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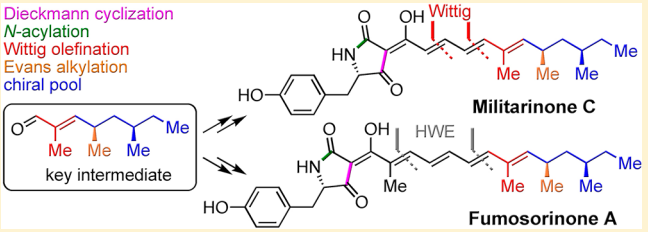
Synthesis of the Entomopathogenic Fungus Metabolites Militarinone C and Fumosorinone A

Sebastian Bruckner, Marie Weise, and Rainer Schobert*

Department of Chemistry, University Bayreuth, Universitaetsstrasse 30, 95440 Bayreuth, Germany

Supporting Information

ABSTRACT: Militarinone C and fumosorinone A, 3-oligoenoyltetramic acids produced by insect pathogenic fungi, were synthesized for the first time. The pyrrolidine-2,4-dione ring was closed through a late-stage Dieckmann condensation of *N*-(*β*-ketoacyl) derivatives of tyrosine, obtained by its acylation with either thioesters or Meldrum's acid derivatives bearing the *all-trans*-polyene side chain. The latter was built up from (*S*)-citronellol via an Evans methylation and Wittig or HWE olefinations.



INTRODUCTION

In 2002 Hamburger et al. reported the isolation of militarinone A (**1**), a neurotrophic 2-pyridone alkaloid, from the entomogenous fungus *Paecilomyces militaris*.[1] Shortly after, they also identified two yellow tetramic acids, militarinone B (**2**) and militarinone C (**3**), as cometabolites (Figure 1).[2] It is

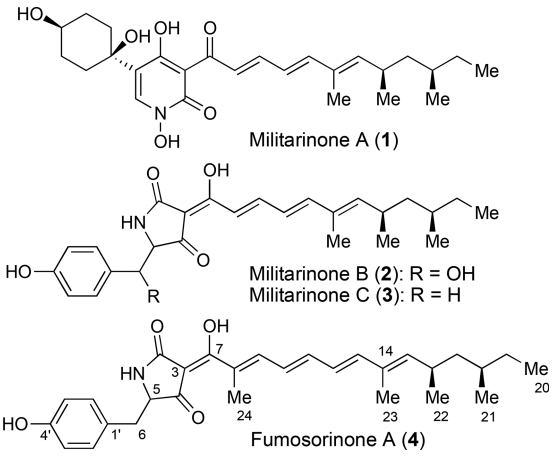


Figure 1. Structures of militarinones A−C (**1**-**3**) and fumosorinone A (**4**).

not uncommon that fungi produce mixtures of tyrosine-derived tetramic acids and 2-pyridones, e.g., the family of torrubiellones, metabolites of the fungus *Torrubiella sp.* BCC 2165,[3] or the (proto)tenellins, produced by the insect pathogenic fungus *Beauveria bassiana*. For the latter, Cox et al. established a radical oxidation−rearrangement conversion of the tetramic acid prototenellin D to the 2-pyridone tenellin.[4] In 2017, Zhang et al.[5] isolated fumosorinone A (**4**) from the entomogenous fungus *Isaria fumosorosea* and found it to inhibit (IC_{50} 3.24 μM) protein tyrosine phosphatase 1B (PTP1B), a major negative regulator[6] of the insulin signaling pathway. Such inhibitors are of interest as potential type II diabetes drugs since Klaman et al. had confirmed a higher sensitivity to insulin for mice deficient in PTP1B.[7] Herein we report short syntheses that procure both compounds in quantities sufficient to study their conversion to 2-pyridones.

RESULTS AND DISCUSSION

The retrosynthetic approach is outlined in Scheme 1. Both target compounds **3** and **4** were finished by a Dieckmann cyclization[8] of the respective functionalized *β*-ketoamide **5** or **6** followed by N,O-deprotection. These *β*-ketoamides were obtained by reaction of N,O-bisprotected methyl tyrosinates **7** with either Meldrum's acid derivative **8** or thioester **9** as N-acylating agents carrying the respective unsaturated side chain. The *β*-ketoesters **8** and **9** were accessible through consecutive Wittig or HWE olefinations of key aldehyde **10** which was built up from (*S*)-citronellol (**11**) using an Evans alkylation[9] to introduce the second methyl group and an *E*-selective Wittig olefination to establish the trisubstituted double bond.

(*S*)-Citronellol (**11**) was first converted to imide **15** following a modified route by Nishida et al.[10] (Scheme 2). It was quantitatively deoxygenated to alkene **13** in two steps via mesylation to give **12** which was reduced with $LiAlH_4$. Olefin **13** was subjected to a ruthenium-catalyzed oxidative cleavage according to a general procedure by Sharpless et al.[11] which afforded carboxylic acid **14**. This was converted to a mixed anhydride with pivaloyl chloride which was reacted with (*R*)-4-benzyloxazolidin-2-one to yield imide **15**. Its methylation at −78 °C gave the desired (*R*,*R*)-product **16** as a separable mixture of two diastereomers. Removal of the Evans auxiliary with $LiBH_4$/MeOH at 0 °C left enantiopure alcohol **17**. This was Swern oxidized to aldehyde **18** which was Wittig olefinated

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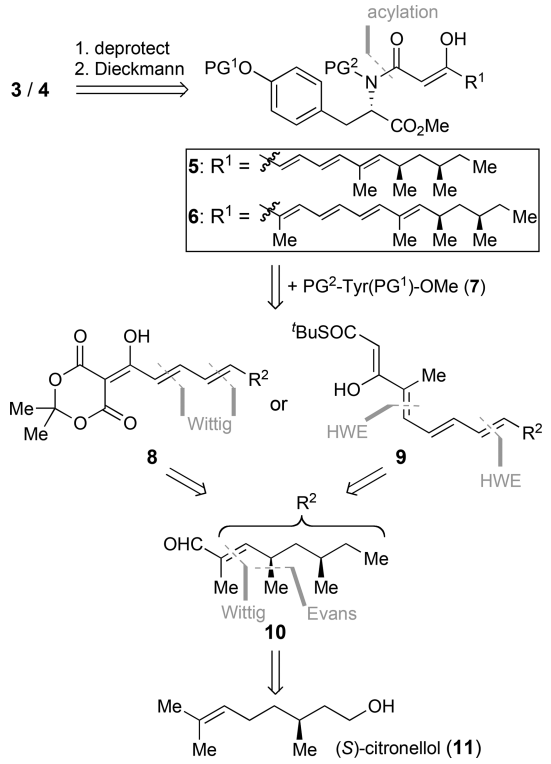
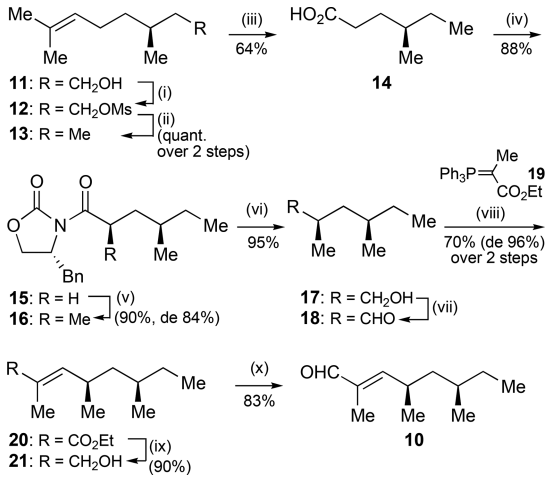
Scheme 1. Retrosynthesis of Militarinone C (3) and Fumosorinone A (4)



Scheme 2. [a]Synthesis of Key Aldehyde 10

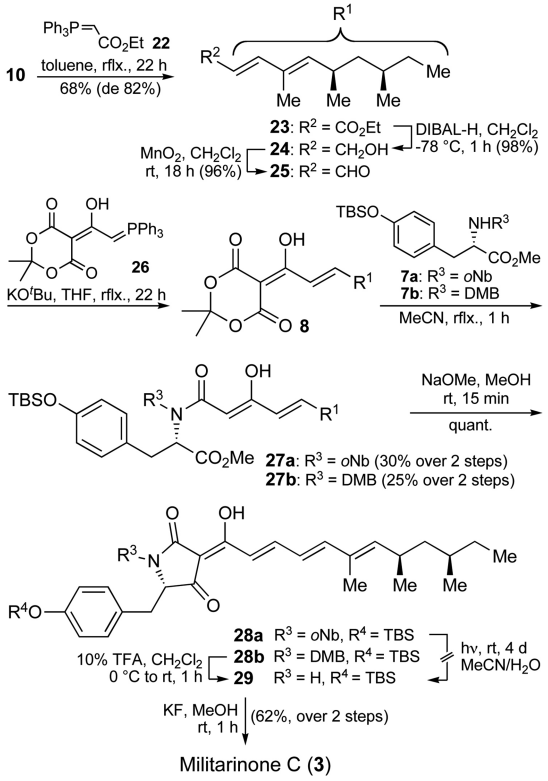


[a]Reagents and conditions: (i) MsCl, NEt_3, CH_2Cl_2, 0 °C to rt, 3.75 h; (ii) $LiAlH_4$, THF, 0 °C to rt, 16 h; (iii) $NaIO_4$ (4 equiv), $RuCl_3$ (2 mol %), $MeCN/CH_2Cl_2/H_2O$, rt, 18 h; (iv) PivCl, NEt_3, THF, 0 °C, 25 min, then LiCl, (*R*)-Evans oxazolidinone, rt, 30 min; (v) NaHMDS, THF, −78 °C, 15 min, then MeI, −78 °C to rt, 2.5 h; (vi) $LiBH_4$, MeOH, Et_2O, 0 °C to rt, 5 h; (vii) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C, 3 h; (viii) + **19**, CH_2Cl_2, rt, 19 h; (ix) DIBAL-H, CH_2Cl_2, −78 °C, 1 h; (x) MnO_2, CH_2Cl_2, rt, 18 h.

without purification to furnish ester **20** in 70% yield over two steps, following a protocol by Ding et al.[12] DIBAL-H reduction to alcohol **21** and its oxidation with MnO_2 afforded aldehyde **10** (10 steps, 25% relative to **11**).

For the synthesis of militarinone C (**3**), aldehyde **10** was elongated, analogously to aldehyde **18**, by a sequence of Wittig olefination with stabilized ylide **22** to give ester **23**, followed by its DIBAL-H reduction to alcohol **24**, and MnO_2 oxidation of the latter to aldehyde **25** (Scheme 3). This aldehyde was

Scheme 3. Synthesis of Militarinone C (3)



reacted with a Meldrum's acid-derived ylide **26**, applying a recent protocol by us,[13] to give *β*-ketoester **8**. Due to its decomposition on silica gel, the crude mixture of **8**, Ph_3PO, and some residual starting material was immediately reacted with either bisprotected methyl L-tyrosinate **7a** (R^3 = *o*-nitrobenzyl) or **7b** (R^3 = 2,4-dimethoxybenzyl). The resulting *β*-ketoamides **27** were treated with NaOMe in methanol to initiate a Dieckmann cyclization affording the respective bisprotected militarinone C **28** in quantitative yield. Unfortunately, irradiation of **28a**, which was previously successfully employed for the cleavage of an *o*Nb group on the nonoligoenoyl tetramic acid F-14329,[8] failed to give N-unprotected tetramic acid **29**. Besides requiring a longer reaction time (4 d vs 1 d), the photolytic deprotection of **28a** also led to cis−trans isomerizations of the 3-oligoenoyl side chain. Gratifyingly, deprotection of **28b** was readily achieved with 10% TFA in dichloromethane, leaving **29**, followed by desilylation to give militarinone C (**3**) in 62% over two steps after purification by MPLC. Its NMR data are in line with those reported[2] for the natural product (cf. Supporting Information Table S1), including the visibility of a second, minor tautomer in the NMR spectra. The specific optical rotation of our synthetic sample, $[\alpha]^{24}_D$ −310 (*c* 0.30, CH_3OH), differed distinctly from that of the natural isolate with $[\alpha]^{25}_D$ −430 (*c* 0.17, CH_3OH). However, because optical rotations of 3-acyltetramic acids are notorious for their volatility depending on many factors including the concentration and even age of the sample solution, they are not suited as proof of purity or identity. Although deviations between optical rotations of otherwise identical compounds have repeatedly been reported in the literature, e.g., lately for

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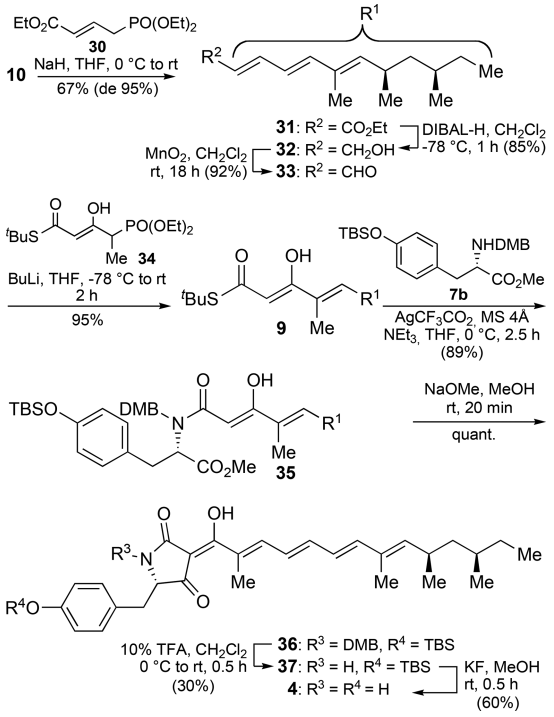
penicillinol A_2[14] and (−)-hymenosetin,[15] our synthesis of militarinone C supports, yet does not prove, the absolute configuration proposed in the literature for the natural product. An unambiguous proof would, for instance, require a comparison of circular dichroism spectra[15] of natural and synthetic samples (for an ECD spectrum of synthetic militarinone C (**3**) cf. Supporting Information).

For the synthesis of fumosorinone A (**4**), aldehyde **10** was submitted to a HWE olefination with phosphonate **30**, followed by a DIBAL-H reduction of product ester **31** to alcohol **32** and its oxidation with MnO_2 to aldehyde **33**, analogously to Dash et al.[16] (Scheme 4). Another HWE

Scheme 4. Synthesis of Fumosorinone A (4)



olefination with phosphonate **34**, according to Loscher et al.,[17] afforded thioester **9** in excellent 95% yield as a 2:3 keto/enol mixture. It was used to acylate aminoester **7b** in a surprisingly good yield of 89% according to Ley's silver(I)-mediated aminolysis protocol.[18] The resulting β-ketoamide **35** was cyclized quantitatively under mild conditions to give doubly protected fumosorinone A **36**. Due to its acid sensitivity, it had to be deprotected in two steps. Treatment with 10% TFA for only 30 min allowed the isolation of 30% TBS-protected fumosorinone A **37** aside of 30% recovered **36**. Desilylation of all accumulated **37** with KF in methanol finally yielded fumosorinone A (**4**) in 60% after semipreparative HPLC. It proved identical to the natural isolate in terms of NMR spectra (cf. Supporting Information Table S2) and also specific optical rotations ($[\alpha]^{24}_D$ −229 (*c* 0.20, CH_3OH) for synthetic and $[\alpha]^{20}_D$ −207 (*c* 0.1, CH_3OH) as reported for natural **4**).

CONCLUSIONS

In summary, fumosorinone A (**4**) and militarinone C (**3**) were each prepared in 18 steps and ca. 2% yield by N-acylating L-tyrosine esters with thioesters or 5-enoyl Meldrum's acids carrying the polyene side chains, followed by Dieckmann cyclization of the resulting β-ketoamides. The side chains were built up from (*S*)-citronellol via an Evans methylation and consecutive Wittig or HWE olefinations. The agreement (good in the case of **4**, reasonable for **3**) between NMR spectra and optical rotations of our synthetic products and those reported for the natural isolates at least does not rule out the origin of the latter from L-tyrosine. Studies of the conversion of compounds **3** and **4** to the respective 2-pyridones by means of radical oxidants are already underway.

EXPERIMENTAL SECTION

General Remarks. IR spectra were recorded with an FT-IR spectrophotometer equipped with an ATR unit. ^1H NMR and ^{13}C NMR spectra were obtained using a 500 MHz spectrometer. Chemical shifts are given in parts per million using the residual solvent peak as an internal standard 7.26 ppm (proton) and 77.16 ppm (carbon) for $CDCl_3$, 3.31 ppm (proton), and 47.60 ppm (carbon) for CD_3OD and 2.50 ppm (proton) and 39.51 ppm (carbon) for DMSO-d_6. Coupling constants (*J*) are quoted in hertz (Hz). Multiplicity abbreviation used: s singlet, d doublet, t triplet, q quartet, m multiplet, br broad. High resolution mass spectra were obtained with a UPLC/Orbitrap MS system in ESI mode. Optical rotations were measured at 589 nm (Na-D line). Photolysis was performed using a Pro Collect UV tester with 366 nm and 4 W.

Chemicals. All reagents were purchased from commercial sources and were used without further purification. All anhydrous solvents were used as supplied, except tetrahydrofuran, diethyl ether, and dichloromethane which were freshly distilled according to standard procedures. Reactions were routinely carried out under an argon atmosphere unless stated otherwise. All glassware was flame-dried before use.

Chromatography. Analytical thin layer chromatography was carried out using Merck silica gel $60GF_{254}$ precoated aluminum-backed plates and/or Merck 60 RP-18 F_{254S} foil plates. The compounds were visualized with UV light (254 nm and/or 360 nm) and/or ceric ammonium molybdate (CAM) and/or potassium permanganate and/or iodine on silica. Flash chromatography was performed at medium pressure using dry-packed Marchery-Nagel silica gel 60, pore size 40−63 μm, with the eluent specified. Analytical HPLC measurements were performed on a Beckman System Gold Programmable Solvent Module 126 using a Phenomenex Kinetex C-18-HPLC column, length 250 × 4.6 mm, pore size 100 Å, particle size 5 μm. Detection was by a Beckman Instruments Diode Array Detection Module 168. MPLC reversed phase chromatography was performed using a Büchi MPLC system with a "MN Polygroprep 100−50 C 18 end-capped" column, length 460 mm, diameter 49 mm. Detection was by a Büchi UV Photometer C-635. Semipreparative reversed phase HPLC was performed using an Amersham Biosciences ÄKTAbasic10 system with a Phenomenex Gemini-NX 5u C18 110A, 250 × 10.00 mm column. Detection was by an Amersham Biosciences ÄKTA UV-900 module.

Militarinone C (3). A solution of protected tetramic acid **28b** (107 mg, 156 μmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C and treated dropwise with 20% trifluoroacetic acid in CH_2Cl_2 (50 mL). The resulting mixture was stirred at ambient temperature for 1 h, sat. aqueous phosphate buffer (pH 7, 50 mL) was added, and the phases were separated. The organic phase was washed with the same buffer (2 × 50 mL) and aqueous $KHSO_4$ (5% wt, 50 mL) and then dried (Na_2SO_4) and concentrated in vacuo to give a mixture of *O*-TBS-protected tetramic acid **29** and militarinone C (**3**) as a yellow oil (93 mg) that was used in the next step without further purification.

The crude mixture of **29** and **3** was taken up in methanol p.a. (6 mL), a 10 M suspension of KF in methanol p.a. (624 μL, 6.24 mmol) was added, and the mixture was stirred at ambient temperature for 1 h. A 1 M aqueous HCl (20 mL) solution and brine (50 mL) were added, and the mixture was extracted with EtOAc (2 × 125 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil which was purified by MPLC on an RP-18 column, eluting with 75% methanol in H_2O (with 0.1% formic acid) to 95% methanol in 10 min with a flow rate of 240 mL/min. The

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product-containing fractions were collected, the methanol was removed in vacuo, and the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with 1 M aqueous HCl (20 mL), dried (Na_2SO_4), and concentrated in vacuo to give militarinone C (**3**) as an orange-yellow solid foam (40.9 mg, 62% over two steps); $[\alpha]^{24}_D$ −310 (*c* 0.30, MeOH) (lit.[2] $[\alpha]^{24}_D$ −430.2 (*c* 0.17, MeOH)); IR ν_{max} 3284, 2959, 2923, 1587, 1551, 1515, 1463, 1429, 1373, 1226, 1172, 1105, 1031, 1000, 895, 868, 822, 733, 626 cm^{-1}; for NMR data cf. Supporting Information Table S1; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{34}NO_4^+$ 424.2482, found 424.2477.

Fumosorinone A (4). A solution of tetramic acid **36** (72 mg, 99 μmol) in CH_2Cl_2 (36 mL) was cooled to 0 °C and treated dropwise with 20% trifluoroacetic acid in CH_2Cl_2 (36 mL), and the mixture was stirred at ambient temperature for 30 min. Saturated aqueous phosphate buffer (pH 7, 100 mL) was added at 0 °C, the phases were separated, and the organic phase was washed with the same buffer (2 × 100 mL) and 1 M aqueous HCl (50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford an orange-yellow oil. It was purified by flash chromatography on RP-18 silica gel, eluting with 95% acetonitrile in H_2O to give *O*-TBS-protected tetramic acid **37** (16 mg, 30%) and residual starting material **36** (22 mg, 30%); R_f = 0.36 (8% MeOH in CH_2Cl_2). A solution of **37** (16 mg, 28 μmol) in MeOH (1.8 mL) was treated with a 10 M suspension of potassium fluoride in MeOH (199 μL, 1.99 mmol), and the mixture was stirred at ambient temperature for 30 min. Saturated aqueous NH_4Cl (20 mL) and 1 M aqueous HCl (10 mL) were added, and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to leave an orange-red oil which was filtered over Sephadex LH-20 (MeOH) to afford an orange-red oil upon evaporation. The oil was further purified by semipreparative HPLC (ÄKTA system, flow rate: 5 mL/min on a Phenomenex Gemini-NX 5u C18 110A, 250 × 10.00 mm column, one column volume (CV) at 70% MeCN in H_2O (with 0.1% formic acid), then three CV at 90% MeCN, t_{ret} = 11.7−12.6 min, UV_{det} = 414 nm) to give fumosorinone A (**4**) as a bright orange-yellow oil (7.7 mg, 60%); $[\alpha]^{24}_D$ −229 (*c* 0.20, MeOH) (lit.[5] $[\alpha]^{24}_D$ −207 (*c* 0.1, MeOH)); IR ν_{max} 3310, 2960, 2925, 1650, 1591, 1516, 1442, 1261, 1171, 988, 812, 620 cm^{-1}; for NMR data cf. Supporting Information Table S2; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{38}NO_4^+$ 464.2795, found 464.2785.

*Methyl (S)-3-(4-((tert-Butyldimethylsilyl)oxy)phenyl)-2-((2-nitrobenzyl)amino)propanoate (**7a**).* A solution of L-tyrosine methyl ester hydrochloride (1.16 g, 5.00 mmol) in 3% acetic acid in methanol (100 mL) was treated with *o*-nitrobenzaldehyde (1.51 g, 10.00 mmol) and MS 3 Å (100 mg), and the resulting mixture was stirred at ambient temperature for 1 h. $NaBH_3CN$ (781 mg, 12.50 mmol) was added, and stirring was continued for 2 h. The molecular sieves were filtered off, and the reaction mixture was quenched with sat. aqueous $NaHCO_3$ (300 mL). Ethyl acetate (300 mL) was added, the phases were separated, and the organic phase was washed with brine (200 mL), dried (Na_2SO_4), and concentrated in vacuo to give a yellowish oil that was adsorbed on silica gel (wt ratio oil/silica 1:10) and purified by flash chromatography (silica gel, 1% MeOH in CH_2Cl_2 ⇒ 1.5% MeOH ⇒ 2% MeOH) to give *o*Nb-L-Tyr-OMe as a yellow oil (1.145 g, 69%); R_f = 0.30 (4% MeOH in CH_2Cl_2); $[\alpha]^{24}_D$ +33.6 (*c* 1.00, $CHCl_3$); IR ν_{max} 3324, 2953, 1732, 1613, 1596, 1578, 1516, 1444, 1344, 1206, 1173, 1107, 991, 829, 789, 731, 702, 666, 556 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.90 (dd, *J* = 1.1, 8.1 Hz, 1H), 7.49 (ddd, *J* = 1.1, 7.2, 7.3 Hz, 1H), 7.46 (dd, *J* = 1.5, 7.3 Hz, 1H), 7.36 (ddd, *J* = 1.5, 7.2, 8.1 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 4.08 (d, *J* = 15.0 Hz, 1H), 3.93 (d, *J* = 15.0 Hz, 1H), 3.64 (s, 3H), 3.47 (dd, *J* = 6.1, 7.3 Hz, 1H), 2.91 (dd, *J* = 6.1, 13.4 Hz, 1H), 2.86 (dd, *J* = 7.3, 13.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.0, 155.0, 149.0, 134.9, 133.3, 131.2, 130.4, 128.5, 128.2, 124.9, 115.5, 62.6, 52.0, 49.2, 38.8; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{19}N_2O_5^+$ 331.1288, found 331.1284.

A solution of *o*Nb-L-Tyr-OMe (610 mg, 1.85 mmol) in CH_2Cl_2 p.a. (19 mL) was cooled to 0 °C and treated with imidazole (378 mg, 5.55 mmol) and TBSCl (613 mg, 4.07 mmol). The resulting mixture was stirred for 19 h while reaching room temperature. The mixture was filtered, the filtrate was taken up in CH_2Cl_2 (50 mL), the organic phase was washed with sat. aqueous NH_4Cl (100 mL), and the aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with brine (150 mL), dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil that was purified by flash chromatography (silica gel, 12% ethyl acetate in hexane) to afford **7a** as a yellow oil (746 mg, 91%); R_f = 0.74 (hexane/EtOAc 1:1); $[\alpha]^{24}_D$ +26.8 (*c* 1.00, $CHCl_3$); IR ν_{max} 2954, 2931, 2858, 1737, 1609, 1580, 1527, 1510, 1471, 1444, 1346, 1255, 1200, 1170, 1131, 1105, 1007, 914, 840, 782, 729, 691, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.91 (d, *J* = 8.2 Hz, 1H), 7.45−7.54 (m, 2H), 7.34−7.41 (m, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 4.09 (d, *J* = 15.0 Hz, 1H), 3.92 (d, *J* = 15.0 Hz, 1H), 3.63 (s, 3H), 3.45 (dd, *J* = 6.4, 7.3 Hz, 1H), 2.91 (dd, *J* = 6.4, 13.7 Hz, 1H), 2.86 (dd, *J* = 7.3, 13.7 Hz, 1H), 2.07 (br. s, 1H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.9, 154.6, 149.1, 135.3, 133.2, 130.9, 130.3, 129.8, 128.0, 124.8, 120.1, 62.7, 51.9, 49.1, 39.1, 25.8, 18.3, −4.3; HRMS (ESI) *m* /*z* $[M + H]^+$ calcd for $C_{23}H_{33}N\ _2O_5Si^+$ 445.2153, found 445.2137.

*Methyl (S)-3-(4-((tert-Butyldimethylsilyl)oxy)phenyl)-2-((2,4-dimethoxybenzyl)amino)propanoate (**7b**).* According to a modified literature procedure,[19] a suspension of L-tyrosine methyl ester hydrochloride (580 mg, 2.50 mmol) in CH_2Cl_2 (12 mL) was treated with imidazole (510 mg, 15.00 mmol) and TBSCl (452 mg, 6.00 mmol). The resulting mixture was stirred at room temperature for 19 h. Saturated aqueous $NaHCO_3$ (50 mL) was added, and the jellylike mixture was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic phases were washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated in vacuo to give an oil that was purified by flash chromatography (silica gel, 90% ethyl acetate in hexane) to afford L-Tyr(OTBS)-OMe as a clear oil (479 mg, 77%); R_f = 0.24 (hexane/EtOAc 1:4); $[\alpha]^{24}_D$ +10.0 (*c* 1.00, $CHCl_3$); IR ν_{max} 2954, 2931, 2893, 2858, 1739, 1609, 1509, 1472, 1464, 1438, 1252, 1195, 1169, 1109, 1102, 1008, 911, 837, 802, 779, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.03 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 3.70 (s, 3H), 3.68 (dd, *J* = 5.2, 7.6 Hz, 1H), 3.00 (dd, *J* = 5.2, 13.7 Hz, 1H), 2.80 (dd, *J* = 7.6, 13.7 Hz, 1H), 1.45 (br. s., 2H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.7, 154.7, 130.3, 129.9, 120.3, 56.1, 52.1, 40.5, 25.8, 18.3, −4.3.

A solution of L-Tyr(OTBS)-OMe (881 mg, 2.85 mmol) in 3% acetic acid in methanol (10 mL) was treated with 2,4-dimethoxybenzaldehyde (450 mg, 2.71 mmol), and the mixture was stirred at room temperature for 30 min. $NaBH(OAc)_3$ (804 mg, 3.79 mmol) was added, stirring continued for 1.5 h, and the reaction mixture was quenched with sat. aqueous $NaHCO_3$ (50 mL). The mixture was extracted with ethyl acetate (3 × 75 mL), and the combined organic phases were washed with brine (75 mL), dried (Na_2SO_4), and concentrated in vacuo to give an oil that was purified by flash chromatography (silica gel, 15% EtOAc with 0.5% NEt_3 in hexane ⇒ 30% EtOAc with 0.5% NEt_3) to leave **7b** as a clear oil (870 mg, 71%); R_f = 0.68 (hexane/EtOAc 1:1); $[\alpha]^{24}_D$ +1.98 (*c* 1.00, $CHCl_3$); IR ν_{max} 2952, 2931, 2858, 1735, 1611, 1589, 1508, 1463, 1438, 1418, 1278, 1250, 1207, 1156, 1132, 1104, 1036, 911, 835, 797, 779, 688, 634 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.02 (d, *J* = 8.9 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 2H), 6.73 (d, *J* = 8.2 Hz, 2H), 6.36−6.40 (m, 2H), 3.78 (s, 3H), 3.68 (s, 3H), 3.58 (s, 3H), 3.45 (t, *J* = 7.2 Hz, 1H), 2.89 (dd, *J* = 6.7, 13.4 Hz, 1H), 2.85 (dd, *J* = 7.6, 13.4 Hz, 1H), 1.87−2.05 (m, 1H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.2, 160.2, 158.7, 154.5, 130.5, 130.21, 130.17, 120.2, 120.1, 103.7, 98.5, 62.4, 55.5, 55.3, 51.7, 47.3, 39.1, 25.8, 18.3, −4.3.

*S-(tert-Butyl) (2Z,4E,6E,8E,10E,12R,14R)-3-Hydroxy-4,10,12,14-tetramethylhexadeca-2,4,6,8,10-pentaenethioate (**9**).* Following a general literature protocol,[17] thioester **9** (236 mg, 95%) was prepared from phosphonate **34** (289 mg, 889 μmol) and aldehyde **33** (140 mg, 635 μmol) as an orange-yellow oil and as a 2:3 keto/enol mixture; R_f = 0.86 (10% EtOAc in hexane); $[\alpha]^{24}_D$ −43.2 (*c* 0.50, $CHCl_3$); IR ν_{max} 2960, 2923, 2871, 1688, 1651, 1614, 1586, 1456, 1376, 1364, 1311, 1250, 1163, 1100, 1062, 986, 907, 859, 797, 769, 652 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 12.96 (s, 1H), 7.15 (d, *J* = 11.0 Hz, 1H),

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7.11 (d, J = 11.0 Hz, 1H), 6.22−6.75 (m, 8H), 5.57 (s, 1H, HCCOS enol), 5.41 (d, J = 9.8 Hz, 1H), 5.36 (d, J = 9.8 Hz, 1H), 3.88 (s, 2H, H_2CCOS keto), 2.56−2.69 (m, 2H), 1.92 (s, 3H), 1.86 (d, J = 0.9 Hz, 3H), 1.81 (d, J = 0.9 Hz, 3H), 1.80 (d, J = 0.9 Hz, 3H), 1.53 (s, 9H), 1.47 (s, 9H), 1.21−1.35 (m, 6H), 1.05−1.17 (m, 4H), 0.96 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H), 0.80−0.88 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.2, 193.6, 193.3, 169.6, 144.3, 143.2, 142.4, 141.8, 141.5, 139.9, 134.7, 132.6, 127.3, 127.2, 127.0, 126.4, 126.0, 98.1, 54.1, 49.0, 48.5, 45.0, 44.9, 32.5, 32.4, 30.84, 30.76, 30.35, 30.27, 30.25, 29.8, 21.63, 21.56, 19.2, 12.6, 12.4, 11.8, 11.5; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{38}O_2NaS^+$ 413.2485, found 413.2482.

*(4R,6R,E)-2,4,6-Trimethyloct-2-enal (**10**).* A solution of alcohol **21** (1.60 g, 9.37 mmol) in CH_2Cl_2 p.a. (94 mL) was treated with MnO_2 (29.48 g, 327.95 mmol), and the mixture was stirred at ambient temperature for 18 h and then filtered over Celite. The filtrate was concentrated in vacuo to give a clear liquid that was purified by flash chromatography (silica gel, 10% ethyl acetate in hexane) to afford aldehyde **10** (1.31 g, 83%) as a clear oil; R_f = 0.38 (6% ethyl acetate in hexane); $[\alpha]^{24}_D$ −36.3 (c 1.00, $CHCl_3$) (lit.[20] $[\alpha]^{20}_D$ −43 (c 0.75, $CHCl_3$)); IR ν_{max} 2961, 2928, 2875, 2707, 1688, 1644, 1457, 1405, 1379, 1313, 1243, 1201, 1128, 1051, 1015, 874, 827, 805, 675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.38 (s, 1H), 6.21 (dd, J = 1.2, 10.1 Hz, 1H), 2.75−2.86 (m, 1H), 1.72−1.78 (m, 3H), 1.10−1.39 (m, 5H), 1.03 (d, J = 6.7 Hz, 3H), 0.81−0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.8, 161.0, 138.0, 44.1, 32.5, 31.4, 30.1, 20.5, 19.2, 11.4, 9.5.

*(S)-3,7-Dimethyloct-6-en-1-yl Methanesulfonate (**12**).* According to a literature procedure,[21] compound **12**[22] (4.67 g, 100%) was prepared from (*S*)-citronellol (**11**) (3.63 mL, 20.00 mmol), MsCl (1.6 mL, 21.00 mmol), and NEt_3 (2.9 mL, 21.00 mmol) as a yellow oil; R_f = 0.55 (hexane/EtOAc 5:1); $[\alpha]^{24}_D$ −2.11 (c 1.00, $CHCl_3$); IR ν_{max} 2964, 2914, 2859, 1456, 1378, 1351, 1333, 1171, 1036, 973, 938, 889, 818, 796, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.04−5.11 (m, 1H), 4.21−4.32 (m, 2H), 3.00 (s, 3H), 1.90−2.07 (m, 2H), 1.75−1.85 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.50−1.65 (m, 2H), 1.30−1.40 (m, 1H), 1.15−1.25 (m, 1H), 0.93 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 131.8, 124.4, 68.7, 37.5, 36.9, 36.0, 29.1, 25.9, 25.4, 19.3, 17.8.

*(R)-2,6-Dimethyloct-2-ene (**13**).* According to a literature protocol,[23] compound **13** (6.13 g, 100%) was prepared from **12** (10.30 g, 43.95 mmol) and $LiAlH_4$ (3.34 g, 88.00 mmol) as a clear oil; R_f = 0.89 (hexane); $[\alpha]^{24}_D$ −6.2 (c 1.00, $CHCl_3$) (lit.[24] $[\alpha]^{25}_D$ −7.55 (neat)); IR ν_{max} 2963, 2915, 2875, 2853, 1456, 1377, 833 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.06−5.14 (m, 1H), 1.89−2.04 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.28−1.39 (m, 3H), 1.08−1.18 (m, 2H), 0.86 (d, J = 6.3 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 131.1, 125.3, 36.9, 34.2, 29.6, 25.9, 25.8, 19.3, 17.8, 11.5.

*(R)-4-Methylhexanoic Acid (**14**).* According to a modified literature protocol,[11] a solution of alkene **13** (6.15 g, 43.65 mmol) in CH_2Cl_2 p.a. (130 mL) was treated with acetonitrile p.a. (130 mL), H_2O (170 mL), $NaIO_4$ (37.35 g, 174.60 mmol), and $RuCl_3 \times H_2O$ (181 mg, 873 μmol, 2 mol %), and the mixture was stirred at ambient temperature for 18 h. $Na_2S_2O_3$ (3 g) was added, and the mixture was stirred for 15 min. The solids were filtered off, and the filtrate was concentrated in vacuo. A 1 M aqueous NaOH (100 mL) solution was added, and the resulting mixture was washed with diethyl ether (2 × 200 mL). The aqueous phase was acidified with 1 M aqueous HCl (175 mL), and the brown mixture was extracted with diethyl ether (3 × 200 mL). The combined organic phases were washed with aqueous $Na_2S_2O_3$ (20% wt, 2 × 150 mL) and brine (150 mL), dried (Na_2SO_4), and concentrated in vacuo to give acid **14** (3.66 g, 64%) as a brownish oil; R_f = 0.61 (hexane/EtOAc 4:1); $[\alpha]^{24}_D$ −10.9 (c 1.00, $CHCl_3$) (lit.[25] $[\alpha]^{10}_D$ −10.1 (c 1.00, $CHCl_3$)); IR ν_{max} 3042, 2962, 2931, 2876, 2654, 1705, 1463, 1413, 1380, 1281, 1250, 1216, 936 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.45 (br. s, 1H), 2.27−2.44 (m, 2H), 1.63−1.74 (m, 1H), 1.40−1.50 (m, 1H), 1.30−1.40 (m, 2H), 1.12−1.22 (m, 1H), 0.88 (d, J = 6.4 Hz, 3H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.6, 34.1, 32.0, 31.3, 29.2, 18.9, 11.4.

*(R)-4-Benzyl-3-((R)-4-methylhexanoyl)oxazolidin-2-one (**15**).* According to a literature procedure,[9] compound **15** (526 mg, 88%) was prepared from **14** (268 mg, 2.06 mmol), pivaloyl chloride (0.27 mL, 2.16 mmol), and (*R*)-benzyloxazolidin-2-one (383 mg, 2.16 mmol) as a colorless solid; R_f = 0.64 (hexane/EtOAc 4:1); $[\alpha]^{24}_D$ −56.9 (c 1.00, $CHCl_3$) (lit.[26] $[\alpha]^{27}_D$ −57.5 (c 1.00, $CHCl_3$)); mp 36−37 °C; IR ν_{max} 2961, 2925, 2874, 1777, 1698, 1455, 1384, 1351, 1324, 1280, 1210, 1194, 1138, 1097, 1052, 1015, 761, 741, 700, 628, 595, 564 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31−7.36 (m, 2H), 7.27−7.30 (m, 1H), 7.19−7.23 (m, 2H), 4.64−4.71 (m, 1H), 4.20 (dd, J = 7.6, 9.0 Hz, 1H), 4.16 (dd, J = 3.0, 9.0 Hz, 1H), 3.30 (dd, J = 3.3, 13.3 Hz, 1H), 2.99 (ddd, J = 5.4, 10.0, 16.7 Hz, 1H), 2.89 (ddd, J = 5.7, 9.8, 16.7 Hz, 1H), 2.76 (dd, J = 9.6, 13.3 Hz, 1H), 1.66−1.76 (m, 1H), 1.47−1.55 (m, 1H), 1.35−1.47 (m, 2H), 1.15−1.24 (m, 1H), 0.92 (d, J = 6.4 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.9, 153.6, 135.5, 129.6, 129.1, 127.5, 66.3, 55.3, 38.1, 34.1, 33.5, 31.0, 29.4, 19.1, 11.5.

*(R)-4-Benzyl-3-((2R,4R)-2,4-dimethylhexanoyl)oxazolidin-2-one (**16**).* According to a literature procedure,[9] compound **16** (5.63 g, 90%) was prepared from **15** (5.98 g, 20.65 mmol) as a colorless solid of mp 32−33 °C; R_f = 0.54 (hexane/EtOAc 7:1); $[\alpha]^{24}_D$ −66.6 (c 1.00, $CHCl_3$) (lit.[27] $[\alpha]^{27}_D$ −68.6 (c 4.13, $CHCl_3$)); IR ν_{max} 2962, 2929, 2875, 1775, 1695, 1455, 1384, 1349, 1290, 1239, 1207, 1098, 1075, 1052, 1015, 971, 917, 761, 739, 701, 625, 593 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30−7.36 (m, 2H), 7.26−7.30 (m, 1H), 7.19−7.24 (m, 2H), 4.65−4.71 (m, 1H), 4.20 (dd, J = 7.4, 9.0 Hz, 1H), 4.17 (dd, J = 2.8, 9.0 Hz, 1H), 3.82−3.92 (m, 1H), 3.26 (dd, J = 3.1, 13.3 Hz, 1H), 2.76 (dd, J = 9.6, 13.3 Hz, 1H), 1.85 (ddd, J = 5.5, 8.6, 13.2 Hz, 1H), 1.29−1.43 (m, 2H), 1.22 (d, J = 6.8 Hz, 3H), 1.09−1.20 (m, 2H), 0.86 (d, J = 6.4 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.6, 153.2, 135.5, 129.6, 129.1, 127.5, 66.1, 55.5, 40.6, 38.0, 35.5, 32.4, 29.6, 19.5, 18.5, 11.4.

*(2R,4R)-2,4-Dimethylhexan-1-ol (**17**).* According to a literature procedure,[28] alcohol **17** (2.11 g, 95%) was prepared from **16** (5.19 g, 17.10 mmol) and $LiBH_4$ (4 M in THF, 4.9 mL, 19.67 mmol) as a clear oil; R_f = 0.33 (hexane/EtOAc 5:1); $[\alpha]^{24}_D$ +4.7 (c 1.00, $CHCl_3$) (lit. $[\alpha]_D$ +3.7 (c 1.67, $CHCl_3$)); IR ν_{max} 3342, 2959, 2915, 2875, 1462, 1378, 1028, 986, 612 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.48−3.56 (m, 1H), 3.34−3.42 (m, 1H), 1.66−1.76 (m, 1H), 1.40−1.48 (m, 1H), 1.35−1.40 (m, 1H), 1.24−1.35 (m, 2H), 1.03−1.13 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.90 (s, 1H), 0.87 (d, J = 6.5 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 68.6, 40.7, 33.3, 31.7, 29.2, 19.9, 17.4, 11.3.

*Triphenyl(1-ethoxycarbonylethyl)phosphorane (**19**).* According to literature procedure,[29] ylide **19**[30] (10.13 g, 50.00 mmol, 64%) was prepared as a beige solid from 2-bromoethyl propanoate (6.5 mL, 50.00 mmol) and PPh_3 (13.12 g, 50.00 mmol); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44−7.63 (m, 15H), 3.56−4.00 (m, 2H), 1.61 (d, J = 13.7 Hz, 3H), 0.22−0.92 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.8, 133.7, 131.7, 128.6, 128.5, 57.6, 12.8; IR ν_{max} 3055, 2979, 2927, 1626, 1589, 1571, 1484, 1435, 1381, 1365, 1310, 1298, 1185, 1158, 1087, 1071, 1029, 998, 950, 861, 773, 760, 747, 714, 692, 618, 576 cm^{-1}.

*Ethyl (4R,6R,E)-2,4,6-Trimethyloct-2-enoate (**20**).* According to a modified literature procedure,[12] a cooled (−78 °C) solution of oxalyl chloride (2.2 mL, 25.87 mmol) in CH_2Cl_2 (27 mL) was treated with a solution of dimethyl sulfoxide (2.9 mL, 40.43 mmol) in CH_2Cl_2 (13.5 mL), and the mixture was stirred at −78 °C for 30 min. A solution of alcohol **17** (2.11 g, 16.17 mmol) in CH_2Cl_2 (13.5 mL) was added, and stirring was continued at −78 °C for 30 min. NEt_3 (11.2 mL, 80.85 mmol) was added, and the mixture was stirred at −78 °C for 1 h before it was warmed to ambient temperature and stirred for 1 h. Then 1 M aqueous HCl (100 mL) was added, and the mixture was extracted with *n*-pentane (3 × 100 mL). The combined organic phases were washed with H_2O (100 mL), dried (Na_2SO_4), and concentrated in vacuo to give aldehyde **18** as a pale-yellow liquid that was used in the next step without purification.

A solution of aldehyde **18** (2.07 g, 16.17 mmol) in CH_2Cl_2 p.a. (35 mL) was treated with $Ph_3P{=}C(CH_3)CO_2Et$ (**19**) (8.79 g, 24.26 mmol), and the mixture was stirred at ambient temperature for 19 h.

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The solvent was removed in vacuo to give a brownish oil that was purified by flash chromatography (silica gel, 2% diethyl ether in hexane) to give ester **20** (2.41 g, 70% over two steps) as an 98:2 mixture of *E*/*Z* isomers as a pale yellow liquid; R_f = 0.34 (2% diethyl ether in hexane); IR ν_{max} 2961, 2929, 2875, 1710, 1650, 1462, 1367, 1311, 1271, 1249, 1217, 1152, 1099, 1035, 991, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.50 (d, J = 9.8 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 2.56−2.64 (m, 1H), 1.84 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.20−1.34 (m, 3H), 1.08−1.18 (m, 2H), 0.98 (d, J = 6.4 Hz, 3H), 0.80−0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.7, 148.4, 126.3, 60.5, 44.3, 32.4, 31.0, 30.2, 20.7, 19.1, 14.4, 12.6, 11.4.

*(4R,6R,E)-2,4,6-Trimethyloct-2-en-1-ol (**21**).* [16] According to a modified literature procedure,[12] a cooled (−78 °C) solution of ester **20** (2.29 g, 10.79 mmol) in CH_2Cl_2 (36 mL) was treated with DIBAL-H (1 M in hexane, 27 mL, 26.98 mmol) using a syringe pump (2 mL/min). The mixture was stirred at −78 °C for 1 h, treated with aqueous citric acid (20% wt, 150 mL), stirred at room temperature for 20 min, and then extracted with ethyl acetate (3 × 150 mL). The combined organic phases were washed with aqueous citric acid (20% wt, 100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to give a clear oil which was purified by flash chromatography (silica gel, 15% ethyl acetate in hexane) to afford alcohol **21** (1.66 g, 90%) as a clear oil; R_f = 0.31 (16% ethyl acetate in hexane); $[\alpha]^{24}_D$ −27.9 (c 1.00, $CHCl_3$); IR ν_{max} 3315, 2959, 2923, 2871, 1457, 1378, 1010, 850, 618 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.12 (dd, J = 1.2, 9.5 Hz, 1H), 3.99 (d, J = 5.8 Hz, 2H), 2.43−2.55 (m, 1H), 1.68 (d, J = 1.2 Hz, 3H), 1.23−1.31 (m, 3H), 1.01−1.16 (m, 2H), 0.92 (d, J = 6.7 Hz, 3H), 0.80−0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.25, 133.16, 69.3, 44.9, 32.2, 30.2, 29.7, 21.8, 19.3, 14.0, 11.4.

*Ethyl (2E,4E,6R,8R)-4,6,8-Trimethyldeca-2,4-dienoate (**23**).* According to a literature procedure,[12] compound **23** (990 mg, 68%) was prepared from **10** (1.03 g, 6.09 mmol) and Ph_3PCHCO_2Et (**22**) (4.24 g, 12.18 mmol) as a colorless oil; R_f = 0.32 (6% ethyl acetate in hexane); $[\alpha]^{24}_D$ −66.6 (c 1.00, $CHCl_3$) (lit.[12] $[\alpha]^{22.5}_D$ −41.8 (c 1.00, $CHCl_3$)); IR ν_{max} 2961, 2926, 2874, 1713, 1623, 1461, 1393, 1366, 1289, 1260, 1239, 1162, 1131, 1096, 1033, 982, 846 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31 (d, J = 15.6 Hz, 1H), 5.78 (d, J = 15.6 Hz, 1H), 5.63 (d, J = 9.8 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.58−2.70 (m, 1H), 1.76−1.80 (m, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.19−1.35 (m, 3H), 1.07−1.17 (m, 2H), 0.96 (d, J = 6.7 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8, 150.1, 148.9, 131.3, 115.6, 60.3, 44.6, 32.5, 31.0, 30.3, 21.2, 19.2, 14.5, 12.4, 11.4.

*(2E,4E,6R,8R)-4,6,8-Trimethyldeca-2,4-dien-1-ol (**24**).* Analogously to **21**, alcohol **24** (383 mg, 98%) was prepared as a colorless oil from ester **23** (477 mg, 2.00 mmol) and DIBAL-H (1 M in hexane, 5.0 mL, 5.00 mmol); R_f = 0.15 (16% ethyl acetate in hexane); $[\alpha]^{24}_D$ −40.3 (c 1.00, $CHCl_3$) (lit.[12] $[\alpha]^{22.5}_D$ −37.1 (c 1.00, $CHCl_3$)); IR ν_{max} 3313, 2960, 2923, 2871, 1651, 1457, 1377, 1097, 1024, 995, 964, 872, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.25 (qd, J = 0.8, 15.6 Hz, 1H), 5.71 (td, J = 6.1, 15.6 Hz, 1H), 5.23 (d, J = 9.8 Hz, 1H), 4.20 (dd, J = 0.8, 6.1 Hz, 2H), 2.53−2.65 (m, 1H), 1.76 (d, J = 1.2 Hz, 3H), 1.36 (br. s, 1H), 1.20−1.32 (m, 3H), 1.03−1.18 (m, 2H), 0.93 (d, J = 6.7 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H), 0.81 (d, J = 6.41 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.7, 137.4, 131.3, 125.1, 64.2, 45.0, 32.4, 30.4, 30.3, 21.7, 19.2, 12.8, 11.5.

*(2E,4E,6R,8R)-4,6,8-Trimethyldeca-2,4-dienal (**25**).* Analogously to **10**, aldehyde **25** (363 mg, 96%) was prepared as a colorless oil from alcohol **24** (383 mg, 1.95 mmol) and MnO_2 (3.39 g, 39.02 mmol); R_f = 0.55 (16% ethyl acetate in hexane); $[\alpha]^{24}_D$ −47.3 (c 1.00, $CHCl_3$) (lit.[12] $[\alpha]^{22.5}_D$ −61.4 (c 1.00, $CHCl_3$)); IR ν_{max} 2961, 2925, 2873, 2722, 1680, 1623, 1605, 1456, 1379, 1315, 1127, 1010, 969, 822, 595 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 9.55 (d, J = 7.9 Hz, 1H), 7.11 (d, J = 15.6 Hz, 1H), 6.09 (dd, J = 7.9, 15.6 Hz, 1H), 5.76 (d, J = 9.8 Hz, 1H), 2.62−2.74 (m, 1H), 1.83 (d, J = 1.2 Hz, 3H), 1.19−1.39 (m, 3H), 1.10−1.19 (m, 2H), 1.00 (d, J = 6.7 Hz, 3H), 0.85 (t, J = 7.3 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.4, 158.4, 151.3, 132.0, 126.9, 44.5, 32.5, 31.3, 30.2, 21.1, 19.2, 12.6, 11.4.

*2,2-Dimethyl-5-(triphenylphosphoranylidene)acetyl-1,3-dioxan-4,6-dione (**26**).* According to a literature procedure,[13] ylide **26** (2.31 g, 56%) was prepared as a colorless solid from Meldrum's acid (1.32 g, 9.18 mmol) and ketenylidenetriphenylphosphorane (2.78 g, 9.18 mmol); IR ν_{max} 3062, 2984, 1685, 1626, 1587, 1573, 1548, 1516, 1375, 1314, 1272, 1258, 1204, 1175, 1158, 1104, 1055, 1029, 996, 985, 935, 86, 798, 783, 757, 747, 723, 716, 692, 659, 651, 579 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 13.53 (dd, J = 0.8, 2.9 Hz, 1H), 7.60−7.69 (m, 9H), 7.49−7.55 (m, 6H), 5.76 (dd, J = 2.9, 21.7 Hz, 1H), 1.70 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.9, 133.3 (d, J = 10.9 Hz), 133.0 (d, J = 2.7 Hz), 129.3 (d, J = 11.8 Hz), 124.9 (d, J = 91.7 Hz), 102.4, 57.0 (d, J = 108.1 Hz), 26.4.

*(5S,3Z)-5-(4-((tert-Butyldimethylsilyl)oxy)benzyl)-3-((2E,4E,6E,8R,10R)-1-hydroxy-6,8,10-trimethyldodeca-2,4,6-trien-1-ylidene)-1-(2-nitrobenzyl)pyrrolidine-2,4-dione (**28a**) and (5S,3Z)-5-(4-((tert-Butyldimethylsilyl)oxy)benzyl)-1-(2,4-dimethoxybenzyl)-3-((2E,4E,6E,8R,10R)-1-hydroxy-6,8,10-trimethyldodeca-2,4,6-trien-1-ylidene)pyrrolidine-2,4-dione (**28b**).* (A) A suspension of ylide **26** (790 mg, 1.77 mmol) and KO^{t}Bu (199 mg, 1.77 mmol) in THF (20 mL) was treated with a solution of aldehyde **25** (344 mg, 1.77 mmol) in THF (15 mL), and the resulting mixture was heated at reflux for 22 h. It was concentrated in vacuo, and the remainder was taken up in CH_2Cl_2 (150 mL) and sat. aqueous $NaHCO_3$ (100 mL). The phases were separated, and the organic one was washed with sat. aqueous $NaHCO_3$ (2 × 150 mL) and 1 M aqueous HCl (100 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give an inseparable mixture of 42% of Meldrum's acid derivative **8**, 42% PPh_3O, and 16% residual ylide **26**. It was taken up in acetonitrile p.a. (30 mL), and the resulting solution was split in two 15 mL portions which were used in the next step without further purification.

(B) The first 15 mL portion was treated with *o*Nb-L-Tyr(OTBS)-OMe **7a** (326 mg, 734 μmol, 1.00 equiv), the resulting mixture was heated at reflux for 1 h, and all volatiles were removed in vacuo to leave an orange oil that was purified by flash chromatography (silica gel, 30% EtOAc in hexane, R_f = 0.67) to give β-ketoamide **27a** as a yellow oil (161 mg, 30% over two steps) that was used in the next step without further purification.

The second 15 mL portion was reacted analogously with DMB-L-Tyr(OTBS)-OMe **7b** (381 mg, 829 μmol, 1.13 equiv) to give β-ketoamide **27b** as a yellow oil (120 mg, 25% over two steps) that was also used in the next step without further purification; R_f = 0.57 (30% EtOAc in hexane). (C) A solution of β-ketoamide **27a** (161 mg, 228 μmol) in methanol p.a. (23 mL) was treated with sodium methoxide (62 mg, 1.140 mmol), and the resulting mixture was stirred at ambient temperature for 15 min. A 1 M aqueous HCl (15 mL) solution and brine (10 mL) were added, and the mixture was extracted with EtOAc (2 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to afford tetramic acid **28a** as a foamy orange yellow solid (152 mg, quant); R_f = 0.15 (30% EtOAc in hexane); $[\alpha]^{24}_D$ −415 (c 0.50, $CHCl_3$); IR ν_{max} 2957, 2927, 2857, 1698, 1645, 1626, 1592, 1556, 1525, 1510, 1443, 1353, 1338, 1305, 1259, 1173, 1120, 1001, 920, 875, 857, 839, 809, 781, 749, 727, 688, 608, 571 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.02 (dd, J = 1.2, 8.2 Hz, 1H), 7.58 (ddd, J = 1.2, 7.6, 7.6 Hz, 1H), 7.53 (dd, J = 11.3, 15.0 Hz, 1H), 7.44 (ddd, J = 1.2, 7.6, 8.2 Hz, 1H), 7.31 (dd, J = 1.2, 7.6 Hz, 1H), 7.17 (d, J = 15.0 Hz, 1H), 6.87 (d, J = 8.5 Hz, 2H), 6.69 (d, J = 15.3 Hz, 1H), 6.64 (d, J = 8.5 Hz, 2H), 6.43 (dd, J = 11.3, 15.3 Hz, 1H), 5.56 (d, J = 9.8 Hz, 1H), 5.22 (d, J = 17.1 Hz, 1H), 4.72 (d, J = 17.1 Hz, 1H), 4.00 (dd, J = 4.3, 5.2 Hz, 1H), 3.14 (dd, J = 4.3, 14.7 Hz, 1H), 3.04 (dd, J = 5.2, 14.7 Hz, 1H), 2.60−2.71 (m, 1H), 1.82 (s, 3H), 1.20−1.36 (m, 3H), 1.08−1.17 (m, 2H), 0.97 (d, J = 6.4 Hz, 3H), 0.94 (s, 9H), 0.81−0.87 (m, 6H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.7, 174.6, 173.9, 154.8, 149.5, 148.3, 147.9, 146.6, 133.9, 132.9, 132.1, 130.3, 129.4, 128.6, 127.6, 125.4, 125.2, 120.2, 119.8, 99.7, 66.0, 44.7, 41.1, 35.0, 32.5, 31.1, 30.2, 25.8, 21.3, 19.2, 18.3, 12.5, 11.4, −4.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{39}H_{53}N_2O_6Si^+$ 673.3667, found 673.3651.

Analogously, tetramic acid **28b** (113 mg, quant) was obtained as a solid yellow foam from β-ketoamide **27b** (120 mg, 167 μmol) and sodium methoxide (45 mg, 835 μmol); R_f = 0.41 (30% EtOAc in

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hexane); $[\alpha]^{24}_D$ −412 (*c* 0.50, $CHCl_3$); IR ν_{max} 2958, 2928, 2858, 1697, 1609, 1593, 1558, 1509, 1451, 1361, 1260, 1209, 1158, 1131, 1108, 1035, 1000, 915, 838, 782, 686, 610 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.44 (dd, *J* = 11.3, 15.0 Hz, 1H), 7.06−7.12 (m, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 6.64 (d, *J* = 15.3 Hz, 1H), 6.41−6.45 (m, 2H), 6.39 (dd, *J* = 11.3, 15.3 Hz, 1H), 5.51 (d, *J* = 9.8 Hz, 1H), 4.99 (d, *J* = 14.6 Hz, 1H), 4.19 (d, *J* = 14.6 Hz, 1H), 3.83−3.87 (m, 1H), 3.76−3.82 (m, 6H), 3.06−3.14 (m, 2H), 2.59−2.73 (m, 1H), 1.82 (s, 3H), 1.21−1.34 (m, 3H), 1.08−1.16 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.94 (s, 9H), 0.80−0.86 (m, 6H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.8, 173.8, 173.1, 160.9, 158.7, 154.6, 148.5, 147.2, 145.3, 132.9, 131.5, 130.7, 128.1, 125.3, 120.3, 120.1, 116.4, 104.4, 100.6, 98.5, 65.1, 55.51, 55.48, 44.7, 38.4, 34.4, 32.5, 31.0, 30.2, 25.8, 21.4, 19.2, 18.3, 12.5, 11.4, −4.3; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{41}H_{58}NO_6Si^+$ 688.4028, found 688.4031.

*Ethyl (2E,4E,6E,8R,10R)-6,8,10-Trimethyldodeca-2,4,6-trienoate (**31**).* According to a literature procedure,[16] ester **31** (248 mg, 67%) was prepared as a colorless oil from aldehyde **10** (235 mg, 1.394 mmol) and phosphonate **30** (1.12 g, 4.46 mmol); R_f = 0.40 (6% EtOAc in hexane); $[\alpha]^{24}_D$ −51.7 (*c* 1.00, $CHCl_3$) (lit.[16] $[\alpha]^{19}_D$ −41.8 (*c* 1.00, $CHCl_3$)); IR ν_{max} 2960, 2925, 2872, 1710, 1613, 1457, 1392, 1367, 1329, 1304, 1256, 1234, 1201, 1178, 1136, 1096, 1039, 996, 861, 718 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34 (dd, *J* = 11.0, 15.3 Hz, 1H), 6.56 (d, *J* = 15.3 Hz, 1H), 6.22 (dd, *J* = 11.0, 15.3 Hz, 1H), 5.85 (d, *J* = 15.3 Hz, 1H), 5.44 (d, *J* = 9.8 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.55−2.69 (m, 1H), 1.80 (d, *J* = 1.2 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.20−1.33 (m, 3H), 1.07−1.17 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.80−0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.5, 146.4, 145.6, 145.5, 132.3, 123.8, 119.6, 60.3, 44.8, 32.4, 30.8, 30.2, 21.5, 19.2, 14.5, 12.6, 11.4.

*(2E,4E,6E,8R,10R)-6,8,10-Trimethyldodeca-2,4,6-trien-1-ol (**32**).* Analogously to **21**, alcohol **32** (179 mg, 85%) was prepared as a colorless cloudy oil from ester **31** (226 mg, 948 μmol) and DIBAL-H (1 M in hexane, 2.4 mL, 2.40 mmol) in 179 mg (85%); R_f = 0.19 (16% EtOAc in hexane); $[\alpha]^{24}_D$ −37.5 (*c* 1.00, $CHCl_3$) (lit.[16] $[\alpha]^{20}_D$ −28.8 (*c* 1.00, $CHCl_3$)); IR ν_{max} 3306, 3024, 2959, 2922, 2870, 1625, 1455, 1376, 1309, 1087, 982, 842 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.10−6.33 (m, 3H), 5.82 (td, *J* = 6.1, 15.2 Hz, 1H), 5.25 (d, *J* = 9.5 Hz, 1H), 4.19 (d, *J* = 6.1 Hz, 2H), 2.54−2.65 (m, 1H), 1.77 (d, *J* = 1.2 Hz, 3H), 1.22−1.31 (m, 3H), 1.04−1.16 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.79−0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.3, 138.9, 132.7, 132.1, 130.6, 125.3, 63.8, 45.0, 32.4, 30.5, 30.3, 21.7, 19.2, 12.7, 11.5.

*(2E,4E,6E,8R,10R)-6,8,10-Trimethyldodeca-2,4,6-trienal (**33**).* Analogously to **10**, aldehyde **33** (150 mg, 92%) was prepared as a yellowish oil from alcohol **32** (165 mg, 742 μmol) and MnO_2 (1.29 g, 14.84 mmol); R_f = 0.68 (16% EtOAc in hexane); $[\alpha]^{24}_D$ −49.4 (*c* 0.50, $CHCl_3$); IR ν_{max} 2960, 2925, 2874, 2730, 1676, 1603, 1457, 1377, 1315, 1159, 1129, 1114, 1009, 984, 858, 647 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.55 (d, *J* = 7.9 Hz, 1H), 7.15 (dd, *J* = 11.0, 15.3 Hz, 1H), 6.68 (d, *J* = 15.3 Hz, 1H), 6.36 (dd, *J* = 11.0, 15.3 Hz, 1H), 6.16 (dd, *J* = 8.1, 15.1 Hz, 1H), 5.55 (d, *J* = 9.8 Hz, 1H), 2.60−2.72 (m, 1H), 1.83 (d, *J* = 1.2 Hz, 3H), 1.21−1.35 (m, 3H), 1.09−1.17 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.80−0.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.9, 153.5, 148.6, 147.5, 132.4, 130.5, 124.0, 44.7, 32.5, 31.0, 30.2, 21.4, 19.2, 12.6, 11.4; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{25}O^+$ 221.1900, found 221.1901.

*S-tert-Butyl-4-(diethoxyphosphoryl)-3-oxopentanethioate (**34**).* According to a literature procedure,[17] phosphonate **34**[31] (4.32 g, 59%) was prepared from bromopropionyl bromide (2.3 mL, 22.30 mmol) and Meldrum's acid (2.900 g, 20.20 mmol) as a pale orange oil and as a keto/enol mixture (5.6:1); IR ν_{max} 2966, 1723, 1674, 1614, 1478, 1456, 1398, 1365, 1314, 1250, 1163, 1016, 959, 836, 789, 688, 644, 591 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 13.01−13.06 (m, 1H), 5.42−5.47 (m, 1H), 4.06−4.16 (m, 4H), 4.03 (d, *J* = 15.3 Hz, 1H), 3.72 (d, *J* = 15.3 Hz, 1H), 3.46 (qd, *J* = 7.0, 26.2 Hz, 1H), 2.67 (qd, *J* = 7.3, 23.5 Hz, 1H), 1.41−1.50 (m, 9H), 1.35 (d, *J* = 7.0 Hz, 1H), 1.29−1.33 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.3 (d, *J* = 4.5 Hz), 192.9, 171.6 (d, *J* = 6.4 Hz), 101.0 (d, *J* = 7.3 Hz), 62.9 (dd, *J* = 18.2, 7.3 Hz), 58.3, 49.2, 48.5, 47.2 (d, *J* = 126.3 Hz), 38.9 (d, *J* = 135.3 Hz), 30.2, 29.7, 16.5 (d, *J* = 8.2 Hz), 12.7 (d, *J* = 5.4 Hz), 10.7 (d, *J* = 6.4 Hz).

*(5S,3Z)-5-(4-((tert-Butyldimethylsilyl)oxy)benzyl)-1-(2,4-dimethoxybenzyl)-3-((2E,4E,6E,8E,10R,12R)-1-hydroxy-2,8,10,12-tetramethyltetradeca-2,4,6,8-tetraen-1-ylidene)pyrrolidine-2,4-dione (**36**).* A mixture of thioester **9** (100 mg, 256 μmol), THF (3.2 mL), and 4 Å molecular sieves (powdered, 40 mg) was cooled to 0 °C and treated with a solution of DMB-L-Tyr(OTBS)-OMe **7b** (130 mg, 282 μmol), NEt_3 (0.14 mL, 1.024 mmol), and silver trifluoroacetate (113 mg, 512 μmol) in THF (3.2 mL). The mixture was stirred at 0 °C under exclusion of light for 2.5 h, diluted with diethyl ether (100 mL), and filtered over Celite. The filtrate was washed with sat. aqueous NH_4Cl (75 mL) and brine (75 mL), dried (Na_2SO_4), and concentrated in vacuo to give an orange oil. It was purified by flash chromatography (silica gel, 50% EtOAc in hexane; R_f = 0.76) to give β-ketoamide **35** as a yellow oil (173 mg, 89%) that was used in the next step without further purification. A solution of β-ketoamide **35** (159 mg, 209 μmol) in methanol (21 mL) was treated with sodium methoxide (56 mg, 1.05 mmol), and the mixture was stirred at ambient temperature for 20 min. Saturated aqueous NH_4Cl (40 mL) and 1 M aqueous HCl (30 mL) were added, the mixture was extracted with EtOAc (100 mL), and the organic phase was dried (Na_2SO_4) and concentrated in vacuo to give bisprotected fumosorinone A (**36**) as a red gum (149 mg, quant); R_f = 0.56 (50% EtOAc in hexane); $[\alpha]^{24}_D$ −367.1 (*c* 0.75, $CHCl_3$); IR ν_{max} 2958, 2928, 2859, 1652, 1611, 1590, 1544, 1508, 1452, 1389, 1361, 1255, 1209, 1171, 1158, 1119, 1034, 988, 913, 837, 807, 781, 725, 687, 640, 605, 578 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, *J* = 11.6 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.68−6.75 (m, 3H), 6.57 (dd, *J* = 11.6, 14.3 Hz, 1H), 6.41−6.49 (m, 3H), 6.31 (dd, *J* = 10.7, 15.0 Hz, 1H), 5.40 (d, *J* = 9.5 Hz, 1H), 4.99 (d, *J* = 14.6 Hz, 1H), 4.24 (d, *J* = 14.6 Hz, 1H), 3.82−3.86 (m, 1H), 3.78−3.82 (m, 6H), 3.15 (dd, *J* = 4.6, 14.3 Hz, 1H), 3.10 (dd, *J* = 4.0, 14.3 Hz, 1H), 2.56−2.70 (m, 1H), 1.95 (s, 3H), 1.81 (s, 3H), 1.22−1.35 (m, 3H), 1.06−1.17 (m, 2H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.95 (br. s., 9H), 0.85 (dd, *J* = 7.0, 7.6 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.6, 182.7, 175.9, 160.9, 158.7, 154.6, 144.1, 143.2, 142.9, 142.6, 132.7, 131.5, 130.8, 128.21, 128.18, 126.9, 126.3, 120.1, 116.4, 104.4, 99.4, 98.5, 64.5, 55.51, 55.49, 44.9, 38.7, 34.5, 32.4, 30.8, 30.2, 25.8, 21.5, 19.2, 18.3, 12.64, 12.61, 11.4, −4.32, −4.34; HRMS (ESI) *m* /*z* $[M + H]^+$ calcd for $C_{44}H_{62}NO_6Si^+$ 728.4341, found 728.4340.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01530.

NMR spectra of all compounds, HPLC chromatogramms of target compounds **3** and **4**, ECD spectrum of compound **3** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Rainer.Schobert@uni-bayreuth.de. Fax: +49 (0)921 552671.

ORCID

Rainer Schobert: 0000-0002-8413-4342

Notes

The authors declare no competing financial interest.

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