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

Bharath Kumar Yasam\textsuperscript{a,b}  
Srihari Pabbaraja*\textsuperscript{a,b}  
\textsuperscript{a} Department of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad-500007, India  
\textsuperscript{b} Academy of Scientific and Innovative Research (AcSIR), Ghaziabad-201002, India  

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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.\textsuperscript{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.\textsuperscript{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*.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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](https://example.com/figure1.png)  
**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 macrocycles 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 and three reported synthetic routes for PF1163B.

In a continuation of our interest in the total synthesis of biologically active natural products, we report herein the synthesis on melearoride A and three reported synthetic members of this class. To our knowledge, there is only one synthetic group and culminated in the synthesis of individual building blocks.

Our retrosynthetic analysis (Scheme 1) revealed a common macrocyclic core, 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 frameworks could be obtained from two key fragments, PF1163B, respectively. The macrocyclic framework, which can be alkylated with 1-bromo-3-methylbut-2-ene, was synthesized from commercially available amino acid L-tyrosine, 9, which was used for the stereoselective synthesis of two 13-membered macrolides, melearoride-A and PF1163B, by following a similar strategy and by two different approaches.

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Our synthetic efforts began with the synthesis of precursor building block 9 from commercially available 1-hexanal. Initially, n-hexanal was subjected to Keck asymmetric alkylation to afford homallylic alcohol 10 (Scheme 2). The TBS protected homo allylic alcohol 12 was synthesized from commercially available L-tyrosine. Accordingly, L-tyrosine was treated with SOCl2 in methanol under reflux to provide the corresponding methyl ester 20. Boc protection followed by benzylaion was achieved with Boc2O in the presence of triethylamine and then BnBr in the presence of KI and K2CO3 in acetone to provide 21, followed by 22, respectively.

The amino acid fragment 10 was synthesized from commercially available L-tyrosine. The syntheses involved Keck allylation, cross-metathesis and auxiliary-based chiral alkylation reaction.
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). Boc deprotection with TFA afforded secondary amine, which was then acylated with pent-4-enoic acid using DIPEA / Pybop to give the corresponding acylated \( \text{a,\text{O}} \)-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 debenzylolation 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% yield. 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-1H-tetrazole-5-thiol (Scheme 6). \( \text{m-CPBA} \) oxidation of sulfide 29 afforded the required sulfone fragment 26 in 90% yield. Deprotection of the TBS group in 27 was achieved with TBAF in THF to provide secondary alcohol 30 in 85% yield. 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, 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.
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 Cs2CO3 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

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. CH2Cl2 was stirred over CaH2 and distilled prior to use. THF was dried with Na/benzophenone and distilled prior to use. Toluene was freshly distilled from CaH2 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 13C NMR spectra were recorded in CDCl3 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 CDCl3 (δ: 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 TiCl4 (0.54 mL, 5 mmol) in CH2Cl2 (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 CH2Cl2 (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) 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 mixture was diluted with CH2Cl2 (160 mL) and 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 Na2SO4, and concentrated in vacuo.

IR (neat): 3405, 3359, 3077, 2925, 1453, 1129 cm–1. HPLC [Chiral Pak-IC (2504.6 mm, 5 μm)]; 9.0 (c = 1.0, CHCl3), 14.571 (major isomer 99.4%) and 13.196 min (minor isomer 0.6%).

At 0 °C, stirred for 8 h, and then quenched with saturated NaHCO3 (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 Na2SO4, and concentrated in vacuo. Purification by flash column chromatography on silica gel (5% EtOAc/hexanes to 8% 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% iso-propanol (IPA) in hexane; tR = 14.571 (major isomer 99.4%) and 13.196 min (minor isomer 0.6%).

Colorless oil; Rf = 0.7 (20% EtOAc/hexanes); [α]D25 9.0 (c = 1.0, CHCl3), IR ( neat); 3405, 3359, 3077, 2925, 1453, 1129 cm–1.

1H NMR (500 MHz, CDCl3): δ = 5.16–5.11 (m, 2 H), 4.41–4.35 (s, 1 H), 4.40–4.25 (m, 1 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).

13C NMR (101 MHz, CDCl3): δ = 134.9, 118.1, 70.7, 42.0, 36.8, 31.9, 25.4, 22.7, 14.1.


(R)-tert-Butyldimethyl Non-1-en-4-olysosilane (12)

To a stirred solution of alcohol 11 (5.0 g, 35.21 mmol) in CH2Cl2 (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 aque-
ous NH₄Cl and the mixture was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, 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. Rₜ = 0.7 (5% EtOAc/hexanes); [α]₂³¹ = 9.9 (c = 1.0, CHCl₃).

IR (neat): 2933, 2860, 1737, 1463, 1374, 1250, 1165 cm⁻¹.

1H NMR (500 MHz, CDCl₃): 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, 9 H), 0.88–0.85 (m, 12 H), 0.04 (s, 6 H).

13C NMR (101 MHz, CDCl₃): 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 C₁₉H₂₃NO₄Si: 321.2663; found 321.2653.

(E)-5-tert-Butyldimethylsilyloxydecanoyloxazolidine-2-ene (13)

To a stirred solution of 12 (6.4 g, 26.5 mmol) in CH₂Cl₂ (60 mL) and MeOH (60 mL), O₃ was passed through a gas dispersion tube. When the color of the solution turned blue, dimethyl sulfoxide (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 colourless oil that was used directly in next step. To the aldehyde (6 g, 23.25 mmol) in CH₂Cl₂ (60 mL) was added (ethoxycarbonylmethylenetriphenylphosphorane (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 colourless oil. Rₜ = 0.2 (5% EtOAc/hexanes); [α]₂³¹ = 6.6 (c = 1.0, CHCl₃).

IR (neat): 2937, 2860, 1787, 1704, 1464, 1387, 1255, 1083 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 3.69–3.63 (m, 1 H), 2.35 (t, J = 7.4 Hz, 2 H), 1.74–1.64 (m, 4 H), 1.35–1.20 (m, 7 H), 0.89–0.86 (m, 12 H), 0.04 (s, 6 H).

13C NMR (101 MHz, CDCl₃): 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 C₁₉H₃₈NO₄Si: 303.2356; found 303.2355.

(5)-4-Benzyl-3-(R,S)-5-tert-Butyldimethylsilyloxydecanoxyloxoazolidin-2-one (16)

To a stirred solution of acid 15 (6 g, 19.86 mmol) in THF (60 mL) at –20 °C was added Et₃N (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 NH₄Cl (30 mL) and extracted with EtOAc (2 × 80 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na₂SO₄, filtered, and evaporated, and the crude product was purified by silica gel column chromatography (petroleum ether/EtOAc, 90:10) to afford 16 (7.8 g, 85%) as a viscous liquid. Rₜ = 0.5 (20% EtOAc/hexanes); [α]₂³¹ = –1.0 (c = 0.4, CHCl₃).

IR (neat): 2934, 2860, 1712, 1643, 1375, 1255, 1075 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 3.67–3.63 (m, 1 H), 2.33 (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).

13C NMR (101 MHz, CDCl₃): 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 C₁₉H₃₈NO₄Si: 303.2356; found 303.2355.
were washed with brine (50 mL), dried over anhydrous Na₂SO₄, 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.

IR (neat): 3545, 3418, 3160, 2930, 2861, 1459 cm⁻¹.


**Tert-Butyldimethyl (35,6R)-3-Methylundec-1-ene-6-yloxy silane (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 this was added dropwise to 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 NH₄Cl solution (20 mL) and extracted with EtOAc (20 mL). The organic extracts were washed with brine (10 mL) and dried over anhydrous Na₂SO₄. The solvent was filtered, evaporated under reduced pressure and the resulting crude product was purified by silica gel column chromatography (petroleum ether/EtOAc, 95:5) to afford 20 (as a colorless liquid (106 mg, 86%).

IR (neat): 3545, 3418, 3160, 2930, 2861, 1459 cm⁻¹.


**Methyl N-tert-Butoxycarbonyl-l-tyrosine (21)**

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.).

IR (neat): 3545, 3418, 3160, 2930, 2861, 1459 cm⁻¹.


**13C NMR (100 MHz, CDCl₃): 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.


**Methyl 3,4-L-tyrosine (20)**

To a stirred solution of 0-TBS protected alkyne 19 (200 mg, 0.67 mmol) at 0 °C in THF (5 mL), tetrabutylammonium fluoride (1.34 mL, 1.34 mmol, 1 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 Na₂SO₄, 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 19 as a colorless liquid (106 mg, 86%).

IR (neat): 3545, 3418, 3160, 2930, 2861, 1459 cm⁻¹.


**IR (neat): 3545, 3418, 3160, 2930, 2861, 1459 cm⁻¹.

86%.

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

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 a white solid (0.85 g, 82% yield).

HRMS (ESI): \( m/z \) [M + Na]\(^{+}\) calcd. for C\(_{15}\)H\(_{21}\)NO\(_{5}\)Na: 318.2107; found: 318.1978.

HRMS (ESI): \( m/z \) [M + H]\(^{+}\) calcd. for C\(_{22}\)H\(_{27}\)NO\(_{5}\): 386.1967; found: 386.1963.

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

To a mixture of Boc-L-Tyr-OMe (22) (20.0 g, 6.77 mmol), K₂CO₃ (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 (3 × 50 mL), the combined organic layers were separated, and the aqueous layer was washed with brine (2 × 10 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated. The residue was dissolved in CH\(_2\)Cl\(_2\) (5 mL). This solution was cooled to 0 °C before the sequential addition of 4-pentanone (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 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) (0.40 g, 86%) as a colorless oil.

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

HRMS (ESI): \( m/z \) [M + H]\(^{+}\) calcd. for C\(_{34}\)H\(_{50}\)NO\(_{5}\): 552.3689; found: 552.3675.

**2-(tert-butoxycarbonylmethylamino)propanoic Acid (23)**

To a solution of 6-3-Methylundec-1-en-6-yl (trans) (25) (200 mg, 0.362 mmol) in CH\(_2\)Cl\(_2\) (5 mL) cooled to 0 °C, was added trifluoroacetic acid (0.55 mL, 7.24 mmol) dropwise. The reaction mixture was 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\(_2\)Cl\(_2\) (5 mL). This solution was cooled to 0 °C before the sequential addition of 4-tert-butoxycarbonyl)[methylamino]propanoic acid (23) (1.0 g, 2.69 mmol) in THF (5 mL) slowly, the mixture was stirred for 30 min and then methanol (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\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure to give the crude product (10) as a white solid (0.85 g, 82% yield).

HRMS (ESI): \( m/z \) [M + Na]\(^{+}\) calcd. for C\(_{15}\)H\(_{23}\)NO\(_{5}\): 392.1851; found: 392.1842.

IR (neat): 3424, 2978, 1747, 1727, 1576, 1442, 1371, 1299, 1286, 1279, 1275, 1150, 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\(_{22}\)H\(_{28}\)NO\(_{5}\): 552.3689; found: 552.3675.
combined organic layers were washed with saturated aqueous NaHCO3, brine, dried over Na2SO4, 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).

\[ R_2 = 0.5 \times (20 \text{EtOAc} / \text{hexane}) \] (c = 0.14, CHCl3).

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

1\(^{H}\) NMR (500 MHz, CDCl3): \( \delta = 7.44-7.30 \) (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, \( J = 11.4 \) 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, CDCl3): \( \delta = 172.7, 170.9, 170.0, 157.9, 157.6, 144.3, 137.5, 137.1, 129.8, 128.5, 128.8, 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.


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 40° inclination) to afford the desired product 26 as a colorless liquid, which was taken into the next step without purification.

IR (neat): 3418, 3292, 2935, 2861, 1733, 1456, 1231 cm\(^{-1}\).

1\(^{H}\) NMR (500 MHz, CDCl3): \( \delta = 7.10-6.98 \) (m, 2 H), 6.78-6.67 (m, 2 H), 5.32-5.15 (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, 2 H), 1.72-2.09 (m, 1 H), 1.49-1.25 (m, 20 H), 0.92-0.80 (m, 7 H).

13\(^{C}\) NMR (101 MHz, CDCl3): \( \delta = 156.8, 137.1, 129.8, 128.5, 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.


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

To a cooled, stirred solution of 4-(benzyloxy)butan-1-ol (28) (20 g, 111 mmol) in anhydrous THF (20 mL) was added PPh3 (6.64 g, 16.46 mmol), 1-phenyl-1H-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 sulfone 29 (34.9 g, 90%) as a colorless liquid.

1\(^{H}\) NMR (500 MHz, CDCl3): \( \delta = 7.59-7.51 \) (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, CDCl3): \( \delta = 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 C20H19NO4S: 341.1431; found: 341.1432.

5-(4-Benzoylbutyl)sulfonyl)-1-phenyl-1H-tetrazole (26)

To a solution of 29 (3.0 g, 2.94 mmol) in CH2Cl2 (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 NaHCO3, dried over Na2SO4, 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.

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

1\(^{H}\) NMR (500 MHz, CDCl3): \( \delta = 7.79-7.51 \) (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, CDCl3): \( \delta = 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 C18H19NO4S2: 372.1256; found: 372.1255.
To a solution of sulfone 26 (500 mg, 1.34 mmol) in anhydrous THF (10 mL) at -78 °C, was added KHMD (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 NH₄Cl was added, the mixture was warmed to ambient temperature and extracted with Et₂O (3 x 30 mL). The combined organic layers were dried with Na₂SO₄, 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.

Rₛ = 0.5 using 5% EtOAc/hexane; [α]ₛ²⁰ = 3.8 (c = 1.0, CHCl₃).

IR (neat): 3405, 3070, 2925, 1733, 1225, 1175 cm⁻¹.


(6R,9E)-14-Benzylxoy-9-methyltetradec-10-en-6-ol (30)

To a stirred solution of diastereometric 0-TBS protected alkenol 27 (200 mg, 2.35 mmol) in THF (5 mL), tetra-tert-butyllammonium 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 Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (petroleum ether/EtOAc, 96:4) to afford alcohol 30 (126 mg, 85%) as a colorless liquid.

Rₛ = 0.5 (10% EtOAc/hexane); [α]ₛ²⁰ = 1.8 (c = 1.0, CHCl₃).

IR (neat): 3405, 3025, 2925, 1733, 1225, 1175 cm⁻¹.


(6R,9S,E)-14-Hydroxy-9-methyltetradecan-6-yl N-tert-Butyloxycarbonyl-N-methyl-t-rosyloxylate (31)

A solution of 31 (0.2 g, 0.286 mmol) in EtOAc (20 mL) was passed through a 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.

Rₛ = 0.5 (40% EtOAc/hexane); [α]ₛ²⁰ = -23.5 (c = 1.6, CHCl₃).

IR: 3316, 3268, 2935, 2861, 1733, 1513, 1456, 1090 cm⁻¹.

HRMS (ESI): [M + H]⁺ calcd. for C₃₃H₆₃NO₅: 547.4577; found: 547.4570.

(6R,9R,9)-9-(N-tert-Butyloxycarbonyl-N-methyl-t-rosyloxyl)-6-methyltetradecanoic Acid (33)

BABB (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 Na₂SO₄ (5 mL) and Et₂O (10 mL) were added and the organic layer was separated. The organic layer was washed with saturated aqueous NaHCO₃ (5 mL), dried over anhydrous Na₂SO₄, 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.

Rₛ = 0.5 (80% EtOAc/hexane); [α]ₛ²⁰ = 2.5 (c = 0.6, CHCl₃).

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IR: 3539, 3423, 1712, 1463, 1255, 1054 cm⁻¹.

1H NMR (500 MHz, CDCl₃): 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).

13C NMR (126 MHz, CDCl₃): 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, 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 C₃₀H₄₈NO₄: 486.3216; found: 486.3216.

(3S,10R,13R)-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 CH₂Cl₂ (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. 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 Na₂SO₄, filtered and concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography (petroleum ether/EtOAc, 70:30) to afford PF1163B (4 mg, 86%) as a colorless oil.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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References


