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Total Synthesis of *epi*-Trichosetin

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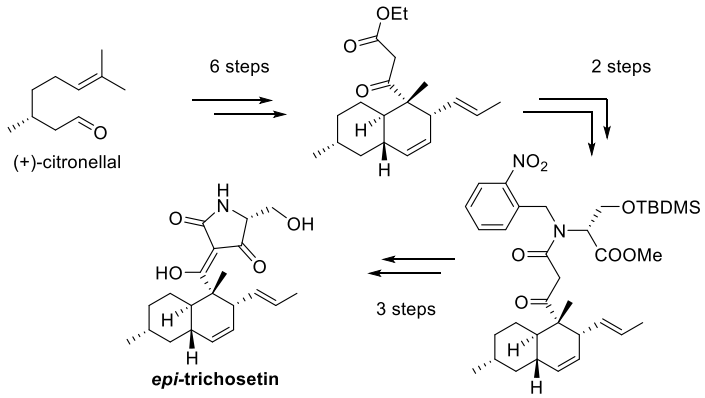
GRAPHICAL ABSTRACT



ABSTRACT

The natural 3-decalinoyltetramic acid *epi*-trichosetin was synthesized in ten steps starting from (*R*)-(+)-citronellal using an intramolecular Diels-Alder reaction and a Lacey-Dieckmann cyclization as the key steps. The use of a 2-nitrobenzyl protecting group resulted in an efficient synthetic endgame. The natural product was obtained in 4.1% overall yield.

INTRODUCTION

3-Acyltetramic acids represent a large and truly remarkable class of natural products. Being produced by bacteria and fungi, they have been found to possess a variety of biological activities ranging, including antibacterial, phytotoxic, fungicidal and anti-malarial effects. As a consequence, they have been the subject of investigation not only in academic but also in industrial settings and virtually all major companies became at some point interested in their pharmacological properties. As an example, equisetin (**1**), the first discovered member of the 3-decalinoyltetramic acids, not only exhibits antibacterial effects[1] but also acts as a HIV-1 integrase inhibitor (Figure 1). For the structurally related (–)-hymenosetin (**2**), both fungicidal and antibacterial activities against various strains including *S. aureus* have been reported.[2] In 2013, *epi*-trichosetin (**4**) was isolated by Inokoshi *et al.* from a culture of the plant pathogenic mold fungus *Fusarium oxysporum*.[3] This 3-decalinoyltetramic acid possesses the same decalin system as equisetin but a D- instead of an L-serine-derived side chain in the tetramic acid moiety and the ring nitrogen is not methylated. Like its C-5'-epimer trichosetin (**3**), it acts as an inhibitor of undecaprenyl phyrophosphate (UPP) synthase and is active against both Gram-positive and -negative bacteria.[4] The acyltetramic acid "warhead" with its largely enolized tris-β-keto-motif is thought to be mainly responsible for the observed biological effects of this compound class. So far, three different modes of action have been determined.[5] First, the tetramic acids can act as ionophores by shuttling di- or trivalent metal ions through biological membranes, which may explain at least part of the observed antibacterial effects.[5b] On the other hand, the negatively charged 3-acyltetramate moiety is thought to mimic a phosphate residue, which could explain the observed effective kinase or phosphatase inhibitory effects.[6] The chelating 3-acyltetramate motif is also responsible for the fact that some representatives can bind via a metal ion to specific binding sites of their target molecules, such as cyclopiazonic acid to the calcium transporter SERCA.[7] As can be seen from the different biological effects of structurally closely related members of the 3-decalinoyltetramic acid class, the configuration of both the decalin part and of the amino acid-derived tetramic acid side chain play important roles. For the determination of the absolute

configuration of the C2- and C5'-stereocenters of the natural 3-decalinoyltetramic acids, their ECD characteristics (Cotton effect) at ~235 nm and ~275 nm are generally used.[3]

To determine the relative configuration of threonine-derived side chains as in (–)-hymenosetin (**2**), Halecker *et* al. successfully applied a HSQC-NMR-based method developed by Matsumori *et al.*[2,8] For comparison of the ECD-characteristics, the data of equisetin, trichosetin and *epi*-trichosetin have been used so far. In contrast, the assignment of the configuration of trichosetin (**3**) was made based on the comparison of the optical rotation of the isolated natural product with that of equisetin and was not confirmed by total synthesis.[4a] Due to the aforementioned chelating effects as well as other influences, a comparison of optical rotations of tetramic acids is error-prone.[4a,5a] The absolute configuration of equisetin (**1**) was however independently confirmed by several total syntheses.[9] Still there are contradictory statements in the literature regarding the influence of the C5'-stereocenter of equisetin on its ECD spectra.[3,10] To unequivocally confirm the utility of the ECD characteristics used so far for the structure elucidation of 3-decalinoyltetramic acids, a total synthesis of *epi*-trichosetin (**4**) is required.

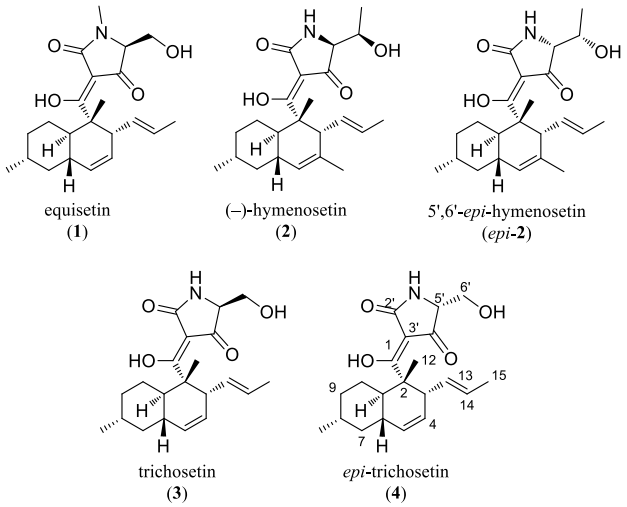
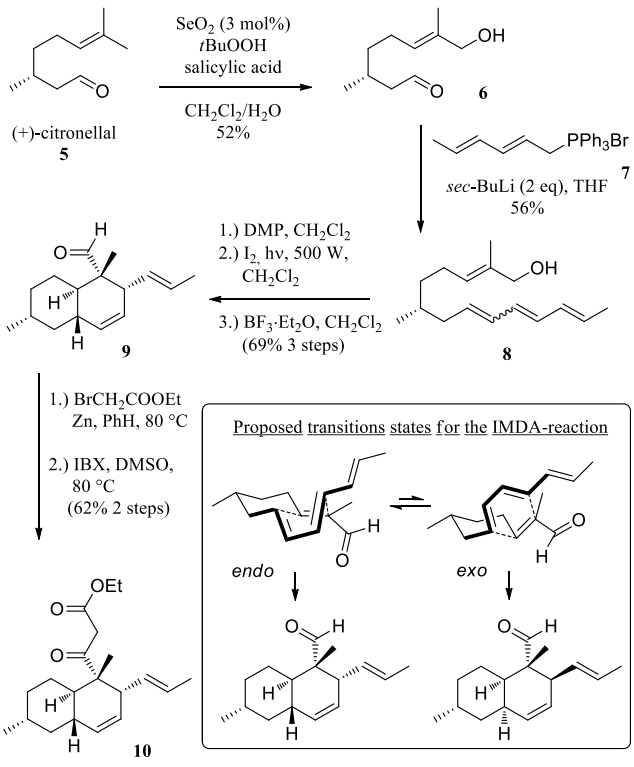


Figure 1. Structures of equisetin (**1**), (–)-hymenosetin (**2**), 5',6'-*epi*-hymenosetin (*epi*-**2**), trichosetin (**3**) and *epi*-trichosetin (**4**).

RESULTS AND DISCUSSION

For the total synthesis of **4**, the decalin system was synthesized according to procedures of Theodorakis, Gao and Ley e*t al*. starting from (+)-citronellal (**5**), which was converted by SeO_2-catalyzed allylic oxidation (Riley-Oxidation) into allylic alcohol **6** in 52% yield (Scheme 1).[9a-c,11] Due to problems with the regioselective Wittig reaction of the corresponsing dialdehyde employed by Theodorakis, the route via **6** proved beneficial in our hands.

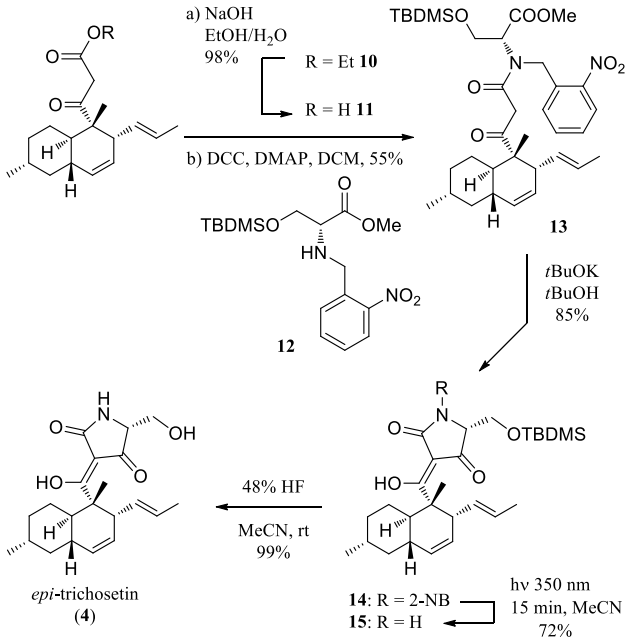
Scheme 1. Synthesis of the *trans*-decalin ring system starting from (+)-citronellal



Phosphonium bromide **7** was obtained in a yield of 84% from commercial (*E*,*E*)-hexa-2,4-dienol after bromination with PBr_3 and reaction with PPh_3.[9b] Subsequent Wittig olefination of aldehyde **6** afforded the desired tetraene alcohol **8** in 56% yield and moderate stereoselectivity (3:2 *E*/*Z*). Oxidation with DMP gave the corresponding aldehyde (isomeric mixture), which was converted into the all-*trans* isomer by irradiation with a 500 W incandescent lamp in dichloromethane in the presence of 5 mol%

I_2.[9b,12] By adding $BF_3{\cdot}Et_2O$ at –78 °C, an intramolecular Diels-Alder reaction (IMDA) was initiated to give the *trans*-decalin carbaldehyde **9** in 69% yield and high diastereoselectivity (9:1 as judged by ^1H NMR spectroscopy, the configuration of the minor product was not elucidated). Along the same lines as our earlier apporoach to (–)-hymenosetin,[13] a Reformatsky reaction and subsequent IBX oxidation converted aldehyde **9** into *β*-keto ester **10**, which was saponified to *β*-keto acid **11** (Scheme 2).

Scheme 2. Synthesis of *epi*-trichosetin (**4**)



Due to the known difficulties in the Lacey-Dieckmann cyclization of derivatives with a free NH moiety,[13] the use of the 2-nitrobenzyl (2-NB) protecting group was evaluated, which can be cleaved photochemically in a single step.[13] Therefore, *β*-keto acid **11** was coupled to *O*-TBDMS- and *N*-2-nitrobenzyl-protected (*R*)-serine **12** using Steglich conditions.[14] The required amino acid building block **12** was obtained after TBDMS protection of (*R*)-serine methyl ester with TBDMSCl and imidazole, followed by a reductive amination with *ortho*-nitrobenzaldehyde in the presence of $NaCNBH_3$. The Lacey-Dieckmann cyclization was promoted with *t*BuOK in *t*BuOH to produce tetramic acid **14** in 85% yield after acidic workup. The 2-nitrobenzyl-protecting group was removed by irradiation with UV light (350 nm) in acetonitrile for 15 min to give the silyl protected tetramic

acid **15** in 72% yield.[15] Desilylation with 48% HF in acetonitrile finally led to *epi*-trichosetin (**4**) in 99% yield (4.1% overall from (+)-citronellal).

The ^{13}C NMR data are consistent with the literature values of *epi*-trichosetin (Table 1) but due to the minute chemical shift differences between trichosetin (**3**) and its epimer **4**, further analytical data should be used for the assessment.[3] The optical rotation of the synthetic compound **4** ($[\alpha]_D^{22}$ = –248; c = 0.1; MeOH) agrees with the value reported for *epi*-trichosetin (($[\alpha]_D^{22}$ = –233; c = 0.1; MeOH) and clearly deviates from that reported for its C-5'-epimer trichosetin ($[\alpha]_D^{22}$ = –413; c = 0.1; MeOH).[3] These values should however be handled with great care since large discrepancies can result from slight changes in temperature, pH, and metal content of the sample. The ECD spectrum of the synthetic compound is in perfect accordance with literature data and with those of the 5',6'-epimer of hymenosetin, which bears the same (2*S*,5'*R*)-configuration (Figure 2).[13] This supports the suitability of the ECD characteristics used so far for the assignment of the C-2 and C-5' stereocenters of 3-decalinoyl tetramic acids.

Table 1. ^{13}C NMR shifts ($CDCl_3$, 150.9 MHz), specific optical rotation and Cotton effects of synthetic *epi*-trichosetin (**4**) and literature values of natural trichosetin (**3**) and *epi*-trichosetin (**4**).[3] ^{13}C NMR shifts were assigned based on HSQC and HMBC correlations.

synth. *epi*-trichosetin (4)	***epi*-trichosetin (4)**	**trichosetin (3)**	**assignment**
$\delta\ ^{13}C$	$\delta\ ^{13}C$	$\delta\ ^{13}C$	
200.7	200.8	200.6	C-1
49.1	49.3	49.0	C-2
14.0	14.1	13.9	C-2-*Me*
45.1	45.2	45.0	C-3
126.4	126.8	126.6	C-4
130.1	130.2	130.0	C-5
38.6	38.7	38.5	C-6

42.2	42.5	42.1	C-7
33.6	33.7	33.4	C-8
22.6	22.7	22.4	C-8-*Me*
35.8	35.9	35.6	C-9
28.5	28.6	28.3	C-10
40.1	40.2	40.0	C-11
130.9	131.0	130.8	C-13
127.2	127.2	127.2	C-14
18.1	18.1	17.9	C-15
179.4	179.5	179.1	C-2'
100.2	100.3	99.9	C-3'
191.1	191.1	190.6	C-4'
61.7	61.8	62.2	C-5'
63.1	63.2	62.9	C-6'

α_D^{26} (c = 0.1, MeOH)		
–248 °	–233 °	–413 °

CD (MeOH): λ in nm (Mol. CD)		
238 (0.23)	238 (0.17)	230 (–4.6)
276 (–4.2)	272 (–5.5)	277 (–8.2)

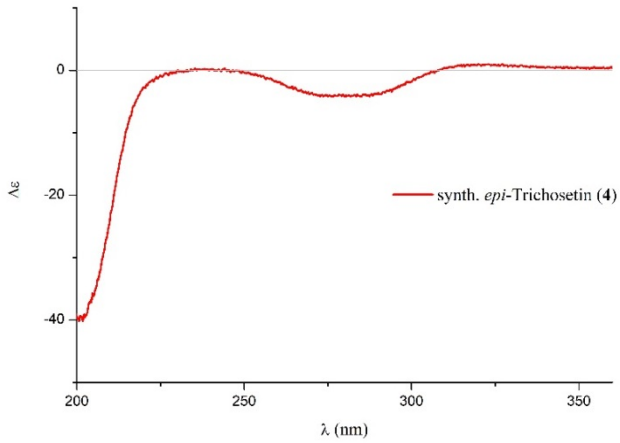


Figure 2. ECD spectrum of synthetic *epi*-trichosetin (**4**, 0.05 mg/mL in MeOH).

In addition, we recorded VCD spectra of *epi*-trichosetin (**4**) which proved to be very helpful for the distinction of different stereoisomers of 3-decalinoyltetramic acids in the case of hymenosetin (**2**) and its 5',6'-epimer *epi*-**2**.[13] Figure 3 compares the VCD spectra of **4**, **2** and *epi*-**2** and illustrates the higher information content of the VCD versus the ECD technique, with the ECD spectra of **4** and *epi*-**2** being highly similar.[13] Thus, the VCD technique might facilitate the stereochemical analysis of different tetramic acid derivatives.

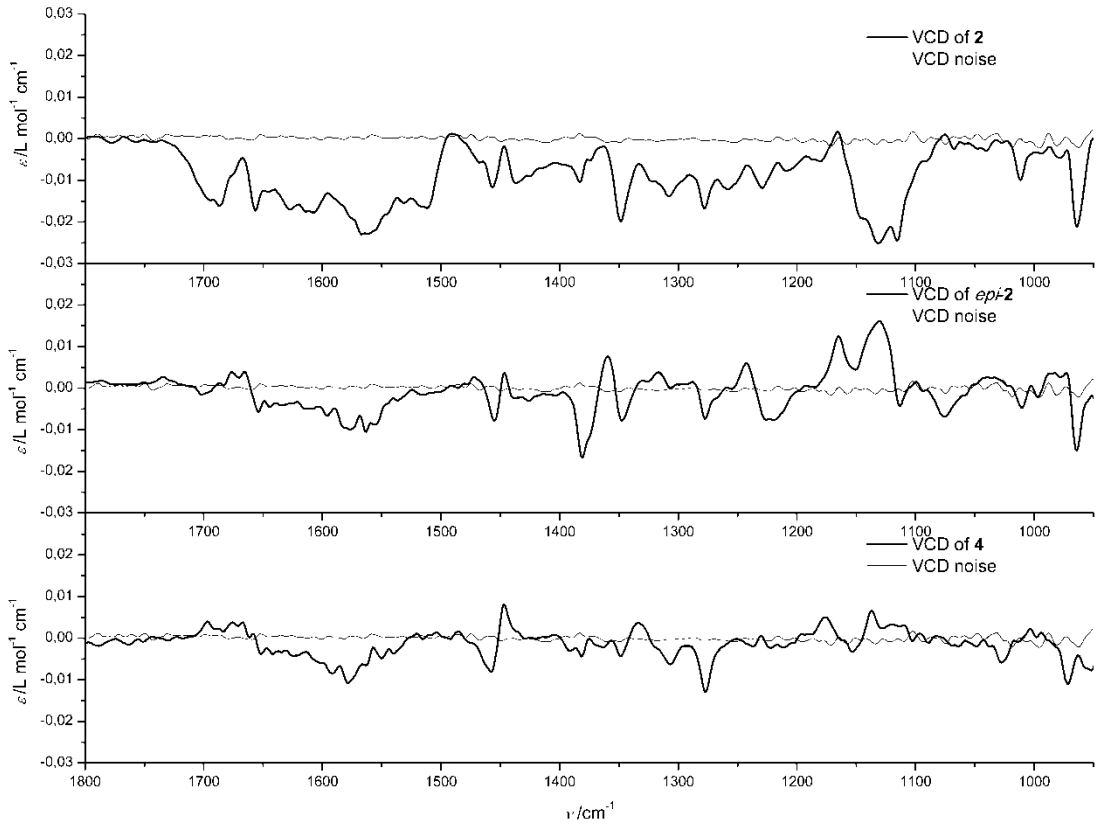


Figure 3. VCD spectra of *epi*-trichosetin (**4**), (–)-hymenosetin (**2**) and 5',6'-*epi*-hymenosetin (*epi*-**2**).

CONCLUSION

In summary, the 3-decalinoyltetramic acid *epi*-trichosetin (**4**) was synthesized for the first time in ten linear steps from (+)-citronellal using the photocleavable 2-nitrobenzyl protecting group for the intermediate protection of the NH moiety to allow the Lacey-Dieckmann cyclization. The proposed absolute configuration of this natural product was thus confirmed, as was the general applicability of the ECD characteristics for the stereochemical analysis of 3-acyltetramic acids. As can be seen from the similarity of the ^{13}C-NMR shifts of **3** and **4** and the known issues with the optical rotation, chiroptical methods such as ECD and VCD spectroscopy are required for an unequivocal configurational assignment.

EXPERIMENTAL SECTION

General Procedures. All reagents were purchased in reagent grade quality 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. Reactions at elevated temperatures were performed using oil baths for heat transfer. The photochemical reactions using UV-A radiation were carried out in a photoreactor with 16 lamps (8 W, λ = 350 nm) arranged cylindrically around a magnetic stirrer. 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. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz, 400 MHz or 600 MHz spectrometer. Chemical shifts were referenced to the residual/deuterated solvent (e.g., for $CDCl_3$, δ= 7.26 ppm and 77.16 ppm for ^{1}H and ^{13}C NMR, respectively) and reported in parts per million (ppm, δ) relative to tetramethyl silane (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 agent. 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 electrospray-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}). ECD spectra were recorded on a ECD spectrometer in a 1.00 mm quartz cuvette at 21 °C and at a scan rate of 20 nm/min (3 repetitions) over a wavelength range of 180–400 nm. VCD spectra were recorded using a polarization modulation accessory attached to a FT-IR spectrometer equipped with one photoelastic modulator optimized for 1400 cm^{-1}. An accumulation time of 360 minutes, a spectral range of 1800–800 cm^{-1}, a resolution of 4 cm^{-1}, a 100 µm path length BaF_2 sample cell and a concentration of 0.22 mol/L in $CDCl_3$ were used for all measurements. The spectra were baseline corrected by subtraction of a solvent spectrum recorded with the same parameters. 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.

(2E,4E)-Hexa-2,4-dien-1-yl(triphenyl)phosphonium bromide (7).

Using the method of Theodorakis *et al*.,[9b,11] PBr_3 (9.39 g, 34.6 mmol, 0.34 eq.) was dissolved in DCM (10 mL), and added dropwise at –8 °C to a solution of (2*E*,4*E*)-hexadien-1-ol (10.00 g, 102 mmol, 1.00 eq.) in DCM (20 mL). After stirring for 20 min, the solution 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 (3x 50 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated. The residue was dissolved in toluene (160 mL), and PPh_3 (26.68 g, 102 mmol, 1.11 eq.) was added. After stirring for 72 h at rt, the product was collected by filtration, washed with toluene and dried under reduced pressure. Phosphonium bromide **7** was obtained as a beige solid (36.16 g, 84%): m.p..: 158–160 °C (lit. 159–161 °C)[9b]; IR (ATR) ν (cm^{-1}) = 3054, 3018, 2991, 1437, 1112, 996, 738, 723, 691; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.84 – 7.73 (m, 9H, Ar-H2/6, Ar-H4), 7.68 – 7.62 (m, 6H, Ar-H3/5), 6.33 (ddd, J = 15.5, 10.4, 5.3 Hz, 1H, H-3), 5.88 (ddt, J = 15.3, 10.4, 1.7 Hz, 1H, H-4), 5.63 (dqd, J = 15.3, 6.7, 2.7 Hz, 1H, H-5), 5.33 – 5.21 (m, 1H, H-2), 4.72 (dd, J = 15.4, 7.5 Hz, 2H, H-1), 1.66 (ddd, J = 6.9, 3.0, 1.5 Hz, 3H, H-6); ^{13}C{^{1}H} NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 140.7 (d, $J_{C,P}$ = 13.6 Hz, C-3), 135.1 (d, $J_{C,P}$ = 2.9 Hz, Ar-C4), 133.9 (d, $J_{C,P}$ = 9.8 Hz, Ar-C2/6), 132.7 (d, $J_{C,P}$ = 4.6 Hz, C-5), 130.4 (d, $J_{C,P}$ = 12.5 Hz, Ar-C3/5), 130.0 (d, $J_{C,P}$ = 5.1 Hz, C-4), 118.1 (d, $J_{C,P}$ = 85.5 Hz, Ar-C1), 113.2 (d, $J_{C,P}$ = 11.2 Hz, C-2), 28.2 (d, $J_{C,P}$ = 49.4 Hz, C-1), 18.2 (d, $J_{C,P}$ = 1.5 Hz, C-6); MS (ESI): *m/z* (%) = 343.2 (100) $[M - Br]^+$. The data are in accordance with the literature.[9b,11]

(2E,6R,8E,10E,12E)-2,6-Dimethyltetradeca-2,8,10,12-tetraenal.

Using the method of Gao *et al*.[9c], alcohol **8** (808 mg, 3.45 mmol, 1.00 eq.) was dissolved in DCM (20 mL) and added dropwise to a suspension of DMP (95%, 2.19 g, 5.17 mmol, 1.50 eq.) in DCM (8 mL). After stirring for 10 min, water (93 µL) was added and stirred or an additional 10 min before the solution was evaporated. The residue was dissolved in EtOAc (40 mL) and stirred vigorously together with sat. $NaHCO_3$/ 10% $Na_2S_2O_3$ (20 mL) for 15 min. The aqueous layer was extracted with EtOAc (2x 25 mL), and the combined organic layers were washed with sat. $NaHCO_3$ (3x 25 mL), brine (1x 25

mL) and dried over Na_2SO_4. Evaporation gave the crude product as yellow oil (798 mg), which was used directly for the next step: R_f = 0.48 (Pent/Et_2O, 3:1); IR (ATR) ν (cm^{-1}) = 2956, 2929, 2873, 1720, 1684, 1640, 1456, 1378, 1245, 992; $[\alpha]_D^{31}$ = –15.6 (*c* 0.3, $CHCl_3$); ^1H NMR, COSY (400 MHz, $CDCl_3$) *δ* (ppm) = 9.38 (s, 1H, C*H*O), 6.46 (ddt, *J* = 7.3, 5.9, 1.4 Hz, 1H, H-3), 6.21 – 5.99 (m, 4H, H-8–H-13), 5.72 – 5.54 (m, 2H, H-8–H-13), 2.43 – 2.27 (m, 2H, H-4), 2.15 – 2.05 (m, 1H, H-7a), 1.98 (dt, *J* = 14.2, 7.2 Hz, 1H, H-7b), 1.75 (d, *J* = 6.2 Hz, 3H, H-14), 1.74 (s, 3H, C-2-*Me*), 1.63 – 1.48 (m, 2H, H-5a, H-6), 1.36 – 1.20 (m, 1H, H-5b), 0.92 (dd, *J* = 6.6, 3.0 Hz, 3H, C-6-*Me*); $^{13}C\{^1H\}$ NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) *δ* (ppm) = 195.5 (C-1), 155.1 (C-3), 139.4 (C-2), 132.28, 132.07, 131.81, 131.30, 130.41, 129.34 (C-8–C-13), 40.3 (C-7), 35.1 (C-5), 33.2 (C-6), 26.8 (C-4), 19.5 (C-6-*Me*), 18.4 (C-14), 9.3 (C-2-*Me*); MS (ESI): *m/z* (%) = 233.1 (100) $[M + H]^+$. Data are in accordance with the literature.[9c]

O-[tert-Butyl(dimethyl)silyl]-D-serine methyl ester.

Using the method of Novachek *et al.*[16], D-serine hydrochloride methyl ester (1.00 g, 6.43 mmol, 1.00 eq.) and imidazole (1.31 g, 19.3 mmol, 3.00 eq.) were dissolved in DCM (20 mL). TBDMSCl (1.16 g, 7.70 mmol, 1.20 eq.) was added, and the solution was stirred overnight at rt. The solvent was evaporated, and the residue was partitioned between water (10 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (3x 10 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (100% ethyl acetate) to give the TBDMS-protected amino acid as colourless liquid (755 mg, 3.23 mmol, 50%): R_f = 0.21 (silica gel, EtOAc/cyclohexane, 9:1); IR (ATR) ν (cm^{-1}) = 2954, 2929, 2857, 1746, 1680, 1464, 1256, 1111, 837, 778; $[\alpha]_D^{31}$ = +7.3 (*c* 0.15; $CHCl_3$); ^1H NMR, COSY (400 MHz, $CDCl_3$) *δ* (ppm) = 3.90 (dd, *J* = 9.7, 4.5 Hz, 1H, H-3a), 3.79 (dd, *J* = 9.7, 3.8 Hz, 1H, H-3b), 3.71 (s, 3H, COO*Me*), 3.51 (pseudo-t, *J* = 4.1 Hz, 1H), 1.70 (s, br, 2H, NH), 0.86 (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) = 174.7 (C-1), 65.5 (C-3), 56.6 (C-2), 52.1 (COO*Me*), 25.9 ($C(CH_3)_3$), 18.3 ($C(CH_3)_3$), –5.4 (Si*Me*), –5.5 (Si*Me*). The data are in accordance to the literature.[16]

*(1S,2R,4aS,6R,8aR)-1,6-Dimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-carbaldehyde (**9**).*

Using the method of Theodorakis, Burke and Gao *et al.*[9b,c,11,17] a solution of I_2 (7.3 mg, 0.03 mmol, 0.05 eq.) in DCM (5 mL) was added dropwise to a solution of the unsaturated aldehyde (133 mg, 0.57 mmol, 1.00 eq.) in DCM (25 mL). After irradiation with a 500 W incandescent lamp (visible light), the reaction mixture was cooled to –78 °C, and $BF_3 \cdot Et_2O$ (243 mg, 1.72 mmol, 3.00 eq.) was added slowly. After stirring at this temperature for 10 min, sat. $Na_2S_2O_3$/sat. $NaHCO_3$ (1:1, 10 mL) was added and the reaction mixture was allowed to warm to rt under vigorous stirring. The aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. Purification by flash column chromatography (PE 9.5/0.5 Et_2O) gave aldehyde **9** (93 mg, 70%) as colorless oil: R_f = 0.54 (Pent/Et_2O, 9.5:0.5); IR (ATR) ν (cm^{-1}) = 3017, 2948, 2916, 2856, 1724, 1455, 1374, 974, 725; $[\alpha]_D^{31}$ = –253.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR, COSY (300 MHz, $CDCl_3$) *δ* (ppm) = 9.47 (s, 1H, H-1), 5.53 – 5.33 (m, 4H, H-5, H-1‘, H-2‘, H-4), 2.57 – 2.49 (m, 1H, H-3), 1.89 – 1.69 (m, 3H, H-7a, H-11, H-9a), 1.66 (d, *J* = 4.8 Hz, 4H, H-3‘, H-6), 1.53 – 1.43 (m, 1H, H-8), 1.40 – 1.33 (m, 1H, H-10a), 1.16 – 1.03 (m, 2H, H-10b, H-9b), 1.00 (s, 3H, C2-*Me*), 0.92 (d, *J* = 6.6 Hz, 3H, C8-*Me*), 0.90 – 0.81 (m, 1H, H-7b); ^{13}C{^{1}H} NMR, HSQC, HMBC (75 MHz, $CDCl_3$) *δ* (ppm) = 209.1 (C-1), 131.0 (C-5), 129.6 (C-1‘), 128.6 (C-2‘), 126.9 (C-4), 50.4 (C-2), 49.2 (C-3), 41.8 (C-7), 38.9 (C-6), 37.4 (C-11), 35.5 (C-9), 33.3 (C-8), 27.2 (C-10), 22.6 (C8-*Me*), 18.1 (C-3‘), 13.9 (C2-*Me*); MS (ESI): *m/z* (%) = 233.2 (100) $[M + H]^+$. The data are in accordance with the literature.[9b,11]

*Ethyl 3-{(1S,2R,4aS,6R,8aR)-1,6-dimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}-3-oxopropanoate (**10**).*

Using the method of Theodorakis *et al.*[9b,11], ethyl 2-bromoacetate (835 mg, 5.00 mmol, 3.00 eq.) was added dropwise to a suspension of activated zinc dust (545 mg, 8.33 mmol, 3.00 eq.) in benzene (3 mL) and refluxed for 5 min. The reaction mixture was diluted with further benzene (6 mL), and a solution of **9** (387 mg, 1.67 mmol, 1.00 eq.) in benzene (4 mL) was slowly added. After refluxing for 30 min, the reaction mixture was allowed to cool to room temperature, acidified with 1 n HCl (25 mL), and extracted with EtOAc (4x 30 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 (7 mL), IBX (933 mg, 3.33 mmol, 2.00 eq.) 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 Et_2O (50 mL) was added. After vigorous stirring for 10 min, the reaction mixture was filtered and the aqueous phase extracted with Et_2O (4 x 35 mL). The combined organic layers were washed with 10% NaOH (2 x 35 mL) and brine (1 x 35 mL), dried over Na_2SO_4 and evaporated. After purification by silica gel column chromatography (PE/Et_2O, 5% Et_2O), the product was obtained as clear, colorless oil (284 mg, 54%) along with the the *β*-hydroxy intermediate (120 mg, 22%) which was again oxidized by IBX. *β*-Ketoester **10** was achieved in a total yield of 329 mg (62%). NMR shows a mixture of keto/enol tautomers: R_f = 0.31 (Pent/Et_2O, 9:1); IR (ATR) ν (cm^{-1}) = 3016, 2947, 2915, 1745, 1708, 1455, 1377, 1310, 1135, 1036, 732; $[\alpha]_D^{31}$ = –159.8 (*c* 0.25, $CHCl_3$); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) *δ* (ppm) = 12.43 (s, 0.01H, enol-OH), 12.41 (s, 0.06H, enol-OH), 5.45 – 5.31 (m, 3H, H-5, H-4, H-2‘), 5.12 (ddq, *J* = 15.0, 9.2, 1.6 Hz, 1H, H-1‘), 5.06 (s, 0.06H, C=C*H*-COOEt, enol), 4.20–4.10 (m, 2H, C*H*$_2$CH$_3$), 3.48 (d, *J* = 15.8 Hz, 1H, CO-C*H*$_2$-COOEt a), 3.31 (d, *J* = 15.8 Hz, 1H, CO-C*H*$_2$-COOEt a), 3.25 (d, *J* = 15.7 Hz, 0.06H, CO-C*H*$_2$-COOEt b rotamer), 2.59 – 2.48 (m, 1H, H-3), 2.21 (dtd, *J* = 6.6, 3.6, 1.6 Hz, 0.06H, H-3), 1.82 – 1.66 (m, 4H, H-7a, H-9a, H-10a, H-11), 1.65 – 1.61 (m, 1H, H-6), 1.60 (dd, *J* = 6.4, 1.6 Hz, 3H, H-3‘), 1.51 – 1.39 (m, 1H, H-8), 1.24 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.16 (s, 3H, C2-*Me*), 1.11 – 1.02 (m, 1H, H-9b), 1.07 (s, 0.18H, C2-*Me* enol), 0.97 – 0.91 (m, 1H, H-10b), 0.88 (d, *J* = 6.5 Hz, 3H, C8-*Me*), 0.87 – 0.79 (m, 1H, H-7b); ^{13}C{^{1}H} NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) *δ* (ppm) = 205.7 (C-1), 183.7 (C-1 enol), 167.9 (*C*OOEt), 130.7 (H-5), 130.5 (H-1‘), 127.1 (H-2‘), 126.4 (H-4), 89.0 (C=*C*H-COOEt enol), 61.1 (*C*H$_2$CH$_3$), 53.5 (C-2), 49.6 (C-3), 46.6 (CO-*C*H$_2$-COOEt), 45.9 (C-2 enol), 42.0 (C-7), 39.7 (C-6), 38.4 (C-11), 35.6 (C-9), 33.5 (C-8), 27.3 (C-10), 22.6 (C8-*Me*), 17.9 (C-3‘), 1709 (C2-*Me*), 14.3 (CH$_2$*C*H$_3$); MS (ESI): *m/z* (%) = 341.4 (100) $[M + Na]^+$, 319.5 (39) $[M + H]^+$. The data are in accordance to the literature.[9b,11]

*3-Oxo-3-{(1S,2R,4aS,6R,8aR)-1,6-dimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}propanoic acid (**11**).*

A solution of NaOH (60 mg, 1.49 mmol, 1.80 eq.) in H_2O (1 mL) was added dropwise to a solution of ester **10** (275 mg, 0.83 mmol, 1.00 eq.) in EtOH (14 mL). After stirring for 18 h at rt, the mixture was

acidified carefully with 1 N HCl (pH 1–2) under cooling with an ice bath and extracted with EtOAc (3x 10 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give **11** as colorless solid (264 mg, 98%), which was directly used for the next step.

*O-[tert-Butyl(dimethyl)silyl]-N-(2-nitrobenzyl)-D-serine methyl ester (**12**).*

p-Nitrobenzaldehyde (427 mg, 2.83 mmol, 1.10 eq.) and acetic acid (308 mg, 5.14 mmol, 2.00 eq.) were added to a solution of O-TBDMS-protected D-serine methyl ester (600 mg, 2.57 mmol, 1.00 eq.) in methanol (15 mL). After stirring for 30 min at rt, $NaCNBH_3$ (95%, 255 mg, 3.86 mmol, 1.5 eq.) was added, and the solution was stirred for an additional 18 h at rt. $NaHCO_3$ (650 mg, 7.71 mmol, 3.00 eq.) was added, and the solvent was evaporated. The residue was partitioned between water (20 mL) and DCM (40 mL), and the aqueous layer was extracted with DCM (2x 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. Purification by flash column chromatography (cyclohexane/EtOAc, 5% EtOAc) gave the protected amino acid **12** as pale yellow liquid (918 mg, 2.49 mmol, 97%): R_f = 0.26 (cyclohexane/EtOAc, 9.5:0.5); IR (ATR) ν (cm^{-1}) = 2953, 2930, 2857, 1742, 1528, 1463, 1359, 1254, 1109, 837; $[\alpha]_D^{25}$ = +2.4 (*c* 1.0; $CHCl_3$); ^1H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.91 (dd, *J* = 8.1, 1.3 Hz, 1H, Ar-H-3), 7.65 (dd, *J* = 7.5, 1.4 Hz, 1H, Ar-H-6), 7.55 (td, *J* = 7.5, 1.3 Hz, 1H, Ar-H-5), 7.39 (ddd, *J* = 8.1, 7.5, 1.4 Hz, 1H, Ar-H-4), 4.19 (d, *J* = 14.9 Hz, 1H, C*H*$_2$Ar), 4.00 (d, *J* = 14.9 Hz, 1H, C*H*$_2$Ar), 3.86 (dd, *J* = 9.8, 4.7 Hz, 1H, H-3a), 3.79 (dd, *J* = 9.8, 4.7 Hz, 1H, H-3b), 3.69 (s, 3H, COO*Me*), 3.36 (t, *J* = 4.7 Hz, 1H, H-2), 2.44 (s, 1H, NH), 0.84 (s, 9H, C(C*H*$_3$)$_3$), 0.01 (s, 3H, Si-*Me*), 0.00 (s, 3H, Si-*Me*); $^{13}C\{^1H\}$ NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 173.5 (C-1), 149.2 (C-2-Ar), 135.5 (C-1Ar), 133.2 (C-5-Ar), 130.9 (C-6-Ar), 128.0 (C-4-Ar), 124.8 (C-3-Ar), 64.7 (C-3), 62.9 (C-2), 51.9 (COO*Me*), 49.0 (*C*H$_2$Ar), 25.8 (C(*C*H$_3$)$_3$), 18.3 (*C*(CH$_3$)$_3$), –5.4 (Si*Me*), –5.51 (Si*Me*); MS (ESI): *m/z* (%) = 369.2 (100) $[M + H]^+$;

HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{29}N_2O_5Si$ 369.1846; Found 369.1849.

*(2E,6R,8E,10E,12E)-2,6-Dimethyltetradeca-2,8,10,12-tetraen-1-ol (**8**).*

Phosphonium bromide **7** (10.04 g, 23.50 mmol, 1.00 eq.) was suspended in THF (100 mL), and *sec*-BuLi (33.6 mL, 1.4 M in cyclohexane, 23.49 mmol, 2.00 eq.) was added dropwise at –78 °C. After stirring for 10 min at this temperature, a solution of aldehyde **6** (4.05 g, 23.79 mmol, 1.00 eq.) in THF (60 mL) was added slowly. The mixture was allowed to warm to rt and stirred for 48 h. After addition of sat. NH_4Cl (30 mL), the aqueous phase was extracted with *n*-pentane/Et_2O (40 mL, 3:1). The combined organic phases were dried over Na_2SO_4 and evaporated. Purification flash column chromatography (PE/Et_2O, 0% to 40% Et_2O, automatic flash purification system) gave **8** (3.14 g, 13.40 mmol, 56%) as a pale yellow oil, which was an inseparable mixture of *E*/*Z* isomers (*E*/*Z*, 3:2): R_f = 0.17 (Pent/Et_2O, 3:1); IR (ATR) ν (cm^{-1}) = 3322, 3013, 2956, 2913, 1454, 1377, 993; $[\alpha]_D^{31}$ = –13.3 (*c* 0.3, $CHCl_3$); ^1H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 6.42 – 6.31 (m, 0.4H), 6.22 – 5.97 (m, 4.6H, H-9 – H-13 E/Z), 5.76 – 5.57 (m, 1H, H-8 E), 5.43 – 5.33 (m, 1.4H, H-3 E/Z, H-8 Z), 3.99 (s, 2H, H-1 E/Z), 2.23 – 2.12 (m, 1H), 2.12 – 1.99 (m, 3H), 1.94 (ddd, *J* = 12.7, 7.7, 6.7 Hz, 1H), 1.78 (d, *J* = 6.4 Hz, 1H, H-14 E or Z), 1.75 (d, *J* = 6.3 Hz, 2H, H-14 E or Z), 1.66 (t, *J* = 1.3 Hz, 3H, C-2-*Me* E/Z), 1.59 – 1.46 (m, 1H, H-6 E/Z), 1.45 – 1.33 (m, 1H, H-5a E/Z), 1.25 – 1.13 (m, 1H, H-5b E/Z), 0.90 (d, *J* = 6.7 Hz, 1H, C-6-*Me* Z), 0.88 (d, *J* = 6.7 Hz, 2H, C-6-*Me* E); $^{13}C\{^1H\}$ NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 134.7, 134.7 (C-2 E/Z), 132.96, 132.84 (C-8 E), 132.07, 131.92, 131.90, 130.97, 130.67, 130.46 (C-8 Z), 129.74, 129.72, 129.07, 126.72 (C-3 E/Z), 126.02, 69.22 (C-1 E/Z), 40.40 (C-7 E), 36.45, 36.39 (C-5 E/Z), 35.13 (C-7 Z), 33.33 (C-6 Z), 33.09 (C-6 E), 25.38, 25.32 (C-4 E/Z), 19.66 (C-6-*Me* E), 19.61 (C-6-*Me* Z), 18.48, 18.44 (C-14 E/Z), 13.80 (C-2-*Me* E/Z); MS (ESI): *m/z* (%) = 217.1 (100) $[M - H_2O + H]^+$; 235.1 (11) $[M + H]^+$; The data are in accordance to the literature.[9c]

*O-[tert-Butyl(dimethyl)silyl]-N-(3-{(1S,2R,4aS,6R,8aR)-1,6-dimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}-3-oxopropanoyl)-N-(2-nitrobenzyl)-D-serine methyl ester (**13**).*

A solution of DCC (132 mg, 0.64 mmol, 1.01 eq.) and DMAP (4 mg, 0.03 mmol, 0.05 eq.) in DCM (0.8 mL) was added dropwise to a solution of *β*-keto acid **11** (184 mg, 0.63 mmol, 1.00 eq.) and amino acid **12** (233 mg, 0.63 mmol, 1.00 eq.) in DCM (1.3 mL). After stirring for 10 h at rt, the solution was

filtered and evaporated. The residue was resolved in acetone to remove remaining urea by filtration, and the filtrate was evaporated. After purification by reversed phase chromatography (MeCN/H_2O, 5% – 95% MeCN, automatic flash purification system), **13** was obtained as colorless lyophilizate (222 mg, 55%). NMR spectra show a mixture of rotameres and keto-enol tautomers: R_f = 0.35 (silica gel, CH/EtOAc, 8:2); IR (ATR) ν (cm^{-1}) = 3016, 2951, 2857, 1746, 1658, 1528, 1455, 1253, 1118, 838; $[\alpha]_D^{31}$ = –74.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) = 14.43 (s, 1H, enol-OH), 8.12 (dd, *J* = 8.2, 1.1 Hz, 1H, Ar-H3 enol), 8.10 (dd, *J* = 8.1, 1.1 Hz, 1H, Ar-H3 R1), 8.07 (dd, *J* = 8.2, 1.1 Hz, 1H, Ar-H3 R2), 7.96 (d, *J* = 7.6 Hz, 1H, Ar-H6 R1), 7.80 (d, *J* = 7.8 Hz, 1H, Ar-H6 enol), 7.72 (dd, *J* = 8.0, 1.3 Hz, 1H, Ar-H6 R2), 7.70 (td, *J* = 7.6, 1.3 Hz, 1H, Ar-H5 R1), 7.63 (td, *J* = 7.6, 1.3 Hz, 1H, Ar-H5 enol), 7.59 (td, *J* = 7.7, 1.3 Hz, 1H, Ar-H-5 R2), 7.50 – 7.47 (m, 1H, Ar-H3 R1), 7.47 – 7.41 (m, 1H, Ar-H3 enol), 7.35 (t, *J* = 7.5 Hz, 1H, Ar-H3 R2), 5.47 – 5.01 (m, 17H, H-4, H-5, H-1‘, H-2‘, Ar-CH_2 R1, Ar-CH_2 enol, Ar-CH_2 a R2), 4.97 (d, *J* = 18.2 Hz, 1H, Ar-CH_2 b R2), 4.94 – 4.92 (m, 1H, C-2‘‘ enol), 4.71 (s, 1H, C=C*H*-CONR$_2$ enol), 4.55 (dd, *J* = 6.3, 4.0 Hz, 1H, C-2‘‘ R2), 4.47 (dd, *J* = 7.0, 3.3 Hz, 1H, C-2‘‘ R1), 4.25 – 4.20 (m, 1H, C-3‘‘ a enol), 4.20 – 4.17 (m, 2H, C-3‘‘ a R1 & R2), 4.04 – 3.98 (m, 3H, C-3‘‘ b), 3.76 (s, 3H, COO*Me* enol), 3.71 (s, 3H, COO*Me* R2), 3.66 (s, 3H, COO*Me* R1), 3.64 (d, *J* = 16.5, 1H, CO-CH_2-CONR$_2$ a R1), 3.62 (d, *J* = 16.4, 1H, CO-CH_2-CONR$_2$ a R2), 3.33 (d, *J* = 16.4 Hz, 1H, CO-CH_2-CONR$_2$ b R2), 3.15 (d, *J* = 16.5 Hz, 1H, CO-CH_2-CONR$_2$ b R1), 2.60 (dd, *J* = 9.4, 5.0 Hz, 1H, H-3 R2), 2.44 (dd, *J* = 9.2, 5.2 Hz, 1H, H-3 R1), 2.29 – 2.27 (m, 1H, H-3 enol), 1.84 – 1.65 (m, 16H, H-6, H-7a, H-9a, H-10a, H-11 R1 & enol), 1.65 – 1.57 (m, 4H, H-3‘, H-11 R2), 1.55 (dd, *J* = 6.4, 1.6 Hz, 3H, H-3‘), 1.53 – 1.44 (m, 2H, 2xH-8), 1.38 (dd, *J* = 6.4, 1.6 Hz, 3H, H-3‘), 1.37 – 1.33 (m, 2H, 1xH-8, 1xH-10b) 1.23 (s, 3H, C-2-*Me* R2), 1.12 (s, 3H, C-2-*Me* R1), 1.10 – 1.03 (m 2H, 2x H-9b), 0.93 – 0.87 (m, 13H, H-8-*Me* R1 & enol, C-2-*Me* enol, 2xH-10b, 2x H-7b), 0.83–0.81 (m, 3H, C8-*Me* R2), 0.81 (s, 9H, C(CH_3)$_3$), 0.77 (s, 18H, 2x C(CH_3)$_3$), 0.76 – 0.74 (m, 1H, 1x H-7b), 0.50–0.46 (m, 1H, 1x H-9b), 0.02 (s, 3H, Si*Me*), –0.04 (s, 3H, Si*Me*), –0.06 (s, 3H, Si*Me*), –0.07 (s, 3H, Si*Me*), –0.12 (s, 3H, Si*Me*), –0.13 (s, 3H, Si*Me*); ^{13}C{^{1}H} NMR, HSQC, HMBC (150.1 MHz, $CDCl_3$) δ (ppm) = 208.1 (C-1 R2), 206.5 (C-1 R1), 183.9 (C-1 enol), 173.9 (C=CH-*C*ONR$_2$ enol), 169.9 (*C*OOMe enol), 169.8 (*C*ONR$_2$ R1), 169.5 (*C*OOMe R1), 169.4 (*C*OOMe R2), 168.7 (*C*ONR$_2$ R2), 147.8 (Ar-C2 R1), 147.44 (Ar-C2 R2), 147.39 (Ar-C2 enol), 136.7, 134.51 (Ar-C1 R2), 134.48 (Ar-C1 enol), 134.1 (Ar-C5 R1), 133.79 (Ar-C5 R2), 133.76

(Ar-C5 enol), 131.89, 130.86, 130.84, 130.67, 130.66, 130.10, 129.39 (Ar-C6 R1), 129.1 (Ar-C6 enol), 128.7 (Ar-C6 R2), 128.6 (Ar-C4 R1), 128.2 (Ar-C4 enol), 127.35, 127.31, 127.30 (Ar-C4 R2), 126.85, 126.53, 126.46, 126.41, 125.51, 125.45 (Ar-C3 enol), 125.40 (Ar-C3 R1), 125.0 (Ar-C3 R2), 87.2 (C=*C*H-CONR$_2$ enol), 62.9 (C-2'' R2), 62.5 (C-3'' enol), 62.2 (C-3'' R2), 62.1 (C-3'' R1), 61.0 (C-2'' R1), 60.0 (C-2'' enol), 53.9 (C-2 R2), 53.7 (C-2 R1), 52.6 (COO*Me* enol), 52.4 (COO*Me* R2), 52.3 (COO*Me* R1), 50.8 (C-3 enol), 50.7 (Ar-*C*H$_2$ R1), 49.9 (Ar-*C*H$_2$ enol), 49.8 (C-3 R2), 49.2 (C-3 R1), 46.7 (CO-*C*H$_2$-CON R2), 46.5 (Ar-*C*H$_2$ R2), 46.1 (C-2 enol), 45.2 (CO-*C*H$_2$-CON R1), 42.0, 39.87, 39.85 (C-11), 39.8, 38.6, 38.5 (C-6), 35.61, 35.57 (C-9), 33.50, 33.48, 33.33 (C-8), 27.34, 27.23, 27.19 (C-10), 25.82, 25.72, 25.68 (C(*C*H$_3$)$_3$), 22.62, 22.51 (C-8-*Me*), 18.1, 18.0 (*C*(CH$_3$)$_3$), 17.8 (C-3'), 17.2 (C2-*Me* R2), 17.0 (C2-*Me* R1), 16.9 (C-2-*Me* enol), –5.65, –5.71, –5.78, –5.84 (Si-*Me*); MS (ESI) *m/z*: 641.7 (100) [M + H]$^+$, 663.4 (16) [M + Na]$^+$; HRMS (ESI-QTOF) *m/z*: [M + H]$^+$ Calcd for $C_{35}H_{52}N_2O_7SiNa$ 663.3436; Found 663.3435.

*(3Z,5R)-5-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-3-[{(1S,2R,4aS,6R,8aR)-1,6-dimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}(hydroxy)methyliden]-1-(2-nitrobenzyl)pyrrolidin-2,4-dione (**14**).*

KO*t*Bu (34 mg, 0.31 mmol, 1.20 eq.) was added to a solution of **13** (164 mg, 0.26 mmol, 1.00 eq.) in *t*BuOH (1.4 mL). After stirring for 20 min at rt, the mixture was partitioned between sat. NH_4Cl (3 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3x 10 mL), and the combined organic layers were washed with brine (15 mL). The solution was dried over Na_2SO_4 and evaporated. Purification by flash column chromatography (*n*-pentane/Et_2O, 7:3) gave tetramic acid **14** as yellow oil (132 mg, 0.217 mmol, 85%). NMR data show a mixture of different enols: R_f = 0.35 (silica gel, Pent/Et_2O, 6:4); IR (ATR) ν (cm^{-1}) = 3017, 2950, 2858, 1696, 1566, 1528, 1470, 1341, 1114, 837; $[\alpha]_D^{25}$ = –101.6 (*c* 2.00, $CHCl_3$); ^{1}H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) = 16.05 (s, 0.4H, C1-OH), 8.10 (dd, *J* = 8.2, 1.3 Hz, 1H, Ar-H3 *Z*-enol major), 8.04 (dd, *J* = 8.2, 1.3 Hz, 0.5H, Ar-H3 *E*-enol minor), 7.64 – 7.60 (m, 1H, Ar-H5 *Z*), 7.57 (td, *J* = 7.6, 1.3 Hz, 0.5H, Ar-H5 *E*), 7.49 – 7.39 (m, 3H, Ar-H4 *Z* & *E*, Ar-H6 *Z* & *E*), 5.47 – 5.30 (m, 4.5H, H5 *E* & *Z*, H4 *E* & *Z*, H-2' *E* & *Z*), 5.27 (d, *J* = 17.4, 1H, Ar-C*H*$_2$ a *Z*), 5.24 – 5.14 (m, 1.5H, H-1' *E* & *Z*), 5.09 (d, *J* = 17.3 Hz, 0.5H, Ar-C*H*$_2$ a *E*), 4.98 (d, *J* = 17.4 Hz, 1H, Ar-C*H*$_2$ b *Z*), 4.93 (d, *J* = 17.3 Hz, 0.5H, Ar-C*H*$_2$ b *E*), 4.00 – 3.88 (m, 4H,

H-6' *E* & *Z*, H-5' *E*), 3.76 (s br, 1H, H-5' *Z*), 3.71 – 3.66 (m, 1H, H-3 *Z*), 3.36 – 3.28 (m, 0.5H, H-3 *E*), 2.00 – 1.91 (m, 1.5H, H-10[a] *E* & *Z*), 1.89 – 1.79 (m, 3H, H-7a *E* & *Z*, H-11 *E* & *Z*), 1.79 – 1.73 (m, 1.5H, H-9a *E* & *Z*), 1.72 – 1.66 (m, 1.5H, H-6 *E* & *Z*), 1.61 – 1.55 (m, 4.5H, H-3' *E* & *Z*), 1.55 – 1.48 (m, 6H, C2-*Me E* & *Z*, H-8 *E* & *Z*), 1.16 – 0.99 (m, 3H, H-9b *E* & *Z*, H-10b *E* & *Z*), 0.92 (d, J = 6.6 Hz, 4.5H, C8-*Me E* & *Z*), 0.90 – 0.86 (m, 1.5H, H-7b *E* & *Z*), 0.79 (s, 9H, C(CH_3)$_3$ *Z*), 0.78 (s, 4.5H, C(CH_3)$_3$ *E*), 0.00 (s, 3H, Si*Me Z*), -0.04 (s, 3H, 2x Si*Me E*), -0.04 (s, 3H Si*Me Z*); $^{13}C\{^1H\}$ NMR, HSQC, HMBC (150.9 MHz, $CDCl_3$) δ (ppm) = 203.5 (C-1 Z), 198.6 (C-1 E), 196.1 (C-4' E), 189.1 (C-4' Z), 177.8 (C-2' Z), 167.9 (C-2' E), 148.2 (Ar-C2 E), 148.1 (Ar-C2 Z), 133.9 (Ar-C5 Z), 133.7 (Ar-C5 E), 132.6 (Ar-C1 Z), 131.4 (C-1'' E), 131.2 (C-1'' Z), 130.3 (C-5 E), 130.0 (C-5 Z), 129.2 (Ar-C6 E), 128.95 (Ar-C6 Z), 128.5 (Ar-C4 Z), 128.3 (Ar-C4 E), 127.6 (C-2'' E), 127.0 (C-2'' Z), 126.9 (C-4 Z), 126.4 (C-4 E), 125.5 (Ar-C3 Z), 125.2 (Ar-C3 E), 107.1 (C-3' E), 100.5 (C-3' Z), 66.6 (C-5' Z), 63.7 (C-5' E), 61.8 (C-6' Z), 60.3 (C-6' E), 50.1 (C-2 Z), 48.9 (C-2 E), 45.5 (C-3 Z), 44.9 (C-3 E), 42.5 (C-7 E), 42.3 (C-7 Z), 40.2 (C-11 Z), 39.8 (C-11 E), 38.9 (C-6 E), 38.5 (C-6 Z), 35.9 (C-9 E), 35.8 (C-9 Z), 33.67, 33.64 (C-8 *E*/*Z*), 28.4 (C-10 Z), 28.1 (C-10 E), 25.9 (C(CH_3)$_3$ Z), 25.7 (C(CH_3)$_3$ E), 22.7 (C8-*Me E* & *Z*), 18.3 (C-3''' E), 18.2 (*C*(CH_3)$_3$ *E* & *Z*), 18.1 (C-3''' Z), 14.7 (C2-*Me* Z), 14.1 (C2-*Me* E), –5.46 (Si*Me*), –5.55 (Si*Me*), –5.57 (Si*Me*), –5.7 (Si*Me*); MS (ESI): *m/z* (%) = 609.7 (100) $[M + H]^+$, 631.4 (13) $[M + Na]^+$; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ Calcd for $C_{34}H_{49}N_2O_6Si$ 609.3360; Found 609.3350.

*(3Z,5R)-5-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-3-[{(1S,2R,4aS,6R,8aR)-1,6-dimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}(hydroxy)methyliden]pyrrolidin-2,4-dione (**15**).*

A solution of tetramic acid **14** (31.0 mg, 50.9 µmol) in MeCN (3 mL) was irradiated for 15 min at rt, using a photoreactor with 350 nm-UV-A lamps. Water (1–2 mL) was added, and the solution was stirred for 12 h. The solvent was removed by lyophilization, and the residue was purified by reversed phase chromatography (H_2O/MeCN, 5–95%, automatic flash purification system). Compound **15** was obtained as colorless lyophilisate (17.4 mg, 36.7 µmol, 72%): R_f = 0.19 (silica gel, cyclohexane/EtOAc, 8:2); IR (ATR) ν (cm^{-1}) = 3250, 2945, 2950, 1858, 1660, 1572, 1456, 1362, 1256, 1124, 838, 779; $[\alpha]_D^{31}$ = –225 (*c* 0.20, $CHCl_3$); ^1H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) =

6.08 (br s, 1H, NH), 5.44 – 5.36 (m, 2H, H-4, H-5), 5.21 (br s, 1H, H-14), 5.18 (br s, 1H, H-13), 4.00 (br s, 1H, H-6'a), 3.90 (br s, 1H, H-5'), 3.53 (br s, 1H, H-6'b), 3.32 (br s, 1H, H-3), 1.96 (br s, 1H, H-10a), 1.88 – 1.78 (m, 2H, H-6, H-7a), 1.78 – 1.72 (m, 1H, H-9a), 1.70 – 1.63 (m, 1H, H-11), 1.54 (d, *J* = 5.2 Hz, 3H, H-15), 1.48 (br s, 4H, C2-*Me*, H-8), 1.15 – 1.01 (m, 2H, H-10b, H-9b), 0.92 (d, *J* = 6.5 Hz, 3H, C8-*Me*), 0.88 (s, 10H, C(CH_3)$_3$, H-7b), 0.07 (s, 3H, Si-*Me*), 0.07 (s, 3H, Si-*Me*); ^{13}C{^{1}H} NMR, HSQC, HMBC (150.9 MHz, $CDCl_3$) δ (ppm) = 200.2 (C-1), 189.7 (C-4'), 179.0 (C-2'), 131.1 (C-13), 130.1 (C-5), 127.1 (C-14), 126.7 (C-4), 100.5 (C-3'), 64.1 (C-6'), 63.0 (C-5'), 49.0 (C-2), 45.0 (C-3), 42.4 (C-7), 40.1 (C-11), 38.7 (C-6), 35.8 (C-9), 33.6 (C-8), 28.4 (C-10), 26.0 (C(*C*H$_3$)$_3$), 22.6 (C-8-*Me*), 18.4 (*C*(CH$_3$)$_3$), 18.1 (C-15), 14.0 (C-2-*Me*), 2.1 (Si-*Me*), –5.3 (Si-*Me*); MS (ESI): *m/z* (%) = 474.6 (100) [M + H]$^+$, 496.4 (13) [M + Na]$^+$; HRMS (ESI-QTOF) *m/z*: [M + H]$^+$ Calcd for $C_{27}H_{44}NO_4Si$ 474.3040; Found 474.3030.

*(3Z,5R)-3-[{(1S,2R,4aS,6R,8aR)-1,6-Dimethyl-2-[(1E)-prop-1-en-1-yl]-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl}(hydroxy)methyliden]-5-(hydroxymethyl)pyrrolidin-2,4-dione (*epi-*trichosetin, **4**).*

HF (190 µL, 3.83 mmol, 191 eq., 48% in water) was added to a solution of silyl ether **15** (9.5 mg, 20.0 µmol, 1.00 eq.) in MeCN (400 µL). After stirring for 10 min at room temperature, $NaHCO_3$ (327 mg, 3.89 mmol, 194 eq.), dissolved in a small amount of water, was added. EtOAc (8 mL) was added, and the aqueous layer was extracted with EtOAc (2x 8 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and evaporated. The residue was subjected to reversed phase flash chromatography (H_2O/MeCN, automatic flash purification system) to give *epi*-trichosetin (7.2 mg, 20.0 µmol, 99%) as a colorless lyophilizate: R_f = 0.15 (silica gel, EtOAc/MeOH, 9:1); IR (ATR) ν (cm^{-1}) = 3299 br, 3017, 2946, 2920, 2853, 1657, 1566, 1455, 1378, 976; $[\alpha]_D^{31}$ = –248 (*c* 0.10, MeOH); ECD (MeOH) = 238 nm (0.23 deg×cm^2/dmol), 276 nm (–4.2 deg×cm^2/dmol); ^{1}H NMR, COSY (600 MHz, $CDCl_3$) δ (ppm) = 6.06 (br s, 1H, NH), 5.39 (d, *J* = 4.6 Hz, 2H, H-4, H-5), 5.25 (dt, *J* = 12.7, 6.6 Hz, 1H, H-14), 5.16 (br s, 1H, C-13), 3.94 (br s, 1H, H-5'), 3.92 – 3.86 (m, 1H, H-6'a), 3.81 (dd, *J* = 11.2, 5.8 Hz, 1H, H-6'b), 3.39 (br s, 1H, H-3), 1.95 (s, 1H, H-10a), 1.87 – 1.79 (m, 2H, H-6, H-7a), 1.78 – 1.73 (m, 1H, H-9a), 1.68 (br s, 1H, H-11), 1.53 (d, *J* = 6.0 Hz, 3H, H-15), 1.52 – 1.49 (m, 1H, H-8), 1.48 (s, 3H, C-2-*Me*), 1.17 – 1.01 (m, 2H, H-9b, H-10b), 0.92 (d, *J* = 6.7 Hz, 3H,

H-8-*Me*), 0.90 – 0.86 (m, 1H, H-7b); $^{13}C\{^{1}H\}$ NMR, HSQC, HMBC (150.9 MHz, $CDCl_3$) δ (ppm) = 200.7 (C-1), 191.1 (C-4'), 179.4 (C-2'), 130.9 (C-13), 130.1 (C-5), 127.2 (C-14), 126.7 (C-4), 100.2 (C-3'), 63.1 (C-6'), 61.7 (C-5'), 49.1 (C-2), 45.1 (C-3), 42.4 (C-7), 40.1 (C-11), 38.6 (C-6), 35.8 (C-9), 33.6 (C-8), 28.5 (C-10), 22.6 (C-8-*Me*), 18.1 (C-15), 14.0 (C-2-*Me*); MS (ESI): *m/z* (%) = 360.5 (100) $[M + H]^+$; 382.3 (53.2) $[M + Na]^+$, 342.9 (6) $[M - H_2O + H]^+$; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{30}NO_4$ 360.2175; Found 360.2170. The data are in accordance to the literature.[3]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the internet.

^{1}H and ^{13}C NMR spectra of all novel compounds, overlay of VCD spectra of **2**, *epi*-**2** and **4**, IR spectra of **2**, *epi*-**2** and **4** and overlay of IR spectra of **2**, *epi*-**2** and **4**.

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Notes

The authors declare no competing financial interest.

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