h at rt, the reaction was quenched by addition of sat. NH_4Cl (2 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and evaporated. The residue was purified by preparative reversed phase HPLC (water/MeCN, 75%−95% MeCN) to yield compound **26** as a colorless lyophyllisate (81.3 mg, 68%) (NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.35 (cyclohexane/ethyl acetate, 8:2); IR (ATR) ν (cm^{-1}) = 2951, 2928, 2857, 1698, 1656, 1565, 1525, 1472, 1345, 837, 812, 778; $[\alpha]_D^{22}$ = −251.0 (*c* = 1.00, $CDCl_3$); ^1H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.23−8.16 (m, 2H, *m*-Ar-H), 7.43−7.36 (m, 2H, *o*-Ar-H), 5.22−5.12 (m, 4H, Ar-CH_2, H-6, H-13, H-14), 4.64 (d, *J* = 16.4 Hz, 1H, Ar-CH_2), 4.28 (qd, *J* = 6.4, 2.5 Hz, 1H, H-6′), 3.36 (d, *J* = 2.7 Hz, 1H, H-5′), 3.02 (d, *J* = 8.0 Hz, 1H, H-3), 1.99−1.65 (m, 5H, H-10, H-6, H-7, H-9, H-11), 1.63−1.56 (m, 6H, H-17, H-15), 1.55−1.47 (m, 1H, H-8), 1.45 (s, 3H, H-12), 1.26 (d, *J* = 6.7 Hz, 3H, H-7′), 1.17−1.02 (m, 2H, H-9, H-10), 0.96−0.89 (m, 4H, H-16, H-7), 0.84 (s, 9H, C(CH_3)$_3$), 0.03 (s, 3H, Si-*Me*), −0.01 (s, 3H, Si-*Me*); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 198.5 (C-1), 190.4 (C-4′), 178.3 (C-2′), 147.6 (Ar-C-4), 144.1 (Ar-C-1), 132.02 (C-4), 131.2 (C-13), 128.2 (Ar-C-2, Ar-C-6), 127.3 (C-14), 125.8 (C-5), 124.2 (Ar-C-3, Ar-C-5), 100.4 (C-3′), 69.7 (C-5′), 68.8 (C-6′), 50.0 (C-3), 49.7 (C-2), 45.8 (Ar-CH_2), 42.7 (C-7), 40.0 (C-11), 39.2 (C-6), 35.9 (C-9), 33.7 (C-8), 28.4 (C-10), 25.9 (C(CH_3)$_3$), 22.9 (C-7′), 22.7 (C-16), 22.3 (C-17), 18.0 (*C*(CH_3)$_3$), 18.0 (C-3‴), 13.7 (C-12), −4.0 (Si-*Me*), −5.0 (Si-*Me*); HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{36}H_{53}N_2O_6Si$ 637.3673; Found 637.3683.

*(3Z,5S)-1-(4-Aminobenzyl)-5-[(1R)-1-{[tert-butyl(dimethyl)silyl]-oxy}ethyl]-3-(hydroxy{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}-methylidene)pyrrolidine-2,4-dione (**27**).* A solution of $Na_2S_2O_4$ (85%, 124.2 mg, 0.71 mmol, 6.00 equiv) and $NaHCO_3$ (110.4 mg, 1.31 mmol, 13.0 equiv) in water (2.8 mL) was added to a solution of compound **26** (64.3 mg, 0.10 mmol, 1.00 equiv) in EtOH (4.5 mL). After stirring for 20 min at rt, the reaction mixture was partitioned between water (10 mL) and Et_2O (40 mL), and the layers separated. The aqueous layer was extracted with further Et_2O (3 × 40 mL), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and evaporated. The crude product was used for the next step without further purification. An analytical sample was purified via reversed phase chromatography to give **27** in 71% yield as a light yellow amorphous solid (NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.18 (cyclohexane/ethyl acetate, 8:2); IR (ATR) ν (cm^{-1}) = 3373, 3020, 2949, 2857, 1753, 1694, 1624, 1563, 1516, 1472, 1252, 1216, 835; $[\alpha]_D^{22}$ = −400.4 (*c* = 0.10, $CHCl_3$); ^1H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) = 7.01 (d, *J* = 8.0 Hz, 0.3H, *o*-Ar-H minor), 6.94 (d, *J* = 8.3 Hz, 2H, *o*-Ar-H major), 6.65−6.60 (m, 2.3H, *m*-Ar-H), 5.27 (d, *J* = 15.2 Hz, 1H, Ar-CH_2), 5.17−5.13 (m, 3H, H-5, H-13, H-14), 4.21 (qd, *J* = 6.5, 2.5 Hz, 2.2H, H-6′), 4.14 (d, *J* = 15.2 Hz, 1H, Ar-CH_2), 3.67 (br s, 2.3H, NH_2), 3.31 (d, *J* = 2.9 Hz, 1H, H-5′), 3.01 (d, *J* = 7.9 Hz, 1H, H-3), 2.00−1.94 (m, 1H, H-10), 1.85−1.74 (m, 3H, H-6, H-7, H-9), 1.71−1.66 (m, 1H, H-11), 1.62 (s, 0.5H, H-17 minor), 1.58−1.55 (m, 6H, H-17, H-15), 1.53−1.48 (m, 1H, H-8), 1.42 (s, 3H, H-12), 1.30 (d, *J* = 6.6 Hz, 3H, H-7′), 1.17−1.19 (m, 1H, H-9), 1.08−0.98 (m, 1H, H-10), 0.92 (d, *J* = 6.5 Hz, 3H, H-16), 0.90−0.87 (m, 1H, H-7), 0.86 (s, 1H, C(CH_3)$_3$ minor), 0.83 (s, 9H, C(CH_3)$_3$ major), 0.03 (s, 3H, Si-*Me*), 0.00 (s, 0.6H, Si-*Me* minor), −0.03 (s, 3H, Si-*Me*), −0.05 (s, 0.6H, Si-*Me* minor); ^{13}C NMR, HSQC, HMBC (150.9 MHz, $CDCl_3$) δ (ppm) = 198.24 (C-1), 191.16 (C-4′), 178.15 (C-2′), 146.09 (Ar-C-4), 132.30 (C-4), 131.22 (C-13), 129.03 (Ar-C-2/6), 127.35 (C-14), 125.70 (Ar-C-1), 125.60 (C-5), 115.39 (Ar-C-3/5), 100.58 (C-3′), 68.85 (C-6′), 68.22 (C-5′), 49.88 (C-3), 49.51 (C-2), 45.20 (Ar-CH_2), 42.75 (C-7), 39.98 (C-11), 39.16 (C-6), 35.94 (C-9), 33.72 (C-8), 28.37 (C-10), 25.89 (C(CH_3)$_3$), 25.83 (C(CH_3)$_3$ minor), 22.95 (C-7′), 22.70 (C-16), 22.35 (C-12), 18.04 (C(CH_3)$_3$), 17.94 (C-15), 13.56 (C-12), −4.06 (Si-*Me*), −4.71 (Si-*Me* minor), −4.82 (Si-*Me* minor), −4.96 (Si-*Me*); HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{36}H_{55}N_2O_4Si$ 607.3931; Found 607.3941.

*(3Z,5S)-5-[(1R)-1-{[tert-Butyl(dimethyl)silyl]oxy}ethyl]-3-(hydroxy-{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}methylidene)-pyrrolidine-2,4-dione (**28**).* Compound **27** (61.4 mg, 0.10 mmol, 1.0 equiv) was dissolved in a mixture of DCM (770 μL) and water (40 μL) and cooled to 0 °C. DDQ (98%, 25.7 mg, 11.1 μmol, 1.10 equiv) was added, and the mixture was allowed to stir at rt. After 1 h, the mixture was filtered and evaporated, and the residue was resolved in MeCN and filtered through a pad of reversed phase silica gel. Purification through reversed phase chromatography (water/MeCN, 5% to 100%, automatic flash purification system) gave compound **28** (26.7 mg, 53%) as a yellow amorphous solid (NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.28 (cyclohexane/ethyl acetate, 9:1); IR (ATR) ν (cm^{-1}) = 3244, 3023, 2950, 2857, 1678, 1662, 1571, 1472, 1451, 1376, 1254, 836, 777; $[\alpha]_D^{22}$ = −425.5 (*c* = 0.5, $CHCl_3$); ^1H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) = 5.90 (s, 1H, NH), 5.27−5.20 (m, 1H, H-14), 5.18−5.09 (m, 2H, H-5, H-13), 4.08−4.02 (m, 1H, H-6′), 3.53 (d, *J* = 4.8 Hz, 1H, H-5′), 3.04 (d, *J* = 9.4 Hz, 1H, H-3), 1.95 (d, *J* = 11.9 Hz, 1H, H-10), 1.85−1.73 (m, 3H, H-6, H-7, H-9), 1.70−1.57 (m, 4H, H-11, H-17), 1.55 (dd, *J* = 6.3, 1.5 Hz, 3H, H-15), 1.53−1.46 (m, 1H, H-8), 1.42 (s, 3H, H-12), 1.30 (d, *J* = 6.3 Hz, 3H, H-7′), 1.16−1.07 (m, 1H, H-9), 1.07−1.00 (m, 1H, H-10), 0.91 (d, *J* = 6.5 Hz, 3H, H-16), 0.83 (s, 9H, C(CH_3)$_3$), 0.05 (s, 3H, Si-*Me*), 0.01 (s, 3H, Si-*Me*); ^{13}C NMR, HSQC, HMBC (150.9 MHz, $CDCl_3$) δ (ppm) = 199.4 (C-1), 190.6 (C-4′), 179.2 (C-2′), 132.2 (C-4), 130.7 (C-13), 127.7 (C-14), 125.7 (C-5), 100.6 (C-3′), 68.2 (C-6′), 67.0 (C-5′), 49.7 (C-3), 49.6 (C-2), 42.7 (C-7), 39.9 (C-11), 39.2 (C-6), 35.9 (C-9), 33.7 (C-8), 28.4 (C-10), 25.8 (C(*C*H_3)$_3$), 22.7 (C-16), 22.4 (C-17), 21.3 (C-7′), 18.1 (C-15), 18.0 (*C*(CH_3)$_3$), 13.7 (C-12), −3.9 (Si-*Me*), −4.9 (Si-*Me*); HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{29}H_{48}NO_4Si$ 502.3353; Found 502.3356.

*(3Z,5S)-5-[(1R)-1-Hydroxyethyl]-3-(hydroxy{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydro-naphthalen-1-yl}methylidene)pyrrolidine-2,4-dione (**1**).* HF (398 μL, 48 wt % in water) was added to a solution of silyl ether **27** (24.9 mg, 49.6 μmol, 1.0 equiv) in MeCN (1 mL). After 15 min of stirring at room temperature, solid $NaHCO_3$ (820 mg) was added portionwise, and the reaction mixture was evaporated. The residue was partitioned between ethyl acetate (20 mL) and water (5 mL), and the aqueous layer was extracted with further ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was subjected to automatic reversed phase flash chromatography (water/MeCN, 5−70% MeCN) to give compound **1** (13.4 mg, 70%) as a colorless lyophylisate (mixture of enols, NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.59 (silica gel, EtOAc/MeOH, 7:3); IR (ATR) ν (cm^{-1}) = 3299, 2947, 2912, 2842, 1658, 1569, 1452, 1377, 1227, 969; $[\alpha]_D^{22}$ = −403.1 (*c* = 0.10, CH_2Cl_2); ^1H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) = 5.96 (s, 1H, NH), 5.54 (s, 0.3H, NH, minor enol), 5.35−5.29 (m, 0.3H, H-14 minor enol), 5.25 (dq, *J* = 12.9, 6.8, 6.4 Hz, 1H, H-14), 5.19−5.04 (m, 3H, H-5, H-13, H-13 minor), 4.08−4.03 (m, 1H, H-6′), 4.03−4.00 (m, 1H, H-5′ minor), 3.70 (d, *J* = 4.6 Hz, 1H, H-5′), 3.34 (d, *J* = 9.8 Hz, 0.3H, H-3 minor), 3.10 (d, *J* = 9.4 Hz, 1H, H-3), 2.16 (d, *J* = 7.4 Hz, 1H, C-6′-OH), 2.00−1.91 (m, 1H, H-10), 1.86−1.74 (m, 3H, H-7, H-6, H-9), 1.67 (t, *J* = 10.4 Hz, 1H, H-11), 1.60 (s, 3H, H-17), 1.56−1.47 (m, 6H, H-15, H-8, H-15 minor, H-12 minor), 1.41 (s, 3H, H-12), 1.32 (d, *J* = 6.4 Hz, 3H, H-7′), 1.15−1.00 (m, 2H, H-9, H-10), 0.92 (dd, *J* = 6.5, 1.4 Hz, 3H, H-16), 0.90−0.84 (m, 1H, H-10); ^{13}C NMR, HSQC, HMBC (150.9 MHz, $CDCl_3$) δ (ppm) = 205.0 (C-1 minor), 200.4 (C-1), 198.0 (C-4′ minor), 191.0 (C-4′), 179.5 (C-2′), 170.1 (C-2′ minor), 132.1 (C-4), 130.9 (C-13 minor), 130.7 (C-13), 128.1 (C-14 minor), 127.9 (C-14), 125.7 (C-4), 125.7 (C-4 minor), 106.8 (C-3′ minor), 100.5 (C-3′), 67.9 (C-6′), 67.6 (C-6′ minor), 65.6 (C-5′), 62.6 (C-5′ minor), 50.9 (C-2 minor),

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49.6 (C-2), 49.6 (C-3 minor), 49.5 (C-3), 42.7 (C-7), 39.8 (C-11), 39.2 (C-6), 35.9 (C-9), 33.7 (C-8), 28.4 (C-10), 28.2 (C-10 minor), 22.7 (C-16), 22.3 (C-17), 19.9 (C-7′ minor), 19.7 (C-7′), 18.0 (C-15), 17.9 (C-15 minor), 14.2 (C-12 minor), 13.7 (C-12); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{34}NO_4$ 388.2482; Found 388.2493.

*Methyl O-[tert-Butyl(dimethyl)silyl]-N-(4-nitrobenzyl)-N-(3-oxo-3-{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}propanoyl)-D-threoninate (**30**).* Compounds **23** (229 mg, 0.75 mmol, 1.00 equiv) and **29** (288 mg, 0.75 mmol, 1.00 equiv) were dissolved in DCM (2 mL). A solution of DCC (157 mg, 0.76 mmol, 1.01 equiv) and DMAP (5 mg, 0.04 mmol, 0.05 equiv) in DCM (1 mL) was added dropwise under cooling with an ice bath. The solution was allowed to stir for 10 h at room temperature. The solution was filtered and evaporated, and the residue was resolved in acetone. The remaining urea was filtered off, and the solution was evaporated. The product was isolated after purification through reversed phase chromatography (acetonitrile/water, 5% to 95% acetonitrile, automatic flash purification system) as a colorless lyophylisate (370 mg, 74%). NMR spectra show a mixture of rotamers and keto−enol tautomers (NMR shifts are assigned according to the numbering scheme of Figure 1): mp = 78−82 °C; R_f = 0.59 (pentane/Et_2O, 6:4); IR (ATR) ν (cm^{-1}) = 2951, 2857, 1747, 1708, 1655, 1607, 1520, 1344, 1255, 732; $[\alpha]_D^{22}$ = −89.0 (c = 1.00, $CHCl_3$); ^{1}H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) = 14.57 (s, 1H, enol-OH), 8.25−8.22 (m, 2H, *m*-Ar-H R2), 8.22−8.18 (m, 2H, *m*-Ar-H, enol), 8.16−8.12 (m, 2H, *m*-Ar-H, R1), 7.51−7.44 (m, 6H, *o*-Ar-H R1/R2/enol), 5.46 (d, J = 3.4 Hz, 1H, H-2′ R2), 5.44−5.34 (m, 3H, H-14 R1, H-2′ enol, Ar-CH_2 R2), 5.26−5.15 (m, 3H, H-5 R1, H-13 R1, H-14 enol), 5.12 (s, 1H, H-5 R2), 5.11−4.99 (m, 6H, H-5 enol, H-13 enol/R2, H-14 R2, Ar-CH_2 R1/enol), 4.85−4.77 (m, 2H, Ar-CH_2 R2/enol), 4.75 (s, 1H, C═C*H*-$CONR_2$ enol), 4.71−4.64 (m, 2H, H-3′ enol/R2), 4.62 (d, J = 16.4 Hz, 1H, Ar-CH_2 R1), 4.46−4.39 (m, 2H, H-2′ R1, H-3′ R1), 3.76 (d, J = 15.9 Hz, 1H, CO-CH_2-$CONR_2$ R1), 3.72−3.67 (m, 4H, CO-CH_2-$CONR_2$ R1, COO*Me* enol), 3.63 (s, 3H, COO*Me* R2), 3.56 (d, J = 15.6 Hz, 1H, CO-CH_2-$CONR_2$ R2), 3.46 (s, 3H, COO*Me* R1), 3.07 (d, J = 15.7 Hz, 1H, CO-CH_2-$CONR_2$ R2), 2.27 (d, J = 9.6 Hz, 1H, H-3 R1), 2.03 (d, J = 9.1 Hz, 1H, H-3 enol), 1.97 (d, J = 8.0 Hz, 1H, H-3 R2), 1.81−1.64 (m, 10H, H-7 R1/R2/enol, H-6 R1/R2/enol, H-11 R1 or R2, H-9 R1/R2, H-10 R1), 1.63−1.53 (m, 12H, H-9 R2, H-17 R1, H-15 R1/enol, H-11 R1 or R2), 1.53−1.47 (m, 11H, H-9 enol, H-8 R1, C-17 enol/R2, H-15 R2), 1.47−1.41 (m, 2H, H-8 R2, H-10 enol), 1.39−1.33 (m, 1H, H-8 enol), 1.31 (d, J = 6.4 Hz, 3H, H-4′ R2), 1.26−1.15 (m, 10H, H-11 enol, H-4′ enol/R1, H-12 R1), 1.15−1.09 (m, 1H, H-9 R1), 1.07 (s, 3H, H-12 R2), 1.06−0.98 (m, 1H, H-9 R2), 0.98−0.93 (m, 1H, H-10 R1), 0.91 (d, J = 6.4 Hz, 3H, H-16 R1), 0.88−0.84 (m, 14H, H-16 R2, C(CH_3)$_3$, H-9 R1, H-10 R2), 0.84−0.79 (m, 14H, H-16 enol, C(CH_3)$_3$, H-10 enol, H-7 R2), 0.79−0.75 (m, 12H, H-12 enol, C(CH_3)$_3$ enol), 0.69 (q, J = 12.1 Hz, 1H, H-7 enol), 0.57 (q, J = 12.5 Hz, 1H, H-9 enol), 0.08 (s, 3H, Si-*Me*), 0.07 (s, 3H, Si-*Me*), 0.03 (s, 3H, Si-*Me*), 0.01 to −0.01 (m, 9H, Si-*Me*, Si-*Me* enol); ^{13}C NMR, HSQC, HMBC (150.9 MHz, $CDCl_3$) δ (ppm) = 207.2 (C-1 R1), 207.1 (C-1 R2), 184.5 (C-1 enol), 174.6 ($CONR_2$ enol), 170.6 ($CONR_2$ R2), 170.6, 170.2, 169.7 (3 × COOMe R1, R2, enol), 169.2 ($CONR_2$ R1), 147.0 (Ar-C-4 R2), 146.9 (Ar-C-4 enol), 146.8 (Ar-C-1 R2), 146.6 (Ar-C-1 enol), 146.1 (Ar-C-1 R1), 132.9 (C-4 enol), 131.6 (C-13 enol), 131.3 (C-4 R2), 131.2 (C-13 R2), 131.1 (C-4 R1), 131.0 (C-13 R1), 127.7 (Ar-C2/6 R1), 127.5 (Ar-C2/6 enol), 127.3 (Ar-C-2/6 R2), 127.1 (C-14 R1), 126.6 (C-5 R2), 126.5 (C-14 R2), 125.6 (C-5 enol), 123.8 (Ar-C-3/5 R2), 123.7 (Ar-C-3/5 enol), 123.4 (Ar-C-3/5 R1), 87.7 (C═CH-$CONR_2$ enol), 70.4 (C-3′ R2), 69.8 (C-3′ enol), 68.0 (C-3′ R1), 66.4 (C-2′ R1), 61.8 (C-2′ R2), 61.6 (C-2′ enol), 56.3 (C-3 enol), 54.3 (C-3 R1), 54.3 (C-2 R1), 54.2 (C-2 R2), 53.9 (C-3 R2), 52.3 (COO*Me* R1), 52.3 (COO*Me* enol), 52.1 (COO*Me* R2), 51.3 (Ar-CH_2 enol), 50.7 (Ar-CH_2 R2), 47.9 (Ar-CH_2 R1), 46.7 (CO-CH_2-$CONR_2$ R1), 46.6 (C-2 enol), 45.5 (CO-CH_2-$CONR_2$ R2), 42.3 (C-7 enol), 42.3 (C-7), 42.2 (C-7), 39.7 (C-11 R1), 39.6 (C-11 R2), 39.6 (C-11 enol), 39.3, 39.2, 39.1 (3 × C-6 R1, R2, enol), 35.7 (C-9 enol/R1), 35.6 (C-9 R2), 33.5 (C-8 R1), 33.5 (C-8 R2), 33.3 (C-8 enol), 27.3 (C-10 enol), 27.3 (C-10 R1), 27.2 (C-10 R2), 25.8 (C(CH_3)$_3$), 25.8 (C(CH_3)$_3$), 25.7 (C(CH_3)$_3$), 22.7 (C-17), 22.6 (C-16), 22.6 (C-16), 22.6 (C-16), 22.3 (C-17 R1), 22.3 (C-17 R2), 21.3 (C-4′ enol), 21.3 (C-4′ R1), 21.0 (C-4′ R2), 18.0, 17.9 (C-15 R1/enol), 17.9, 17.8, 17.8 (C(CH_3)$_3$ R1/R2/enol), 17.8 (C-15 R2), 17.2 (C-12 R1), 17.0 (C-12 R2), 16.7 (C-12 enol), −4.1 (Si-*Me*), −4.3 (Si-*Me*), −4.4 (Si-*Me*), −4.8 (Si-*Me*), −5.2 (Si-*Me*), −5.3 (Si-*Me*); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{37}H_{56}N_2O_7SiNa$ 691.3755; Found 691.3770.

*(3Z,5R)-5-[(1S)-1-{[tert-Butyl(dimethyl)silyl]oxy}ethyl]-3-(hydroxy-{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}methylidene)-1-(4-nitrobenzyl)pyrrolidine-2,4-dione (**31**).* Amide **30** (100 mg, 0.15 mmol, 1.00 equiv) was dissolved in dry *t*BuOH (800 μL). *t*BuOK (20.2 mg, 0.18 mmol, 1.20 equiv) was added, and the mixture was stirred for 40 min at rt. The reaction was quenched by the addition of sat. NH_4Cl (2 mL), and EtOAc (10 mL) was added. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. After flash chromatography (pentane/Et_2O, 6:4), the tetramic acid **31** was obtained as a colorless oil (89 mg, 94%) (mixture of enols, NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.23 (pentane/Et_2O, 6:4); IR (ATR) ν (cm^{-1}) = 2954, 2926, 2859, 1793, 1697, 1567, 1524, 1345; $[\alpha]_D^{22}$ = −53.1 (c = 1.00, $CHCl_3$); ^{1}H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) = 17.09 (s, 0.05H, enol OH), 17.00 (s, 0.26H, enol OH), 16.22 (s, 0.85H, enol OH), 8.23−8.20 (m, 1H, *m*-Ar-H minor enol), 8.19−8.16 (m, 2H, *m*-Ar-H major enol), 7.48−7.42 (m, 3H, *o*-Ar-H), 5.34−5.24 (m, 1.5H, H-14 major, H-14 minor enol), 5.19 (s, 1H, H-5 minor enol, Ar-CH_2 minor enol), 5.17−5.10 (m, 2.5H, H-5, H-13 major/minor), 4.87 (d, J = 16.8 Hz, 1H, Ar-CH_2), 4.74 (d, J = 16.7 Hz, 1H, Ar-CH_2), 4.71−4.62 (m, 0.5H, Ar-CH_2 minor), 4.33−4.22 (m, 1.5H, H-6′ major/minor), 3.74 (d, J = 2.2 Hz, 1H, H-5′ major), 3.43 (d, J = 9.5 Hz, 1.5H, H-3 major, H-5′ minor), 3.01 (m, 0.5H, H-3 minor), 1.97−1.91 (m, 0.5H, H-10 minor), 1.91−1.84 (m, 1H, H-10 major), 1.84−1.74 (m, 4.5H, H-6, H-7, H-9), 1.71−1.64 (m, 1.5H, H-11), 1.59 (m, 6H, H-17, H-15 minor), 1.56 (dd, J = 6.4, 1.6 Hz, 3H, H-15), 1.53−1.49 (m, 1.5H, H-8), 1.46−1.42 (m, 4.5H, H-12), 1.27 (d, J = 6.6 Hz, 1.5H, H-7′ minor), 1.20 (d, J = 6.7 Hz, 3H, H-7′ major), 1.15−1.07 (m, 1.5H, H-9 major, H-10 minor), 1.06−0.98 (m, 1.5H, H-10 major, H-9 minor), 0.91 (m, 4.5H, H-16), 0.88 (s, 4.5H, C(CH_3)$_3$ minor), 0.87−0.84 (m, 1.5H, H-7), 0.82 (s, 9H, C(CH_3)$_3$ major), 0.06 (s, 1H, Si-*Me* minor), 0.02 (s, 1H, Si-*Me* minor), 0.00 (s, 3H, Si-*Me* major), −0.05 (s, 3H, Si-*Me* major); ^{13}C NMR, HSQC, HMBC (150.9 MHz, $CDCl_3$) δ (ppm) = 203.5 (C-1), 197.1 (C-4′), 189.5 (C-4′ minor enol), 168.6 (C-2′), 147.6 (Ar-C-4 minor), 147.3 (Ar-C-4), 145.5 (Ar-C-1), 143.9 (Ar-C-1 minor), 132.1 (C-4), 131.1 (C-13), 130.6 (C-13 minor), 127.9 (Ar-C-2, Ar-C-6), 127.5 (C-14), 126.1 (C-5 minor), 125.7 (C-5), 124.2 (Ar-C-3/5 minor), 124.0 (Ar-C-3/5), 106.5 (C-3′), 68.8 (C-5′ minor), 68.5 (C-6′ minor), 68.0 (C-6′), 67.4 (C-5′), 50.7 (C-2), 49.9 (C-3 major), 49.5 (C-3 minor), 46.7 (Ar-CH_2 major), 45.5 (Ar-CH_2 minor), 42.7 (C-7), 39.9 (C-11), 39.0 (C-6), 36.0 (C-9), 33.6 (C-8), 28.3 (C-10 minor), 28.0 (C-10), 26.0 (C(CH_3)$_3$) minor), 25.7 (C(CH_3)$_3$), 22.7 (C-16), 22.3 (C-17), 21.7 (C-7′), 18.1 (C(CH_3)$_3$ minor), 18.0 (C(CH_3)$_3$ major), 18.0 (C-3‴), 14.5 (C-12), −4.2 (Si-*Me*), −5.4 (Si-*Me*); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{36}H_{52}N_2O_6SiNa$ 659.3492; Found 659.3481.

*(3Z,5R)-1-(4-Aminobenzyl)-5-[(1S)-1-{[tert-butyl(dimethyl)silyl]-oxy}ethyl]-3-(hydroxy{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}-methylidene)pyrrolidine-2,4-dione (**32**).* A solution of $Na_2S_2O_4$ (297 mg, 1.45 mmol, 3.00 equiv) in water (13 mL) was added to a solution of compound **31** (308 mg, 0.48 mmol, 1.00 equiv) in EtOH (26 mL). After stirring for 30 min at 55 °C, EtOH was removed. The residue was dissolved in EA (10 mL), and the layers were separated. The aqueous layer was extracted with EA (2 × 10 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give crude product **32** (258 mg) as an orange solid. MS analysis showed the expected product along with its desilylated analaogue. The crude material was used for the next step without further purification. An analytical sample (21 mg) was purified by reversed phase chromatography (water/acetonitrile, 5% to 100% acetonitrile, automatic flash purification system). Product **32** (7.7 mg, 36%) and TBDMS-deprotected product (8.0 mg, 46%) were isolated (NMR shows a mixture of enol species, NMR shifts are assigned according to the

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numbering scheme of Figure 1): R_f = 0.17 (cyclohexane/ethyl acetate, 8:2); IR (ATR) ν (cm^{-1}) = 2950, 2928, 2858, 1759, 1683, 1625, 1565, 1518, 1472, 1255, 970, 835, 777; $[\alpha]_D^{22}$ = −38.5° (c = 0.33, $CHCl_3$); ^1H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) = 7.06−7.01 (m, 1H, *o*-Ar-H minor enol), 6.99−6.94 (m, 2H, *o*-Ar-H), 6.66−6.60 (m, 3H, *m*-Ar-H major/minor), 5.40−5.33 (m, 1H, H-14), 5.24 (d, J = 15.2 Hz, 2H, Ar-CH_2, H-14 minor), 5.18−5.09 (m, 4H, H-5 major/minor, Ar-CH_2 minor, H-13 major/minor), 4.26−4.17 (m, 2H, H-6′, Ar-CH_2 minor), 4.02 (d, J = 15.3 Hz, 1H, Ar-CH_2), 3.66 (br s, 2H, NH_2), 3.63 (d, J = 2.9 Hz, 1H, H-5′), 3.55 (d, J = 9.7 Hz, 1H, H-3), 3.42 (s, 1H, H-5′ minor), 3.07−2.97 (m, 1H, H-3 minor), 2.00−1.93 (m, 1H, H-10 minor), 1.92−1.86 (m, 1H, H-10), 1.85−1.72 (m, 5H, H-6 major/minor, H-7 major/minor, H-9 major/minor), 1.70−1.64 (m, 1H, H-10 major/minor), 1.63 (s, 3H, H-17), 1.58 (s, 3H, H-17 minor, H-15 minor), 1.54 (dd, J = 6.5, 1.5 Hz, 3H, H-15), 1.49 (s, 4H, H-12 major, H-8 major/minor), 1.42 (s, 2H, H-12 minor), 1.28 (d, J = 6.4 Hz, 2H, H-7′ minor), 1.24 (d, J = 6.6 Hz, 3H, H-7′), 1.16−1.07 (m, 2H, H-9 minor/major), 1.07−0.98 (m, 2H, H-10 minor/major), 0.91 (dd, J = 6.5, 2.0 Hz, 5H, H-16 major/minor), 0.89 (s, 5H, C(CH_3)$_3$ minor, H-7 major/minor), 0.81 (s, 9H, C(CH_3)$_3$), 0.06 (s, 2H, Si-*Me* minor), 0.01 (s, 4H, Si-*Me* major/minor), −0.06 (s, 3H, Si-*Me*); ^{13}C NMR, HSQC, HMBC (150.9 MHz, $CDCl_3$) δ (ppm) = 203.51 (C-1), 197.16 (C-4′), 190.19 (C-4′ minor enol), 168.33 (C-2′), 146.13 (Ar-C-4 minor), 145.84 (Ar-C-4), 132.44 (C-4), 131.21 (C-13), 130.80 (C-13 minor), 129.54 (Ar-C-2/6 minor), 128.99 (Ar-C-2/6), 127.64 (C-14), 127.46 (C-14 minor), 126.96 (Ar-C-1), 125.99 (C-6 minor), 125.64 (C-6), 125.63 (Ar-C-1 minor), 115.41 (Ar-C-3/5 minor), 115.38 (Ar-C-3/5), 107.22 (C-3′), 68.45 (C-6′ minor), 67.97 (C-6′), 67.57 (C-5′ minor), 64.78 (C-5′), 50.71 (C-2), 49.88 (C-3), 49.42 (C-3 minor), 45.21 (Ar-CH_2), 45.01 (Ar-CH_2 minor), 42.83 (C-7), 42.63 (C-7 minor), 40.09 (C-11), 39.76 (C-11 minor), 39.39 (C-6 minor), 38.94 (C-6), 35.99 (C-9), 35.91 (C-9 minor), 33.71 (C-8 minor), 33.65 (C-8), 28.37 (C-10 minor), 28.09 (C-10), 26.02 (C(CH_3)$_3$ minor), 25.81 (C(CH_3)$_3$), 22.70 (C-16), 22.68 (C-16 minor), 22.44 (C-17 minor), 22.40 (C-17), 21.30 (C-7′), 18.15 (C-15 minor), 18.05 (C(CH_3)$_3$), 17.94 (C-15), 14.53 (C-12), 13.80 (C-12 minor), −4.30 (Si-*Me*), −4.43 (Si-*Me* minor), −4.59 (Si-*Me* minor), −5.20 (Si-*Me*); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{36}H_{55}N_2O_4Si$ 607.3931; Found 607.3930.

*(3Z,5R)-5-[(1S)-1-{[tert-Butyl(dimethyl)silyl]oxy}ethyl]-3-(hydroxy-{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}methylidene)-pyrrolidine-2,4-dione (**33**).* Compound **32** (238 mg, 0.39 mmol, 1.00 equiv) was dissolved in THF (2.9 mL) and cooled to 0 °C. A solution of DDQ (91 mg, 0.4 mmol, 1.0 equiv) in THF (1.0 mL) was added and stirred at this temperature for 2 h. The solvent was evaporated, and the residue was resolved in MeCN, filtered, and purified through reversed phase chromatography (water/MeCN, 5% to 95% MeCN, automatic flash purification system) to give product **33** (76 mg, 39%) beside compound **34** (8.4 mg, 6%) (mixture of enols, NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.27 (cyclohexane/ethyl acetate, 9:1); IR (ATR) ν (cm^{-1}) = 3338−3240, 2949, 2927, 2857, 1732, 1692, 1599, 1451, 1376, 811, 777; $[\alpha]_D^{22}$ = −91.6 (c = 1.00, $CHCl_3$); ^1H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 6.15 (s, 1H, NH major enol), 5.83 (s, 0.6H, NH minor enol), 5.31 (dq, J = 15.1, 6.4 Hz, 0.6H, H-14 minor), 5.26−5.04 (m, 4.2H, H-14 major, H-13 major/minor, H-5 major/minor), 4.18−4.09 (m, 0.6H, H-6′ minor), 3.89−3.79 (m, 1.6H, H-5′ minor, H-6′ major), 3.54 (d, J = 7.2 Hz, 1H, H-5′ major), 3.38 (d, J = 9.5 Hz, 0.6H, H-3 minor), 3.08−2.95 (m, 1H, H-3 major), 1.98−1.87 (m, 1.6H, H-10 major/minor), 1.87−1.70 (m, 4.8H, H-7 major/minor, H-6 major/minor, H-9 major/minor), 1.70−1.62 (m, 1.6H, H-10 major/minor), 1.59 (s, 4.8H, H-17 major/minor), 1.56 (d, J = 5.2 Hz, 3H, H-15 major), 1.52 (dd, J = 6.4, 1.6 Hz, 1.8H, H-15 minor), 1.47 (s, 3H, H-12 major), 1.44−1.38 (m, 4.8H, H-12 minor, H-7′ major), 1.29 (d, J = 6.3 Hz, 1.8H, H-7′ minor), 1.16−0.95 (m, 3.2H, H-9 major/minor, H-10 major/minor), 0.91 (d, J = 6.6 Hz, 4.8H, H-16 major/minor), 0.89 (s, 9H, C(CH_3)$_3$ major), 0.87−0.82 (m, 1.6H, H-7 major/minor), 0.79 (s, 6H, C(CH_3)$_3$ minor), 0.08 (s, 3H, Si-*Me* major), 0.06 (s, 3H, Si-*Me* major), 0.03 (s, 3H, Si-*Me* minor), −0.02 (s, 2H, Si-*Me* minor); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 204.2 (C-1 major), 197.6 (C-4′ minor), 190.1 (C-4′ major), 178.8 (C-2′ major), 169.4 (C-2′ minor), 132.4 (C-4 major), 132.0 (C-4 minor), 131.0 (C-13 minor), 131.0 (C-13 major), 127.8 (C-14 minor), 127.5 (C-14 major), 125.9 (C-5 major), 125.6 (C-5 minor), 106.9 (C-3′ minor), 100.66 (C-3′ major), 69.0 (C-6′ major), 67.7 (C-6′ minor), 66.5 (C-5′ major), 63.7 (C-5′ minor), 50.8 (C-2 major), 49.7 (C-3 minor), 49.6 (C-3 major), 42.8 (C-7 minor), 42.7 (C-7 major), 40.0 (C-11 major), 39.8 (C-11 minor), 39.2 (C-6 major), 39.1 (C-6 minor), 36.0 (C-9 minor), 35.9 (C-9 major), 33.7 (C-8 major/minor), 28.4 (C-10 major), 28.0 (C-10 minor), 25.9 (C(CH_3)$_3$ major), 25.8 (C(CH_3)$_3$ minor), 22.7 (C-16 minor), 22.7 (C-16 major), 22.4, 22.4 (C-17 major/minor), 21.6 (C-7′ major), 21.3 (C-7′ minor), 18.1 (C(CH_3)$_3$ major/minor), 18.0 (C-15 major), 17.9 (C-15 minor), 14.3 (C-12 major), 13.7 (C-12 minor), −4.1 (Si-*Me* major), −4.2 (Si-*Me* major), −4.6 (Si-*Me* minor), −5.2 (Si-*Me* minor); HRMS (ESI): calculated for $[C_{29}H_{48}NO_4Si]^+$: 502.3353, found: 502.3364 $[M + H]^+$.

*(3Z,5R)-5-[(1S)-1-Hydroxyethyl]-3-(hydroxy{(1S,2R,4aS,6R,8aR)-1,3,6-trimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}methylidene)pyrrolidine-2,4-dione (**34**).* HF (734 μL, 48 wt % in water) was added to a solution of silyl ether **33** (52 mg, 0.1 mmol, 1.0 equiv) in MeCN (2 mL). After 30 min stirring at room temperature, $NaHCO_3$ (1.69 g) was added portionwise. The reaction mixture was partitioned between water (10 mL) and EtOAc (15 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was subjected to reversed phase HPLC (5% water/MeCN) to give pure compound **34** (12.8 mg, 32%) as a colorless lyophyllisate (NMR shifts are assigned according to the numbering scheme of Figure 1): R_f = 0.67 (silica gel, EtOAc/MeOH, 7:3); IR (ATR) ν (cm^{-1}) = 3439, 3270, 2950, 2917, 2847, 1658, 1565, 1451, 1378; $[\alpha]_D^{22}$ = −195.8 (c = 0.10, CH_2Cl_2); ^1H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) = 6.09 (s, 1H, NH), 5.33−5.21 (m, 1H, H-14), 5.18−5.08 (m, 2H, H-13, H-5), 4.15−4.08 (br m, 1H, H-6′), 3.78−3.72 (br m, 1H, H-5′), 3.07 (d, J = 9.1 Hz, 1H, H-3), 2.36 (s, 1H, OH), 1.94 (d, J = 10.9 Hz, 1H, H-10), 1.86−1.72 (m, 3H, H-7, H-6, H-9), 1.71−1.65 (m, 1H, H-11), 1.60 (s, 3H, H-17), 1.55−1.48 (m, 4H, H-15, H-8), 1.44 (s, 3H, H-12), 1.34−1.28 (br m, 3H, H-7′), 1.18−0.99 (m, 2H, H-9, H-10), 0.94−0.83 (m, 4H, H-16, H-7); ^{13}C NMR, HSQC, HMBC (150.9 MHz, $CDCl_3$) δ (ppm) = 200.5 (C-1), 191.4 (C-4′), 179.6 (C-2′), 132.1 (C-4), 130.6 (C-13), 127.9 (C-14), 125.7 (C-5), 100.8 (C-3′), 67.7 (C-6′), 64.9 (C-5′), 49.7 (C-2), 49.6 (C-3), 42.7 (C-7), 39.9 (C-11), 39.1 (C-6), 35.9 (C-9), 33.7 (C-8), 28.4 (C-10), 22.7 (C-16), 22.3 (C-17), 19.6 (C-7′), 17.9 (C-15), 13.8 (C-12); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{34}NO_4$ 388.2482; Found 388.2488.

Chiroptical Methods. The VCD spectra were recorded using an FTIR spectrometer equipped with one photoelastic modulator optimized for 1400 cm^{-1}. An accumulation time of 720 min, a spectral range of 1800−800 cm^{-1}, a resolution of 4 cm^{-1}, a 50 μm path length BaF_2 sample cell, and a concentration of 0.48 mol/L in CCl_4 were used for all measurements on **4**. For the measurements on **1** and **34**, an accumulation time of 360 min and concentrations of 0.46 mol/L (**1**) and 0.47 mol/L (**34**) were used. All spectra were baseline corrected by subtraction of a solvent spectrum recorded with the same parameters.

The ECD spectra were recorded using a circular dichroism spectropolarimeter with a scan speed of 20 nm/min, two repetitions, a spectral range of 300−180 nm, a quartz glass cuvette with a path length of 1 mm, and solutions in LC/MS grade methanol with a concentration of 0.91 mg/mL. Baseline correction occurred by subtraction of a methanol spectrum recorded with the same parameters.

Computational Methods. A thorough conformational analysis for **4** was carried out with the systematic conformational search algorithm at the AM1 level of theory[41] using Spartan'10.[42] All 14 obtained geometries were optimized at the B3PW91/6-31G(d,p) level of theory[19−22,43,44] using the Gaussian 09 Rev. D01 suite of programs.[18] Subsequently all double-ζ optimized geometries were reoptimized at the B3PW91/6-311G(d,p) level of theory,[19−23] and the IR and VCD spectra were calculated.[13] During all DFT calculations, solvation was treated with the IEFPCM model[45,46] for CCl_4. To obtain Boltzmann weighted IR and VCD spectra, the output files of all conformers were processed with SpecDis[25,26] using the Gibbs free energies for the

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Boltzmann weighting, a half-width at half peak height of 6 cm^{-1}, as well as an empirical anharmonicity scaling factor of 0.982.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02526.

^{1}H and ^{13}C NMR spectra of all novel compounds, HECADE spectra of the natural product, ECD spectra of natural and synthetical **1** and **34** and a table comparing the ^{13}C NMR shifts of natural and synthetic **1** and **34**, atomic coordinates, keywords and energies of **4**, measured and calculated IR spectra of **4**, as well as IR spectra of natural and synthetic **1** and synthetic **34** (PDF)

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Notes

The authors declare no competing financial interest.

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