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Total Synthesis of Marine-Derived Azole Resistant Antifungal Agent (–)-Mearoride A and Antibiotic (–)-PF1163B

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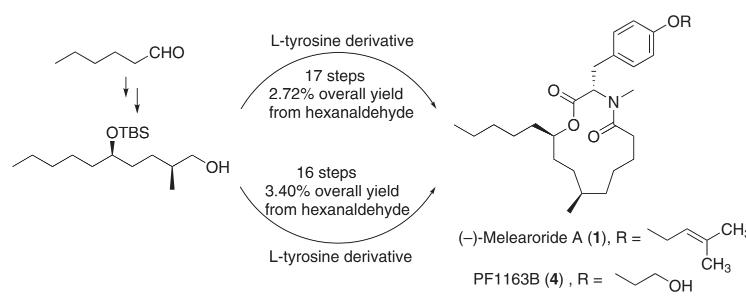

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Abstract A flexible stereoselective and convergent cum divergent approach to the synthesis of two 13-membered macrolides through a common skeleton present in their structure is described featuring two different routes, with good overall yield. The key synthetic reactions utilized include Keck allylation, Evans asymmetric methylation, Grubbs metathesis, and Julia–Kocienski olefination.

Key words macrolides, melearoride A, PF1163B, Julia–Kocienski olefination, ring-closing metathesis

Marine-derived fungi receive significant attention as natural sources of drugs because of their impressive biological activities.[1] During recent decades, the pharmacology of antimycotics has advanced significantly, although common invasive fungal infections are still believed to have a high mortality rate.[2,3] Melearoride-A (**1**), a novel 13-membered macrolide isolated from marine-derived fungus *Penicillium meleagrinum* var. *viridiflavum* by Koyama and co-workers in 2016 has been demonstrated to show synergic effects with fluconazole against azole-resistant *Candida albicans*.[4] The structure of **1** was elucidated from spectroscopic data (NMR, MS, IR). PF1163B (**2**), another 13-membered macrolide (Figure 1) was isolated along with PF1163A as new antifungal antibiotics from the *Penicillium sp*., by Sasaki and co-workers.[5,6] The structure of PF1163B has been deduced by chemical and X-ray crystallographic analyses, and was observed to be the first known inhibitor of ERG25p, a C-4 methyl oxidase.[7] The antifungal activity of PF1163A was found to be four times higher than that of PF1163B, despite possessing a near identical skeleton except for the presence of an additional hydroxyl group in the side chain of PF1163A. The two macrolides, melearoride-A and PF1163B, are structurally and stereochemically similar and differ in alkyl chain appendage; wherein the phenolic group of the amino acid fragment L-tyrosine is coupled with a different alkyl chain.

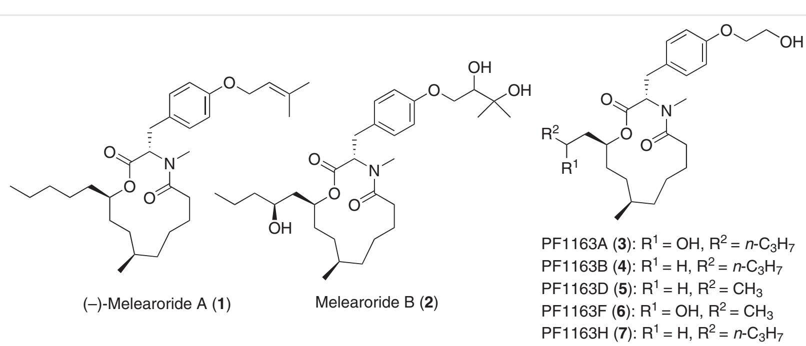
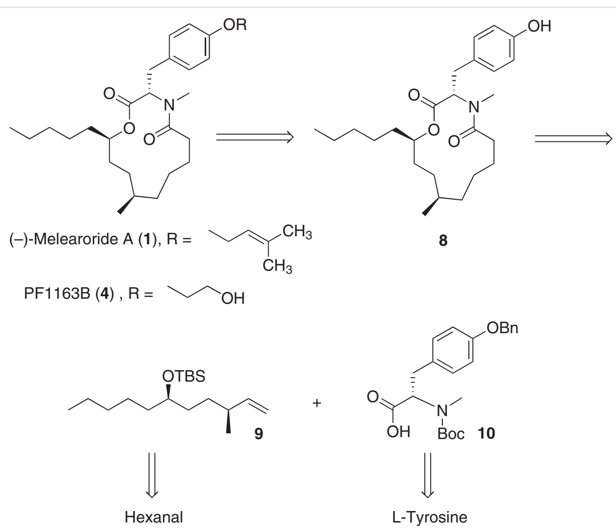


Figure 1 Structures of 13-membered macrolides melearoride-A, B, and members of the PF1163 family

The impressive biological properties and structural architecture of these macrolides have stimulated several synthetic groups and culminated in the synthesis of individual members of this class. To our knowledge, there is only one synthesis on melearoride A[8] and three reported synthetic routes for PF1163B.[9–11]

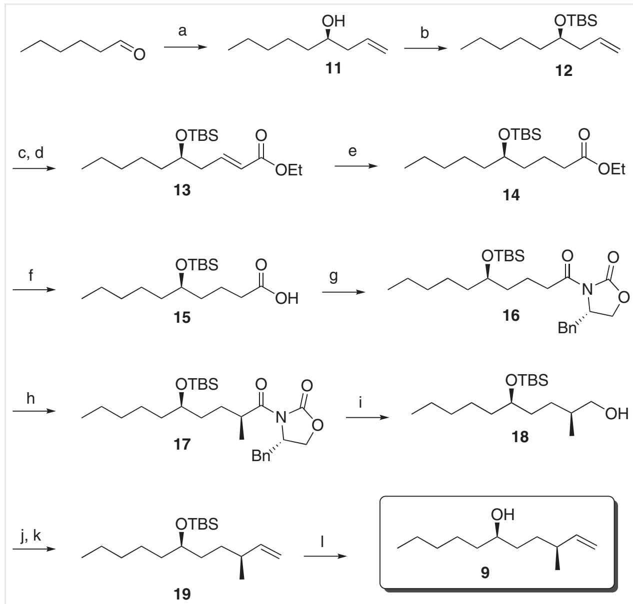
In a continuation of our interest in the total synthesis of biologically active natural products,[12] we report herein the stereoselective synthesis of two 13-membered macrolides, melearoride-A and PF1163B, by following a similar strategy and by two different approaches.

Our retrosynthetic analysis (Scheme 1) revealed a common macrocyclic core **8**, which can be alkylated with 1-bromo-3-methylbut-2-ene or a 2-haloethan-1-ol derivative to furnish the corresponding alkylated ethers melearoride A and PF1163B, respectively. The macrocyclic framework **8** could be obtained from two key fragments, **9** and **10**. While the latter can be synthesized from readily available amino acid L-tyrosine, **9** can be synthesized from commercially available *n*-hexanal through a sequence of synthetic transformations involving Keck allylation, cross-metathesis and auxiliary-based chiral alkylation reaction.



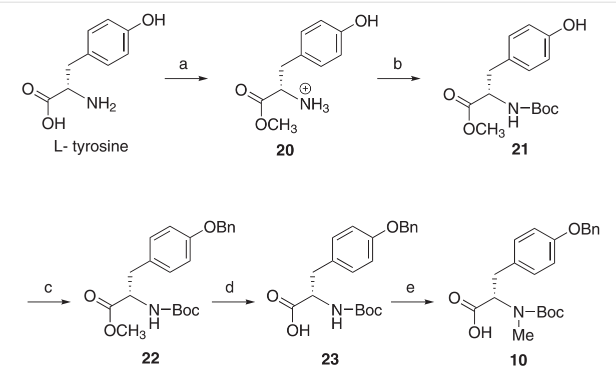
Scheme 1 Retrosynthetic analysis for **1** and **4**

Our synthetic efforts began with the synthesis of precursor building block **9** from commercially available *n*-hexanal. Initially, *n*-hexanal was subjected to Keck asymmetric allylation to afford homallylic alcohol **11** (Scheme 2).[13] The TBS protected homo allylic alcohol **12**,[14] on ozonolysis followed by C-2 Wittig reaction, provided the unsaturated ester **13** in 85% yield over two steps. The unsaturated ester **13**, on reduction with $NaBH_4$ and $NiCl_2·6H_2O$ in methanol, gave saturated ester **14**.[15] Ester **14**, on hydrolysis with $LiOH·H_2O$ in THF/H_2O (3:1), afforded acid **15**, which was used for *N*-acylation of (*S*)-4-benzyl-2-oxazolidinone in the presence of Et_3N, pivaloyl chloride and LiCl in THF to give the corresponding *N*-acyl derivative **16** in 85% yield.[16] Compound **16**, on diastereoselective methylation with CH_3I in the presence of LiHMDS as base, afforded **17** with a 20:1 diastereomeric ratio. Exposure of **17** to $LiBH_4$ provided the primary alcohol **18**,[17] which, upon oxidation with Dess–Martin periodinane in CH_2Cl_2 followed by homologation using the C1 Wittig salt in the presence of n-BuLi, provided alkene **19** in 70% yield over two steps. Finally, deprotection of the TBS protected alcohol under TBAF, THF conditions afforded secondary alcohol fragment **9** in 86% yield.



Scheme 2 Synthesis of **9**. *Reagents and conditions*: (a) (*S*)-BINOL, $TiCl_4$, allyl tributylstannane, Ag_2O, CH_2Cl_2, –15 to 0 °C, 16 h, 85%, 98% ee; (b) TBSCl, imidazole, CH_2Cl_2, 6 h, 96%; (c) O_3, DMS, CH_2Cl_2, 2 h; (d) PPh_3CHCO_2Et, CH_2Cl_2, 4 h, 85% (over two steps) 9:1 (*E*/*Z*); (e) $NiCl_2·6H_2O$, $NaBH_4$, CH_3OH, 1 h, 90%; (f) $LiOH·H_2O$, THF/H_2O (3:1), 2 h, 80%; (g) PivCl, Et_3N, LiCl; (*S*)-4-benzyl-2-oxazolidinone, THF, –20 °C, 4 h, 85%; (h) LiHMDS, CH_3I, THF, 1 h, 80%, 20:1 dr; (i) $LiBH_4$, CH_3CH_2OH, THF, 0 °C to r.t., 86%; (j) DMP, CH_2Cl_2, r.t., 2 h; (k) Ph_3PCH_2Br, n-BuLi, THF, 0 °C to r.t., 70% (over two steps) (l) TBAF, THF, 0 °C to r.t., 86%.

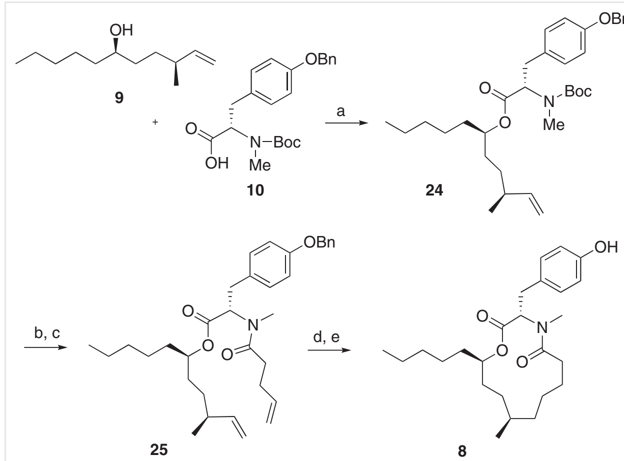
The amino acid fragment **10** was synthesized from commercially available L-tyrosine. Accordingly,L-tyrosine was treated with $SOCl_2$ in methanol under reflux to provide the corresponding methyl ester **20**. Boc protection followed by benzylation was achieved with Boc_2O in the presence of triethylamine and then BnBr in the presence of KI and K_2CO_3 in acetone to provide **21**, followed by **22**, respectively.[18] Ester **22**, upon hydrolysis with LiOH, provided acid **23**, which was subjected to *N*-methylation with MeI and NaH to produce the enantiomerically pure aromatic fragment **10** (Scheme 3).[19]



Scheme 3 Synthesis of **10**. *Reagents and conditions*: (a) $SOCl_2$, CH_3OH, reflux, 3 h, 100%; (b) $(Boc)_2O$, Et_3N, CH_2Cl_2, r.t., overnight, 95%; (c) BnBr, K_2CO_3, KI, acetone, reflux, 6 h, 96%; (d) $LiOH{\cdot}H_2O$, THF/H_2O (3:1), 2 h, 86%; (e) NaH, CH_3I, THF, 6 h, 80%.

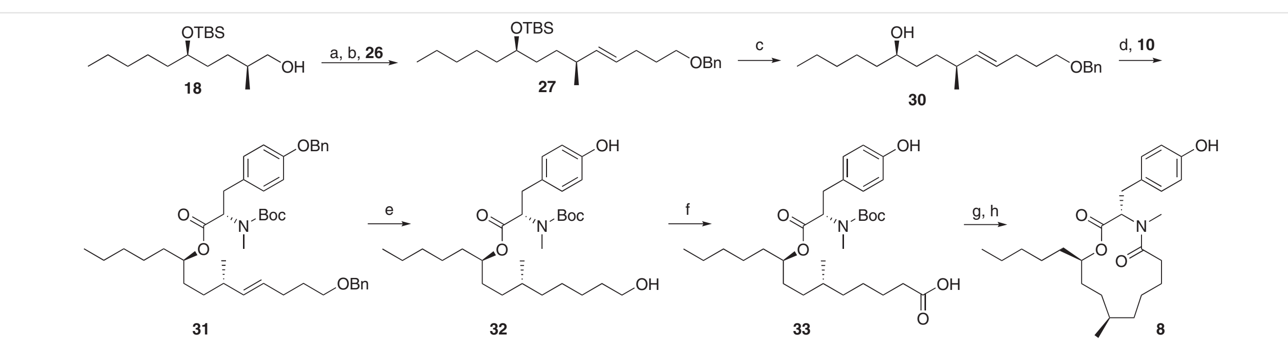
With the two key fragments in hand, we proceeded to the esterification of acid **10** with alcohol **9** under Yamaguchi conditions to afford ester **24** (Scheme 4).[20] Boc deprotection with TFA afforded secondary amine, which was then acylated with pent-4-enoic acid using DIPEA / Pybop to give the corresponding acylated α,ω-diene **25** in 80% yield over two steps. Ring-closing metathesis of diene **25** was achieved in toluene under reflux to provide the requisite macrocycle containing a mixture of (*E*)- and (*Z*)-diastereomers in 70% yield. Since the geometry of the olefin was not of concern, we proceeded to the one-pot reduction of the alkene and debenzylation by hydrogenation with Pd-C in EtOAc to give the desired macrocycle **8** in 85% yield. In this synthetic route, the macrocyclic intermediate **8** was obtained from n-hexanal in 17 steps with 2.7% overall yield.

An alternate strategy to ring-closing metathesis to obtain **8** was also adopted (Scheme 5). Thus, alcohol **18** was oxidized under Dess–Martin periodinane conditions to yield the corresponding aldehyde, which, on Julia–Kocienski olefination with sulfone **26** using KHMDS as base, afforded the alkene **27** as a diastereomeric mixture (*E*/*Z* 14:1) in 80%

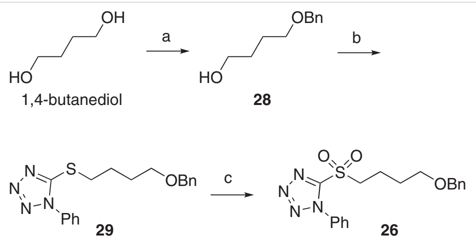


Scheme 4 Synthesis of **8**. *Reagents and conditions*: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 0 °C to r.t., 8 h, 90%; (b) TFA, CH_2Cl_2, 3 h; (c) Pent-4-enoic acid, Pybop, DIPEA, CH_2Cl_2, 6 h, 80% (over two steps); (d) Grubbs' second-generation catalyst (10 mol%), toluene, reflux, 12 h, 70%; (e) H_2, Pd/C, EtOAc, r.t., 85%.

yield.[21] Sulfone **26** was synthesized starting with 1,4-butanediol, which was monoprotected as the corresponding benzyl ether **28** and the alcohol was converted into sulfide **29** under Mitsunobu conditions on treating with 1-phenyl-1*H*-tetrazole-5-thiol (Scheme 6). *m*-CPBA oxidation of sulfide **29** afforded the required sulfone fragment **26** in 90% yield.[22] Deprotection of the TBS group in **27** was achieved with TBAF in THF to provide secondary alcohol **30** in 85% yield (Scheme 5). Esterification of acid **10** with alcohol **30** under Yamaguchi conditions afforded ester **31**. One-pot reduction of the double bond and debenzylation was achieved with Pd-C (10%) in EtOAc, under hydrogen to afford primary alcohol **32** in 80% yield. Then, alcohol **32** was oxidized to acid **33** using BAIB, TEMPO oxidation conditions,[23] in 81% yield. Boc deprotection with TFA followed by intramolecular coupling of acid with secondary amine with DIPEA, PyBOP afforded **8** in 80% yield over two steps.

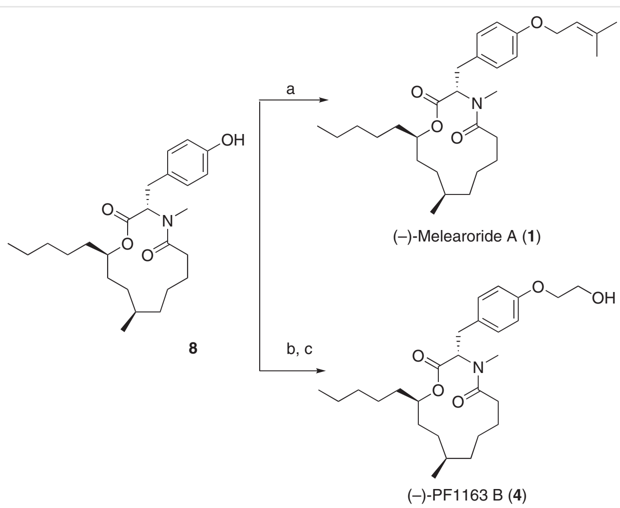


Scheme 5 Alternate approach for the synthesis of **8**. *Reagents and conditions*: (a) DMP, CH_2Cl_2, r.t., 2 h, 76%; (b) **26**, KHMDS, THF, 1 h, –78 °C, 80% (14:1 *E*:*Z* ratio); (c) TBAF, THF, 0 °C to r.t., 85%; (d) **10**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 0 °C to r.t., 8 h, 90%; (e) H_2, Pd/ C, EtOAC, r.t., 80%; (f) BAIB, TEMPO, CH_3CN, pH 7, r.t., 4 h, 81% (g) TFA, CH_2Cl_2, r.t., 3 h; (h) Pybop, DIPEA, CH_2Cl_2, 6 h, 80% (over two steps).



Scheme 6 Synthesis of **26**. *Reagents and conditions*: (a) NaH, BnBr, THF, 4 h, 85% (b) PPh_3, DIAD, 1-phenyl-1*H*-tetrazole-5-thiol, THF, 8 h, 90%; (c) *m*-CPBA, CH_2Cl_2, 16 h, 90%.

In this synthetic route we produced fragment **8** from *n*-hexanal in 16 steps in 3.4% overall yield. Finally, *O*-alkylation of phenol **8** using prenyl bromide with Cs_2CO_3 as base and a catalytic amount of KI in DMF afforded the target molecule (–)-melearoride-A in 90% yield.[24] The broad signals in the ^1H NMR spectrum are attributed to the presence of conformers.[6] Using similar etherification conditions, *O*-alkylation of **8** with 2-bromoethoxy-*tert*-butyldimethylsilane, followed by subsequent TBS deprotection afforded PF1163B in 87% yield over two steps (Scheme 7). The ^1H NMR spectroscopic data of the resulting product were found to be in accordance with previously reported data.[11]



Scheme 7 Synthesis of compound melearoride A (**1**) and PF1163B (**4**). *Reagents and conditions*: (a) K_2CO_3, KI, prenyl bromide, DMF, 4 h, reflux, 90%; (b) (2-bromoethoxy)(*tert*-butyl)dimethylsilane, K_2CO_3, KI, DMF, 4 h, reflux; (c) TBAF, THF, 6 h, 83% (over two steps).

In conclusion, we have accomplished the stereoselective total synthesis of macrolides melearoride A and PF1163B in good overall yields. For the first time, Julia–Kocienski olefination has been applied to extend the C-4 carbon chain in the synthesis of members of this family as an alternative to conventional Grubbs ring-closing metathesis. This strategy allows easy access to various analogues by varying the side chain on the aromatic amino acid fragment for further screening of antifungal and antibiotic properties.

All reagents were used as received from commercial sources unless otherwise noted. All air- and moisture-sensitive reactions were conducted under nitrogen or argon in flame-dried or oven-dried glassware with magnetic stirring. CH_2Cl_2 was stirred over CaH_2 and distilled prior to use. THF was dried with Na/benzophenone and distilled prior to use. Toluene was freshly distilled from CaH_2 before use. Reactions were monitored by thin-layer chromatography, using Merck silica gel 60 F254 and UV light, iodine or *p*-anisaldehyde for visualization. Column chromatography was carried out on silica gel (60–120 mesh or 100–200 mesh). Technical grade ethyl acetate and petroleum ether were used for column chromatography and were distilled prior to use. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on 300 MHz, 400 MHz, 500 MHz or 600 MHz spectrometers. Coupling constants (*J*) are given in Hz. Chemical shifts (δ) are reported in ppm downfield from TMS with use of the residual solvent peak in $CDCl_3$ (H: δ = 7.26 and C: δ = 77.0 ppm) or TMS (δ = 0.0 ppm) as internal standards. Signal patterns are indicated as follows: s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded with a Bruker infrared spectrophotometer and are reported in cm^{-1}. High-resolution mass spectra (HRMS) were recorded with a Waters-TOF. Specific rotations were measured using a 1 mL cell with a 1 dm path length.

(*R*)-Non-1-ene-4-ol (11)

To a solution of $TiCl_4$ (0.54 mL, 5 mmol) in CH_2Cl_2 (100 mL) was added anhydrous $Ti(OiPr)_4$ (4.48 mL, 15 mmol) at 0 °C under argon, and the solution was warmed to r.t. After 1 h, silver(I) oxide (2.3 g, 10 mmol) was added at r.t., and the mixture was stirred for 5 h with the exclusion of direct light. The mixture was diluted with CH_2Cl_2 (160 mL) and then treated with (*S*)-binol (5.72 g, 20 mmol) at r.t. for 2 h to furnish chiral bis-(*S*)-Ti(IV) oxide. The *in situ* generated bis-(*S*)-Ti(IV) oxide was cooled to –15 °C and treated sequentially with hexanal (10 g, 100 mmol) and allyltributylstannane (34 mL, 110 mmol) at –15 °C. The mixture was warmed to 0 °C, stirred for 8 h, and then quenched with saturated $NaHCO_3$ (100 mL). The resulting mixture was extracted with diethyl ether (2 × 500 mL), the combined organic extracts were washed with brine (2 × 200 mL), filtered and dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (5% EtOAc/hexanes to 6% EtOAc/hexanes) afforded compound **11** (12.07 g, 85% yield, 98.74% ee by analytical HPLC analysis).

HPLC [Chiral Pak-IC (2504.6 mm, 5 μm); 5% isopropanol (IPA) in hexane]: t_R = 14.571 (major isomer 99.4%) and 13.196 min (minor isomer 0.6%).

Colorless oil; R_f = 0.7 (20% EtOAc/ hexanes); $[\alpha]_D^{25}$ 9.0 (*c* = 1.0, $CHCl_3$).

IR (neat): 3405, 3359, 3077, 2925, 1453, 1129 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.88–5.79 (m, 1 H), 5.16–5.11 (m, 2 H), 3.65 (s, 1 H), 2.33–2.28 (m, 1 H), 2.17–2.11 (m, 1 H), 1.66–1.57 (m, 1 H), 1.49–1.25 (m, 8 H), 0.89 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.9, 118.1, 70.7, 42.0, 36.8, 31.9, 25.4, 22.7, 14.1.

HRMS (ESI): *m*/*z* $[M + NH_4]^+$ calcd. for $C_8H_{22}NO$: 160.1701; found: 160.1697.

(*R*)-*tert*-Butyldimethyl Non-1-en-4-yloxysilane (12)

To a stirred solution of alcohol **11** (5.0 g, 35.21 mmol) in CH_2Cl_2 (20 mL) was added imidazole (4.78 g, 70.42 mmol), followed by TBDMS-Cl (7.92 g, 52.81 mmol) at 0 °C. The ice bath was removed, and the reaction mixture was allowed to warm to r.t. with continuous stirring over 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated, and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 99:1) to afford **12** (8.65 g, 96%) as a colourless oil.

R_f = 0.7 (5% EtOAc/hexanes); $[\alpha]_D^{25}$ 9.9 (*c* = 1.0, $CHCl_3$).

IR (neat): 2954, 2858, 1466, 1253, 1056, 912 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.84–5.76 (m, 1 H), 5.03–4.98 (m, 2 H), 3.69–3.64 (m, 1 H), 2.24–2.14 (m, 2 H), 1.45–1.19 (m, 8 H), 0.88–0.85 (m, 12 H), 0.04 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.6, 116.5, 72.1, 42.0, 36.8, 32.0, 25.9, 25.7, 25.0, 22.7, 18.2, 14.1, –2.9, –4.3, –4.5.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd. for $C_{15}H_{32}OSiNa$: 279.1591; found: 279.1588.

Ethyl (*R*,*E*)-5-*tert*-Butyldimethylsilyloxydec-2-enoate (13)

To a stirred solution of **12** (6.4 g, 26.5 mmol) in CH_2Cl_2 (60 mL) and MeOH (60 mL), O_3 was passed through a gas dispersion tube. When the color of the solution turned blue, dimethyl sulfide (16.4 mL) and triethylamine (2.4 mL) were added. The solution was stirred for 2 h and was concentrated under reduced pressure to afford the crude aldehyde as a colorless oil that was used directly in next step. To the aldehyde (6 g, 23.25 mmol) in CH_2Cl_2 (60 mL), was added (ethoxycarbonlymethylene)triphenylphosphorane (12.1 g, 34.88 mmol) at r.t. After 4 h, the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (petroleum ether/EtOAc, 95:5) to afford **13** (6.97 g, 85%) over two steps as a colorless oil.

R_f = 0.2 (5% EtOAc/hexane); $[\alpha]_D^{25}$ 6.6 (*c* = 1.0, $CHCl_3$).

IR (neat): 2931, 1722, 1655, 1465, 1257, 1046 cm^{-1}.

^{1}HNMR (500 MHz, $CDCl_3$): δ = 6.99–6.93 (m, 1 H), 5.83 (d, *J* = 15.0 Hz, 1 H), 4.21–4.14 (m, 2 H), 3.82–3.74 (m, 1 H), 2.39–2.28 (m, 2 H), 1.46–1.20 (m, 2 H), 1.37–1.21 (m, 9 H), 0.90–0.87 (m, 12 H), 0.04 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.5, 146.2, 123.2, 71.4, 60.1, 40.2, 37.3, 31.9, 25.9, 25.0, 22.6, 18.1, 14.3, 14.0, –4.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{18}H_{37}O_3Si$: 329.2512; found: 329.2509.

Ethyl (*R*)-5-*tert*-Butyldimethylsilyloxydecanoate (14)

To a solution of **13** (18 g, 57.32 mmol) in MeOH (180 mL) was added $NiCl_2·6H_2O$ (2.7 g 11.46 mmol), then $NaBH_4$ (57.32 mmol) in portions over 5 min at 0 °C. After stirring of 30 min, with completion of reaction being indicated by TLC, the reaction mixture was then filtered through a pad of Celite and solvent was removed under reduced pressure. To the residue was added aqueous NH_4Cl and the mixture extracted with EtOAc (2 × 60 mL). The organic layer was washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude product was purified by column chromatography on silica gel (4% EtOAc/hexanes) to afford **14** (16.29 g, 90%).

$[\alpha]_D^{25}$ –1.3 (*c* = 1.0, $CHCl_3$).

IR (neat): 2933, 2860, 1737, 1463, 1374, 1250, 1165 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.12 (q, *J* = 7 Hz, 2 H), 3.68–3.60 (m, 1 H), 2.29 (t, *J* = 5 Hz, 2 H), 1.73–1.58 (m, 2 H), 1.50–1.38 (m, 4 H), 1.34–1.21 (m, 9 H), 0.90–0.87 (m, 12 H), 0.04 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.7, 72.0, 60.2, 37.0, 36.4, 34.6, 32.1, 25.9, 25.0, 22.7, 20.9, 18.2, 14.3, 14.1, –4.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{19}H_{38}OSi$: 321.2663; found 321.2653.

(*R*)-5-*tert*-Butyldimethylsilyloxydecanoic Acid (15)

To **14** (10 g, 30.30 mmol) in THF/H_2O (3:1) was added LiOH (1.4 g, 60.6 mmol) at 0 °C and the reaction was then allowed to stir at 23 °C for 2 h. The reaction was then quenched with 1 M HCl to raise the pH to 4. The aqueous layer was extracted with EtOAc (3 × 50 mL), the combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the crude acid was purified by silica gel column chromatography (90:10, petroleum ether/EtOAc) to afford acid **15** (7.32 g, 80%) as a colorless oil.

R_f = 0.5 (20% EtOAc/hexane); $[\alpha]_D^{25}$ –1.0 (*c* = 0.4, $CHCl_3$).

IR (neat): 2934, 2860, 1712, 1463, 1375, 1255, 1075 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.67–3.63 (m, 1 H), 2.35 (t, *J* = 7.4 Hz, 2 H), 1.74–1.59 (m, 2 H), 1.52–1.40 (m, 4 H), 1.35–1.20 (m, 7 H), 0.89–0.86 (m, 12 H), 0.04 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.8, 71.9, 37.0, 36.3, 34.2, 32.1, 25.9, 25.0, 22.7, 20.5, 18.1, 14.1, –4.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{16}H_{35}O_3Si$: 303.2356; found: 303.2355.

(*S*)-4-Benzyl-3-(*R*)-5-*tert*-Butyldimethylsilyloxydecanoyloxazolidin-2-one (16)

To a stirred solution of acid **15** (6 g, 19.86 mmol) in THF (60 mL) at –20 °C was added Et_3N (5.67 mL, 39.72 mmol) followed by PivCl (2.4 mL, 19.86 mmol). After stirring for 1 h at –20 °C, LiCl (1.2 g, 29.79 mmol) followed by (*S*)-oxazolidinone (3.5 g, 19.86 mmol) were added. Stirring was continued for 1 h at –20 °C and then 2 h at 0 °C. The mixture was then quenched with saturated aqueous NH_4Cl (30 mL) and extracted with EtOAc (2 × 80 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc 90:10) to afford **16** (7.78 g, 85%) as a viscous liquid.

R_f = 0.5 (20% EtOAc/hexane); $[\alpha]_D^{25}$ 29.15 (*c* = 1.3, $CHCl_3$).

IR (neat): 2937, 2860, 1787, 1704, 1464, 1387, 1255, 1083 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.31 (m, 2 H), 7.29–7.27 (m, 1 H), 7.22–7.19 (m, 2 H), 4.70–4.64 (m, 1 H), 4.22–4.14 (m, 2 H), 3.70–3.65 (m, 1 H), 3.31 (dd, *J* = 11.36 Hz, 3.32 Hz, 1 H), 3.01–2.86 (m, 2 H), 2.76 (dd, *J* = 13.36 Hz, 9.68 Hz, 1 H), 1.54–1.40 (m, 4 H), 1.33–1.22 (m, 8 H), 0.90–0.88 (m, 6 H), 0.06 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 173.2, 153.5, 135.3, 129.4, 129.0, 127.3, 72.0, 66.2, 55.2, 37.9, 37.0, 36.4, 35.7, 32.1, 25.9, 25.0, 22.7, 20.1, 18.2, 14.1, –4.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{26}H_{44}NO_4Si$: 462.3039; found: 462.3033.

(*S*)-4-Benzyl-3-(2*S*,5*R*)-5-*tert*-butyldimethylsilyloxy-2-methyldecanoyloxazolidin-2-one (17)

To a solution of compound **16** (3.0 g, 6.5 mmol) in anhydrous THF (20 mL) at –78 °C, LiHMDS (1 M in THF, 9.75 mL, 9.75 mmol) was added dropwise with stirring under nitrogen. After stirring at –78 °C for 30 min, MeI (0.6 mL, 9.75 mmol) was added and the reaction mixture stirred for an additional 3 h at –78 °C. Then the reaction was quenched with saturated aqueous NH_4Cl (30 mL), warmed to r.t. and extracted with EtOAc (2 × 60 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether/hexane, 95:5) to yield **17** (2.47 g, 80%) as a colorless viscous liquid.

R_f = 0.5 using (10% EtOAc/ hexane); $[\alpha]_D^{25}$ 41.59 (*c* = 0.5, $CHCl_3$).

IR (neat): 2934, 2859, 1781, 1699, 1459, 1382, 1245 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.31 (m, 2 H), 7.28–7.26 (m, 1 H), 7.22–7.20 (m, 2 H), 4.69–4.65 (m, 1 H), 4.20–4.15 (m, 2 H), 3.70–3.59 (m, 2 H), 3.27 (dd, *J* = 13.35, 3.25 Hz, 1 H), 2.77 (dd, *J* = 12.9, 9.5 Hz, 1 H), 1.74–1.67 (m, 1 H), 1.55–1.39 (m, 5 H), 1.32–1.21 (m, 9 H), 0.89–0.86 (m, 6 H), 0.04 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.1, 153.1, 135.4, 129.5, 129.0, 127.4, 72.3, 66.0, 55.4, 37.9, 37.2, 34.5, 32.1, 29.3, 26.0, 24.9, 22.7, 18.2, 17.4, 14.1, –4.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{27}H_{46}NO_4Si$: 476.3190; found: 476.3174.

(2*S*,5*R*)-5-*tert*-Butyldimethylsilyloxy-2-methyldecan-1-ol (18)

To a solution of compound **17** (2 g, 4.22 mmol) in THF (20 mL) at 0 °C was added EtOH (0.99 mL 16.91 mmol) followed by $LiBH_4$ (110 mg, 5.07 mmol) portion-wise and the mixture was stirred at the same temperature for 10 min. The reaction was quenched with saturated aqueous NH_4Cl (15 mL) and the mixture was extracted with EtOAc (2 × 40 mL). The organic extracts were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was filtered, evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (petroleum ether/EtOAc 90:10) to afford alcohol **18** (1.09 g, 86%) as a colorless viscous liquid.

R_f = 0.5 (20% EtOAc/hexane); $[\alpha]_D^{25}$ –5.2 (*c* = 0.5, $CHCl_3$).

IR (neat): 2931, 2859, 1463, 1375, 1252, 1125, 1045 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.64–3.59 (m, 1 H), 3.52 (dd, *J* = 10.4, 5.16 Hz, 1 H), 3.42 (dd, *J* = 10.4 Hz, 6.8 Hz, 1 H), 1.47–1.11 (m, 14 H), 0.92–0.86 (m, 15 H), 0.04 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 72.6, 68.4, 37.1, 36.0, 34.3, 32.1, 28.6, 26.0, 25.1, 22.7, 18.2, 16.7, 14.1, –4.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{17}H_{39}O_2Si$: 303.2718; found: 303.2715

tert-Butyldimethyl (3*S*,6*R*)-3-Methylundec-1-en-6-yloxysilane (19)

The aldehyde obtained from oxidation of alcohol **18** was subjected to C-1 Wittig olefination without purification. To methyl triphenyl phosphonium bromide (1.78 g, 5 mmol) in anhydrous THF was added LiHMDS (1 M in THF, 3.3 mL, 3.32 mmol) at 0 °C. The mixture was stirred for 30 min and to this was added dropwise a solution of aldehyde (500 mg, 1.66 mmol) in THF (5 mL). The reaction mixture was then stirred for 1 h, quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (20 mL). The organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was filtered and evaporated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography using hexane as eluent to give product **19** (0.34 g, 70%).

$[\alpha]_D^{25}$ 3.75 (*c* = 0.4, $CHCl_3$).

IR (neat): 2928, 2858, 1463, 1373, 1252, 1128, 1058 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.72–5.65 (m, 1 H), 4.96–4.89 (m, 2 H), 3.63–3.58 (m, 1 H), 2.09–2.03 (m, 1 H), 1.47–1.26 (m, 12 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 0.89–0.87 (m, 12 H), 0.03 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.9, 112.4, 72.5, 37.9, 37.1, 34.6, 32.2, 26.0, 25.0, 22.7, 20.3, 18.2, 14.1, –4.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{18}H_{39}OSi$: 299.1265; found: 299.1263.

(3*S*,6*R*)-3-Methylundec-1-en-6-ol (9)

To a stirred solution of *O*-TBS protected alkene **19** (200 mg, 0.67 mmol) at 0 °C in THF (5 mL), tetrabutylammonium fluoride (1.34 mL 1.34 mmol, 1.0 M in THF) was added at 0 °C. Stirring was continued from 0 °C to r.t. for 6 h, then the reaction was quenched with ice-cold water (5 mL), and the mixture was extracted with EtOAc (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (petroleum ether/EtOAc, 95:5) to afford alcohol **9** as a colorless liquid (106 mg, 86%).

R_f = 0.5 (10% EtOAc/hexane); $[\alpha]_D^{25}$ 5.2 (*c* = 0.5, $CHCl_3$).

IR (neat): 3545, 3418, 3160, 2930, 2861, 1459 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.73–5.65 (m, 1 H), 4.98–4.90 (m, 2 H), 3.57 (s, 1 H), 2.17–2.05 (m, 1 H), 1.49–1.28 (m, 13 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.6, 112.7, 72.3, 38.0, 37.5, 35.2, 32.6, 31.9, 25.3, 22.7, 20.2, 14.1.

HRMS (ESI): *m/z* [M + NH_4]$^+$ calcd. for $C_{12}H_{28}NO$: 202.1786; found: 202.1794.

Methyl L-Tyrosinate (20)

A solution of L-tyrosine (5.0 g, 27.6 mmol) in MeOH (30 mL) was stirred at 0 °C and thionyl chloride (3.0 mL, 41.4 mmol) was added dropwise. The reaction was then allowed to warm to r.t. before being heated to reflux for 3 h. The solvent and volatiles were evaporated under reduced pressure and the product was triturated with EtOAc to give the methyl ester hydrochloride salt **20** as a colorless solid (5.4 g, quant.).

$[\alpha]_D^{25}$ 8.80 (*c* = 1.0, $CHCl_3$).

IR (neat): 3595, 3423, 2938, 2601, 2141, 1874, 1338 cm^{-1}.

^1H NMR (400 MHz, DMSO): δ = 9.51 (s, 1 H), 8.60 (s, 3 H), 7.01 (d, *J* = 8.2 Hz, 2 H), 6.72 (d, *J* = 8.0 Hz, 2 H), 4.16 (s, 1 H), 3.67 (s, 3 H), 3.08–2.95 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.7, 161.9, 135.6, 129.5, 120.7, 58.7, 57.8, 40.3.

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{10}H_{14}NO_3$: 196.0973; found: 196.0971.

Methyl *N*-*tert*-Butoxycarbonyl-L-tyrosinate (21)

To a mixture of methyl L-tyrosinate **20** (5.0 g, 27.6 mmol) in CH_2Cl_2, was added triethylamine (11.6 mL, 82.9 mmol), and di-*tert*-butyl dicarbonate (7.6 mL, 33.1 mmol) at 0 °C, and the resulting mixture was stirred at r.t. overnight. The resulting mixture was partitioned between CH_2Cl_2 (100 mL) and water (50 mL). The aqueous phase was removed and the organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 90:10) to afford methyl (*tert*-butoxycarbonyl) tyrosinate **21** as a white solid (7.14 g, 95%).

R_f = 0.5 (20% EtOAc/ hexane); $[\alpha]_D^{25}$ 52.6 (*c* = 1.0, $CHCl_3$).

IR (neat): 3381, 2982, 1686, 1512, 1241, 1159, 1054 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (d, *J* = 7.28 Hz, 2 H), 6.73 (d, *J* = 7.68 Hz, 2 H), 5.01 (s, 1 H), 4.54 (dd, *J* = 13.2, 6.08 Hz, 1 H), 3.71 (s, 3 H), 3.05–2.93 (m, 2 H), 1.42 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.7, 155.3, 155.1, 130.4, 127.6, 115.5, 80.2, 54.6, 52.3, 37.6, 28.3.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd. for $C_{15}H_{21}NO_5Na$: 318.2107; found: 318.2108.

Methyl (*S*)-3-[4-(Benzyloxy)phenyl]-2-(*tert*-butoxycarbonylamino)-propanoate (22)

To a mixture of Boc-L-Tyr-OMe **21** (2.0 g, 6.77 mmol), K_2CO_3 (1.4 g, 10.15 mmol), and KI (112 mg, 0.67 mmol), in acetone (20 mL), was added BnBr (0.9 mL, 8.13 mmol), slowly. The mixture was then heated to reflux overnight and then quenched with water (20 mL). The reaction mixture was extracted with EtOAc (30 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by silica gel column chromatography (petroleum ether/EtOAc, 93:7) to afford **22** (2.5 g, 96%).

R_f = 0.3 (10% EtOAc/ hexane); $[\alpha]_D^{25}$ 23.3 (*c* = 0.3, $CHCl_3$).

IR (neat): 3368, 2978, 1691, 1514, 1364, 1229, 1060 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.30 (m, 5 H), 7.04 (d, *J* = 8.52 Hz, 2 H), 6.90 (d, *J* = 8.64 Hz, 2 H), 5.04 (s, 2 H), 4.96 (s, 1 H), 4.54 (dd, *J* = 12.8, 5.8 Hz, 1 H), 3.71 (s, 3 H), 3.07–2.96 (m, 2 H), 1.42 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.5, 157.9, 155.1, 137.0, 130.3, 128.6, 128.3, 128.0, 127.5, 115.0, 79.9, 70.1, 54.6, 52.2, 37.5, 28.3.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd. for $C_{22}H_{27}NO_5Na$: 408.1779; found: 408.1778.

(*S*)-3-[4-(Benzyloxy)phenyl]-2-(*tert*-butoxycarbonylmethylamino)-propanoic Acid (23)

To compound **22** (2.0 g, 5.2 mmol) in THF/H_2O (3:1) was added LiOH (435 mg, 10.38 mmol) at 0 °C. The reaction was allowed to stir at r.t. for 2 h and was then quenched with 1 M HCl to pH 4. The aqueous layer was extracted with EtOAc (3 × 50 mL), the combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. After filtration, the volatiles were removed under reduced pressure, and the crude acid was purified by silica gel column chromatography (petroleum ether/EtOAc, 60:40) to yield **23** as a white solid (1.65 g, 86%).

R_f = 0.2 (60% EtOAc/hexane); $[\alpha]_D^{25}$ 19.8 (*c* = 0.9, $CHCl_3$).

IR (neat): 3424, 2978, 1711, 1509, 1399, 1168, 1025 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.29 (m, 5 H), 7.10 (d, *J* = 8.56 Hz, 2 H), 6.91 (d, *J* = 8.56 Hz, 2 H), 5.03 (s, 2 H), 4.94 (d, *J* = 7.68 Hz, 1 H), 4.56 (d, *J* = 5.88 Hz, 1 H), 3.15–3.00 (m, 2 H), 1.42 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.7, 158.0, 155.5, 137.0, 130.4, 128.6, 128.0, 127.5, 115.0, 80.3, 70.1, 54.4, 36.9, 28.3.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd. for $C_{21}H_{25}NO_5Na$: 394.1742; found: 394.1612.

(*S*)-3-[4-(Benzyloxy)phenyl]-2-(*tert*-butoxycarbonylmethylamino)-propanoic Acid (10)

A suspension of sodium hydride (96 mg, 4.03 mmol) in THF (10 mL) was cooled in an ice-water bath under nitrogen. To the mixture was added a solution of (*S*)-3-(4-(benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)(methyl)amino)propanoic acid **23** (1.0 g, 2.69 mmol) in THF (5 mL) slowly, the mixture was stirred for 30 min and then methyl iodide (0.51 mL, 8.07 mmol) was added dropwise. The reaction mixture was stirred at r.t. for 2 h and then quenched with ice-cold water and diluted with EtOAc (30 mL). The aqueous layer was separated and extracted with EtOAc (2 × 50 mL), the combined organic layers were washed with brine (2 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product **10** as a white solid (0.85 g, 82% yield).

$[\alpha]_D^{25}$ –15.10 (*c* = 1.0, $CHCl_3$).

IR (neat): 3202, 2977, 1695, 1451, 1327, 1241, 767 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.29 (m, 5 H), 7.13–7.08 (m, 2 H), 6.92–6.88 (m, 2 H), 5.04 (s, 2 H), 4.69–4.54 (m, 1 H), 3.24 (dd, *J* = 14, 4.8 Hz, 1 H), 3.12–2.94 (m, 1 H), 2.71 (s, 3 H), 1.41 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.1, 175.5, 157.7, 156.5, 155.1, 137.0, 130.0, 129.7, 129.4, 128.6, 128.0, 127.5, 115.0, 115.0, 80.8, 80.7, 70.1, 61.6, 61.1, 34.5, 33.9, 33.2, 32.6, 28.3.

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{22}H_{28}NO_5$: 386.1967; found: 386.1963.

(3*S*,6*S*)-3-Methylundec-1-en-6-yl (*S*)-3-[4-(Benzyloxy)phenyl]-2-(*tert*-butoxycarbonylmethylamino)propanoate (24)

To a solution of **10** (400 mg, 1.03 mmol) in toluene (5 mL) was added Et_3N (0.22 mL, 1.54 mmol) and 2,4,6-trichlorobenzoyl chloride (0.20 mL, 1.23 mmol) at 0 °C and the mixture was stirred at r.t. for 30 min. After the formation of the mixed anhydride, the solution was cooled to 0 °C and a solution of DMAP (628 mg, 5.15 mmol) and alcohol **7** (229 mg, 1.24 mmol) was introduced dropwise to the reaction mixture. The mixture was then warmed to r.t. and was stirred for an additional 5 h. After completion of the reaction (TLC), the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and the aqueous layer was washed with EtOAc (10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and the solvent was evaporated to give a pale-yellow oil. Purification of the residue by silica gel column chromatography (petroleum ether/EtOAc, 95:5) afforded ester **24** (0.49 g, 86%) as a colorless oil.

R_f = 0.5 (10% EtOAc/hexane); $[\alpha]_D^{25}$ 2.86 (*c* = 0.7, $CHCl_3$).

IR (neat): 3091, 2965, 2867, 1889, 1737, 1622, 1384 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.30 (m, 5 H), 7.12 (dd, *J* = 16, 8 Hz, 2 H), 6.89 (d, *J* = 7.92 Hz, 2 H), 5.69–5.59 (m, 1 H), 5.03 (s, 2 H), 4.97–4.87 (m, 3 H), 3.26–3.18 (m, 1 H), 2.95–2.86 (m, 1 H), 2.76 (s, 3 H), 2.11–2.03 (m, 1 H), 1.52–1.17 (m, 22 H), 1.01–0.86 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.5, 172.7, 157.6, 144.2, 137.1, 129.9, 128.6, 127.9, 127.5, 115.0, 114.8, 112.9, 80.1, 79.8, 75.8, 75.5, 70.1, 60.9, 37.7, 34.4, 34.2, 34.0, 32.0, 31.7, 31.1, 29.7, 28.3, 24.9, 22.5, 20.2, 14.0.

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{34}H_{50}NO_5$: 552.3689; found: 552.3675.

(3*S*,6*S*)-3-Methylundec-1-en-6-yl (*S*)-3-[4-(Benzyloxy)phenyl]-2-(*N*-methylpent-4-enamido)propanoate (25)

To a solution of **24** (200 mg, 0.362 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C was added trifluoroacetic acid (0.55 mL, 7.24 mmol) dropwise. Upon completion of addition, the reaction was warmed to r.t. and stirred for 1 h; at that time, TLC analysis showed complete consumption of starting material. The reaction was concentrated *in vacuo* to afford a red oil that was subsequently dissolved in CH_2Cl_2 (5 mL). This solution was cooled to 0 °C before the sequential addition of 4-pentenoic acid (0.046 mL, 0.66 mmol), PyBoP (343 mg, 0.66 mmol), and *N*,*N*-di-isopropylethylamine (0.3 mL, 1.76 mmol). The reaction was allowed to stir at r.t. for 6 h; whereupon, TLC analysis indicated complete consumption of starting material. The reaction was diluted with CH_2Cl_2 and quenched with saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by silica gel column chromatography using petroleum ether/ EtOAc (90:10) to afford the desired product **25** as a colorless oil (212 mg, 90% yield).

R_f = 0.5 (20% EtOAc/ hexane); $[\alpha]_D^{25}$ 2.36 (*c* = 01.4, $CHCl_3$).

IR (neat): 2941, 2864, 1731, 1510, 1392, 1113 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.30 (m, 2 H), 7.09 (dd, *J* = 23.5, 8.5 Hz, 1 H), 6.92–6.86 (m, 1 H), 5.81–5.59 (m, 1 H), 5.38 (m, 1 H), 5.02 (s, 1 H), 5.00–4.84 (m, 2 H), 4.52 (dd, *J* = 9.8, 5.0 Hz, 1 H), 3.27 (m, 1 H), 2.87 (d, *J* = 31.4 Hz, 1 H), 2.34–1.90 (m, 2 H), 1.57–1.46 (m, 1 H), 1.32–1.19 (m, 3 H), 0.97 (dd, *J* = 6.7, 3.4 Hz, 1 H), 0.90–0.85 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.7, 170.9, 170.0, 157.9, 157.6, 144.3, 137.5, 137.1, 129.8, 128.58, 128.0, 127.5, 115.2, 115.0, 114.8, 113.0, 75.7, 70.0, 62.0, 57.9, 37.7, 34.5, 34.1, 33.9, 32.7, 32.5, 32.0, 31.7, 28.9, 24.9, 22.5, 20.2, 14.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{34}H_{48}NO_4$: 534.3583; found: 534.3580.

(3*S*,10*R*,13*R*)-3-[4-(Hydroxy)benzyl]-4,10-dimethyl-13-pentyl-1-oxa-4-azacyclotridecane-2,5-dione (8)

A solution of compound **25** (180 mg, 0.337 mmol) in toluene (100 mL) was purged with argon, treated with Grubbs' second-generation catalyst (14 mg, 0.016 mmol) and allowed to stir at 90 °C for 6 h. The reaction mixture was filtered through a short pad of silica gel, washed with EtOAc and concentrated to afford a colorless oil (122 mg, 72% yield), which was taken forward to the next step without further purification.

A solution of RCM product (122 mg, 0.240 mmol) in EtOAC (15 mL) was passed through an H-cube R flow reactor® (40 °C, at 6 bar with a 10 mol-% Pd/C cartridge at 1 $mLmin^{-1}$. Additional EtOAc (20 mL) was passed through the apparatus, and the solvent was removed *in vacuo* to give compound **8** (85 mg, 85% yield) as a colorless oil.

$[\alpha]_D^{25}$ –53.8 (*c* = 0.5, $CHCl_3$).

IR (neat): 3316, 3268, 3202, 2935, 2861, 1733, 1456, 1231 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.10–6.98 (m, 2 H), 6.78–6.67 (m, 2 H), 5.88–5.84 (m, 1 H), 4.92–4.81 (m, 1 H), 4.55 (m, 0.2 H), 3.17–3.12 (m, 1 H), 3.03–2.87 (m, 3 H), 2.72–2.58 (m, 1 H), 2.21–2.09 (m, 1 H), 1.49–1.25 (m, 20 H), 0.92–0.80 (m, 7 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.8, 174.4, 171.0, 170.3, 155.4, 129.9, 129.6, 127.6, 127.3, 115.8, 115.4, 75.8, 74.7, 61.9, 55.4, 35.0, 34.9, 33.9, 33.5, 32.9, 32.6, 31.6, 30.7, 29.7, 29.5, 29.4, 28.5, 28.3, 28.1, 26.5, 25.3, 25.1, 24.8, 23.7, 23.4, 23.0, 22.7, 22.5, 20.6, 14.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{25}H_{40}NO_4$: 418.2965; found: 418.2957.

4-Benzyloxybutan-1-ol (28)

To a vigorously stirred suspension of NaH (640 mg, 26.6 mmol, 1.2 equiv, 60% dispersion in mineral oil) in THF (20 mL) at 0 °C was quickly added a solution of 1,4-butanediol (2 g, 22.2 mmol) in THF (10 mL) via an addition funnel. After stirring for 20 min at r.t., the reaction mixture was again cooled to 0 °C and BnBr (0.2 mL, 22.2 mmol, 1.0 equiv) was added dropwise via syringe. After stirring for 14 h at r.t., the reaction was quenched with sat. aqueous NH_4Cl (10 mL) and water (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 2:1 → 1:1) to afford **28** (3.4 g, 85%) as a colorless oil.[13]

R_f = 0.28 (hexane/EtOAc, 2:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H), 4.51 (s, 2 H), 3.62 (t, *J* = 5.9 Hz, 2 H), 3.51 (t, *J* = 5.8 Hz, 2 H,), 2.4 (s, 1 H), 1.74–1.62 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.1, 129.6, 128.5, 127.8, 73.1, 70.4, 62.6, 30.0, 26.6.

5-(4-(Benzyloxy)butylthio)-1-phenyl-1*H*-tetrazole (29)

To a cooled, stirred solution of 4-(benzyloxy)butan-1-ol **28** (2.0 g, 11.1 mmol), in anhydrous THF (20 mL) was added PPh_3 (6.45 g, 16.64 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (4.4 g, 22.18 mmol) and DIAD (2.17 mL, 11.1 mmol) dropwise. The reaction mixture was then vigorously stirred for 8 h at r.t. and then the solvent was removed using a rotary evaporator. The crude material was purified by column chromatography (petroleum ether/EtOAc 95:5) to afford sulfide **29** (3.4 g, 90%) as a colorless liquid.

R_f = 0.5 (10% EtOAc/hexane).

IR: 2928, 2859, 1500, 1397, 1258, 1100 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.51 (m, 1 H), 7.35–7.26 (m, 1 H), 4.50 (s, 2 H), 3.51 (t, *J* = 6.25 Hz, 2 H), 3.45–3.40 (t, *J* = 7.3 Hz, 2 H), 1.97- 1.92 (m, 2 H), 1.79–1.75 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.4, 138.4, 133.7, 130.1, 129.8, 128.4, 127.7, 123.9, 73.0, 69.5, 33.2, 28.7, 26.1.

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{18}H_{21}N_4OS$: 341.1431; found: 341.1432.

5-(4-(Benzyloxybutyl)sulfonyl)-1-phenyl-1*H*-tetrazole (26)

To a solution of **29** (1.00 g, 2.94 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added *m*-CPBA (1.51 g, 8.82 mmol, 70% wt% suspension in water) in portions. The reaction mixture was stirred at ambient temperature for 16 h, quenched with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by silica gel column chromatography (petroleum ether /EtOAc 9:1) to afford the sulfone **26** (0.98 g, 90%) as a colorless oil.

R_f = 0.5 (10% EtOAc/hexane).

IR: 3069, 2949, 2868, 1715, 1495, 1341, 1102 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.08–7.97 (m, 1 H), 7.70–7.57 (m, 5 H), 7.36–7.26 (m, 4 H), 4.50 (s, 2 H), 3.79 (t, *J* = 7.9 Hz, 2 H), 3.53 (t, *J* = 5.9 Hz, 2 H), 2.12–2.06 (m, 2 H), 1.84–1.75 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.7, 153.5, 138.1, 134.7, 133.8, 133.1, 131.5, 131.0, 130.3, 129.7, 128.5, 127.7, 125.1, 73.1, 69.1, 55.9, 28.1, 19.6.

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{18}H_{21}N_4O_3S$: 372.1256; found: 373.1254.

(6*R*,9*S*,*E*)-14-Benzyloxy-9-methyltetradec-10-en-6-yloxy *tert*-Butyldimethylsilane (27)

To a solution of alcohol **18** (0.25 g, 0.82 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added Dess–Martin periodinane (4.77 g, 1.64 mmol). After 4 h at r.t., the reaction mixture was diluted with CH_2Cl_2 (5 mL) and then poured into a mixture of saturated aqueous $NaHCO_3$ and 25% aqueous $Na_2S_2O_3$ (1:1, 5 mL). The separated aqueous layer was extracted with CH_2Cl_2 (5 mL), and the combined organic extracts were washed with brine (2 mL), dried with anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to obtain the aldehyde as a colorless liquid, which was taken into the next step without purification.

To a solution of sulfone **26** (500 mg, 1.34 mmol) in anhydrous THF (10 mL) at –78 °C, was added KHMDS (1.34 mL, 1 M solution in toluene, 1.34 mmol) dropwise. The resulting yellow solution was stirred for 30 min, followed by the dropwise addition of the crude aldehyde (201 mg, 0.67 mmol) in THF (5 mL). The reaction mixture was stirred at –78 °C for 1 h and then quenched at this temperature after the reaction had been demonstrated to be completed by TLC. Saturated aqueous NH_4Cl was added, the mixture was allowed to warm to ambient temperature and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc, 98:2) to afford a mixture of (*E*,*Z*)-diastereomers of **27** (14:1) (0.29 g, 80%, over two steps) as a colorless liquid.

R_f = 0.5 using (5% EtOAc/hexane); $[\alpha]_D^{25}$ 3.8 (*c* = 1.0, $CHCl_3$).

IR (neat): 2941, 2860, 1461, 1368, 1255, 1107, 973 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 5 H), 5.40–5.22 (m, 2 H), 4.49 (s, 2 H), 3.62–3.56 (m, 1 H), 3.48–3.44 (m, 2 H), 2.09–1.94 (m, 3 H), 1.70–1.63 (m, 2 H), 1.43–1.36 (m, 4 H), 1.34–1.19 (m, 9 H), 0.94–0.88 (m, 2 H), 0.89–0.85 (m, 12 H), 0.02–0.01 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.7, 137.0, 130.90, 129.6, 128.3, 127.7, 127.6, 127.5, 72.9, 72.5, 72.4, 72.3, 69.8, 37.2, 37.1, 36.9, 36.6, 34.8, 32.7, 32.7, 32.1, 29.7, 29.7, 29.1, 29.1, 26.0, 25.3, 25.1, 21.0, 14.1, –4.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{28}H_{51}O_2Si$: 447.7919; found: 447.7910.

(6*R*,9*S*,*E*)-14-Benzyloxy-9-methyltetradec-10-en-6-ol (30)

To a cold stirred solution of diastereomeric *O*-TBS protected alkene **27** (200 mg, 2.35 mmol) in THF (5 mL), tetrabutylammonium fluoride (4.71 mL 4.71 mmol, 1.0 M in THF) was added at 0 °C. Stirring was continued at 0 °C to r.t. for 6 h, then the reaction was quenched with ice-cold water (10 mL), extracted with EtOAc (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (petroleum ether/EtOAc, 95:5) to yield an inseparable mixture of (*E*,*Z*)-alcohols **30** (126 mg, 85%) as a colorless liquid.

R_f = 0.5 (10% EtOAc/hexane); $[\alpha]_D^{25}$ 1.8 (*c* = 1.0, $CHCl_3$).

IR (neat): 3405, 3070, 2925, 1733, 1225, 1175 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 5 H), 5.41–5.23 (m, 2 H), 4.50 (s, 2 H), 3.56 (br s, 1 H), 3.49–3.45 (m, 2 H), 2.09–1.97 (m, 3 H), 1.70–1.64 (m, 2 H), 1.47–1.37 (m, 6 H), 1.33–1.25 (m, 8 H), 0.98–0.93 (m, 2 H), 0.89 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.7, 136.7, 130.6, 129.9, 128.4, 128.0, 127.6, 127.5, 72.90, 72.3, 71.9, 69.8, 37.5, 36.9, 35.3, 33.1, 32.6, 31.9, 29.7, 29.6, 29.1, 29.1, 25.6, 25.4, 22.7, 20.9, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{22}H_{37}O_2$: 333.2793; found: 333.2785.

(6*R*,9*R*,*E*)-14-Benzyloxy-9-methyltetradec-10-en-6-yl (*S*)-3-(4-(Benzyloxy)phenyl)-2-(*tert*-butoxycarbonylmethylamino)propanoate (31)

To a solution of **10** (0.5 g, 1.29 mmol) in toluene (5 mL) was added Et_3N (0.27 mL, 1.93 mmol) and 2,4,6-trichlorobenzoyl chloride (0.24 mL, 1.55 mmol) at 0 °C and the resultant mixture was stirred at r.t. for 30 min. After formation of the mixed anhydride, the solution was cooled to 0 °C and a solution of DMAP (0.78 g, 6.45 mmol) and alcohol **30** (0.51 g, 1.55 mmol) was introduced dropwise. The reaction mixture was warmed to r.t. and was stirred for an additional 5 h. After completion of reaction as indicated by TLC, it was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL) and the aqueous layer was washed with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and the solvent was evaporated to give a pale-yellow oil. Purification of the residue by silica gel column chromatography (petroleum ether/EtOAc, 96:4) afforded ester **31** (0.90 g, 86%) as a colorless liquid.

R_f = 0.2 (6% EtOAc/Hexane); $[\alpha]_D^{25}$ –12.89 (c = 0.9, CHCl3).

IR (neat): 3028, 2865, 1735, 1513, 1458, 1328, 1176 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.24 (m, 10 H), 7.11 (dd, *J* = 15.8, 7.6 Hz, 2 H), 6.89 (d, *J* = 8.2 Hz, 2 H), 5.39–5.19 (m, 2 H), 5.03 (s, 2 H), 4.95–4.67 (m, 2 H), 4.50 (s, 2 H), 3.47 (t, *J* = 6.48 Hz, 2 H), 3.26–3.11 (m, 1 H), 2.95–2.86 (m, 1 H), 2.76 (s, 3 H), 2.17–1.93 (m, 3 H), 1.70–1.63 (m, 2 H), 1.51–1.19 (m, 22 H), 0.99–0.85 (m, 5 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.2, 157.5, 138.7, 129.9, 128.6, 128.4, 127.9, 127.6, 127.5, 114.9, 79.8, 72.9, 72.1, 70.1, 69.8, 36.9, 35.0, 34.2, 33.9, 33.5, 32.4, 32.0, 31.7, 29.7, 29.1, 28.3, 24.9, 22.5, 20.9, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{44}H_{62}NO_6$: 700.4577; found: 700.4556.

(6*R*,9*R*)-14-Hydroxy-9-methyltetradecan-6-yl *N*-*tert*-Butoxycarbonyl-*N*-methyl-L-tyrosinate (32)

A solution of **31** (0.2 g, 0.286 mmol) in EtOAc (20 mL) was passed through an H-cube R flow reactor® (40 °C, at 6 bar with a 10 mol% Pd/C cartridge, 1 mL min^{-1}). Additional EtOAc (20 mL) was passed through the apparatus, and the solvent was removed *in vacuo* to obtain a colorless oil, which was purified by silica gel column chromatography (petroleum ether/ EtOAc, 80:20) to afford alcohol **32** (119 mg, 80%) as a colorless liquid.

R_f = 0.5 (40% EtOAc/hexane); $[\alpha]_D^{25}$ –23.5 (*c* = 1.6, $CHCl_3$).

IR: 3316, 3268, 2935, 2861, 1733, 1513, 1456, 1090 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.05–7.02 (m, 2 H), 6.75–6.68 (m, 2 H), 6.2 (s, 1 H), 4.97–4.87 (m, 1 H), 4.70 (s, 1 H), 3.65 (t, *J* = 7.3 Hz, 1 H), 3.24–3.17 (m, 1 H), 2.89 (t, *J* = 12.6 Hz, 1 H), 2.78, 2.73 (s, 3 H), 2.38–2.01 (m, 1 H), 1.56–1.46 (m, 8 H), 1.38–1.27 (m, 22 H), 0.88–0.84 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2, 170.9, 156.1, 155.5, 155.1, 154.8, 129.0, 128.8, 115.4, 115.3, 80.5, 80.1, 75.9, 75.8, 75.7, 75.5, 63.0, 63.0, 61.2, 59.5, 36.8, 34.4, 34.0, 33.8, 32.7, 32.5, 32.3, 32.1, 31.7, 31.5, 31.4, 29.7, 29.3, 29.2, 28.3, 28.2, 26.7, 25.9, 25.6, 25.2, 25.1, 24.9, 22.5, 19.7, 19.6, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd. for $C_{30}H_{51}NO_6Na$: 544.3614; found: 544.3605.

(6*R*,9*R*)-9-(*N*-*tert*-Butoxycarbonyl-*N*-methyl-L-tyrosyloxy)-6-methyltetradecanoic Acid (33)

BAIB (0.86 g, 0.27 mmol) and TEMPO (0.21 mg, 0.13 mmol) were added sequentially to a stirred solution of alcohol **32** (50 mg, 0.09 mmol) in acetonitrile phosphate buffer solution (pH 7) (1:1, 2 mL) at r.t. and the mixture was stirred for 2 h. After completion of reaction, saturated aqueous 1 M $Na_2S_2O_3$ (5 mL) and Et_2O (10 mL) were added and the organic layer was separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography using petroleum ether/EtOAc (6:4) to give acid **33** (41 mg, 81%) as a colorless liquid.

R_f = 0.5 (80% EtOAc/hexane); $[\alpha]_D^{25}$ 2.5 (c = 0.6, $CHCl_3$).

IR: 3539, 3423, 1712, 1463, 1255, 1054 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.9–6.78 (m, 2 H), 6.23–6.14 (m, 2 H), 5.06–4.83 (m, 2 H), 2.76, 2.73 (s, 3 H), 2.59–2.50 (m, 1 H), 2.38–2.30 (m, 3 H), 2.20–2.03 (m, 2 H), 1.48–1.40 (m, 12 H), 1.33–1.25 (m, 15 H), 0.89–0.84 (m, 7 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 185.1, 176.9, 170.8, 156.3, 150.7, 149.6, 149.5, 130.0, 129.0, 128.3, 127.7, 81.3, 81.2, 81.1, 68.5, 55.1, 40.1, 37.2, 36.0, 33.9, 31.9, 31.6, 29.7, 28.3, 28.2, 26.1, 24.9, 22.5, 19.8, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{30}H_{50}NO_7$: 536.1669; found: 536.1655.

(3*S*,10*R*,13*R*)-3-(4-Hydroxybenzyl)-4,10-dimethyl-13-pentyl-1-oxa-4-azacyclotridecane-2,5-dione (8)

To a solution of compound **33** (50 mg, 0.093 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C was added TFA (0.14 mL, 1.86 mmol). The reaction mixture was stirred for 1 h at r.t.; at that time, TLC analysis showed complete consumption of starting material. The reaction was concentrated *in vacuo* to afford a red oil that was subsequently dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C before the sequential addition of *N*,*N*-di-isopropylethylamine (0.09 mL, 0.55 mmol) and BOP-Cl (72 mg, 0.13 mmol). The reaction mixture was stirred at r.t. for 16 h, then it was concentrated and saturated aqueous $NaHCO_3$ (2 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 4 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, evaporated, and the product was purified by silica gel chromatography (petroleum ether/EtOAc, 80:20) to afford **8** (31 mg, 80% over 2 steps) as a colorless oil.

R_f = 0.5 (40% *n*-hexane/EtOAc).

Preparation of (–)-Melearoride A (1)

A mixture of compound **8** (20 mg, 0.047 mmol), prenyl bromide (0.027 mL, 0.235 mmol), cesium carbonate (0.75 g, 5.4 mmol) and DMF (4 mL) was heated under reflux for 4 h. After completion of the reaction, the solid was filtered off and the solvent was evaporated. The residue obtained was purified by silica gel column chromatography (petroleum ether/EtOAc, 70:30 as eluent) to give melearoride-A (**1**) (19 mg, 85%) as a colorless oil.

R_f = 0.2 (60% EtOAc/hexane); $[\alpha]_D^{20}$ –92.5 (*c* = 0.5, CH_3OH); $[\alpha]_D^{25}$ –95.5 (*c* = 0.48, CH_3OH).

IR (neat): 2928, 2862, 1734, 1647, 1510, 1388, 1232, 1078, 823 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.07 (m, 2 H), 6.84–6.80 (m, 2 H), 5.79 (t, *J* = 7.4 Hz, 1 H), 5.48 (t, *J* = 6.4 Hz, 1 H), 4.87–4.83 (m, 1 H), 4.57 (dd, *J* = 9.5, 5.7 Hz, 0.2 H), 4.46 (m, 2 H), 3.48–3.16 (m, 2 H), 3.02–2.70 (m, 3 H), 2.42–2.12 (m, 2 H), 1.79 (s, 3 H), 1.73 (s, 3 H), 1.58–1.08 (m, 19 H), 0.90–0.80 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.0, 173.4, 171.2, 170.3, 158.0, 157.6, 138.3, 138.0, 130.1, 129.6, 128.5, 128.2, 119.8, 119.6, 115.0, 114.6, 75.9, 75.3, 74.6, 67.5, 64.8, 61.7, 55.5, 40.4, 35.2, 35.0, 34.7, 34.1, 33.8, 33.7, 33.0, 32.0, 31.7, 30.7, 30.2, 29.7, 29.5, 29.4, 29.1, 29.0, 28.8, 28.4, 28.3, 27.9, 26.6, 25.9, 25.3, 25.1, 24.8, 24.1, 23.8, 23.5, 23.0, 22.7, 22.5, 20.6, 20.1, 18.2, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{30}H_{48}NO_4$: 486.3583; found: 486.3576.

Synthesis of PF1163 B (4)

A mixture of **8** (15 mg, 0.035 mmol), cesium carbonate (0.75 g, 0.071 mmol), 2-bromoethoxy *tert*-butyldimethylsilane (33 mg, 0.14 mmol), potassium iodide (0.58 mg, 0.003 mmol) and DMF (3 mL) was heated under reflux for 4 h. After completion of reaction, the solid was filtered off and the solvent was evaporated. The residue was filtered through a short pad of silica gel, washing with EtOAc, and concentrated to afford a colorless oil (15 mg, 75%) that was taken forward to the next step without further purification.

A magnetically stirred solution of the crude silyl ether (15 mg, 0.026 mmol) in THF (3 mL) at 0 °C was treated with TBAF (1.0 M solution in THF, 0.104 mL, 0.104 mmol). Stirring was continued for 20 min and then the reaction mixture was warmed to r.t. and stirring was continued for a further 8 h. The reaction was quenched with ice cold water (5 mL), and the mixture was extracted with EtOAc (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (petroleum ether/EtOAc, 70:30) to afford PF1163B **4** (10 mg, 86%) as a colorless oil.

R_f = 0.5 (60% EtOAc/ hexane); $[\alpha]_D^{20}$ –85.24 (*c* = 0.4, CH_3OH).

IR (neat): 3431, 3368, 2939, 2865, 1734, 1634, 1513, 1395, 1248, 1181 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.09 (m, 2 H), 6.86–6.81 (m, 2 H), 5.81–5.77 (m, 0.5 H), 4.92–4.79 (m, 1 H), 4.58–4.55 (m, 0.2 H), 4.06–4.04 (m, 2 H), 3.95 (m, 2 H), 3.74–3.16 (m, 2 H), 3.04–2.71 (m, 3 H), 2.41–1.96 (m, 3 H), 1.47–1.05 (m, 20 H), 0.90–0.80 (m, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.9, 173.5, 170.3, 157.3, 130.2, 129.7, 129.2, 114.9, 114.5, 76.0, 75.4, 74.7, 69.1, 61.5, 55.5, 34.1, 33.0, 31.7, 30.7, 29.7, 29.0, 26.5, 25.1, 23.5, 23.0, 22.5, 21.9, 20.6, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{27}H_{45}NO_5$: 462.3297; found: 462.3216.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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