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Total synthesis of the antifungal antibiotic PF1163A

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ABSTRACT

The total synthesis of a novel antifungal antibiotic PF1163A is reported utilising Keck asymmetric allylation, Sharpless kinetic resolution, regioselective epoxide-ring opening, esterification and ring-closing metathesis as the key reactions.

1. Introduction

Recently two novel antifungal antibiotics, PF1163A **1** and PF1163B **2** (Fig. 1), were isolated from the fermentation broth of *Penicillium* sp.[1a] Both **1** and **2** exhibit potent growth inhibitory activity against the pathogenic fungal strain *Candida albicans* and have been shown to inhibit the biosynthetic pathway from lanosterol to ergosterol in *Candida albicans*, with the inhibiting activity of **1** being equal to fluconazol and four times higher than **2** (Fig. 1). Sasaki et al.[1b] elucidated the structures of **1** and **2** by extensive chemical and spectroscopic analysis. The absolute structure of **2** was unambiguously assigned by extensive spectroscopic analysis of the degradation products and single crystal X-ray diffraction analysis of its de-2-hydroxyethyl derivative. Similar attempts were made to elucidate the absolute structure of **1**, but its de-2-hydroxyl ethyl derivative was obtained as an amorphous powder. The absolute structure of **1** was eventually confirmed by its total synthesis.[3a] The unique structural features of **1** include it having a 13-membered macrolide consisting of an ester and amide functional groups; a 2-hydroxy ethyl derivative of *N*-methyl L-tyrosine, an isolated methyl stereocentre on the macrocyclic core and an aliphatic side chain possessing one hydroxyl group. The structures of **1** and **2** are similar except for the presence of an additional hydroxyl group in the side chain of **1**; this may be responsible for the four times higher biological activity compared to **2**. This attractive biological activity and our interest in the synthesis[2] of biologically active macrolide natural products prompted us to take up the synthesis of **1**. So far two syntheses[3a,b] have been reported for **1**. In the first synthesis,[3a] asymmetric allyltitanation and esterification were the key steps; the second synthesis[3b] was accomplished by Prins cyclisation and an RCM protocol. Herein we report the total synthesis of **1** using Keck asymmetric allylation, Sharpless kinetic resolution, regioselective epoxide-ring opening and ring-closing metathesis, and an RCM reaction between carbons C11–C12 rather than C7–C8 as reported earlier, as the key reactions.

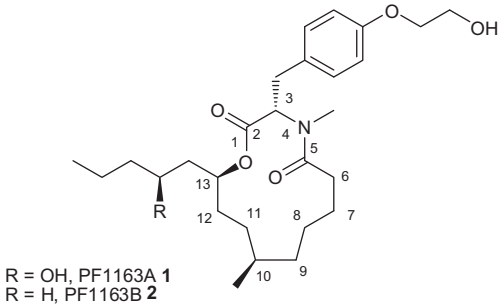

Figure 1.

2. Results and discussions

From our retrosynthetic analysis (Scheme 1) it could be deduced that **6**, **11** and **17** were the key building blocks. Initially, a cross-metathesis based approach between ester **4** and **17** was attempted resulting in the corresponding product. However, this approach was discontinued due to scale up problems. Alternatively, a ring-closing metathesis (RCM) approach was envisioned. Accordingly, fragment **6** identified as one of the key building blocks, could be visualised from compound **5** (vide infra Scheme 2) through a series of reactions such as oxidative cleavage of the olefin, vinylation and Sharpless kinetic resolution. Compound **5** could in turn be obtained from commercially available *n*-butyraldehyde by Keck asymmetric allylation[4] followed by further transformations as reported in the literature.[5] The synthesis of L-tyrosine derivative **11** started from the known compound **7**.[6] In order to introduce the lone methyl stereocentre of **17**, we chose the known allylic alcohol **12**[7] which upon Sharpless asymmetric epoxidation and regioselective ring-opening of the 2,3-epoxy alcohol with trimethyl aluminium in an S_N2 fashion and further transformations of the ensuing product would

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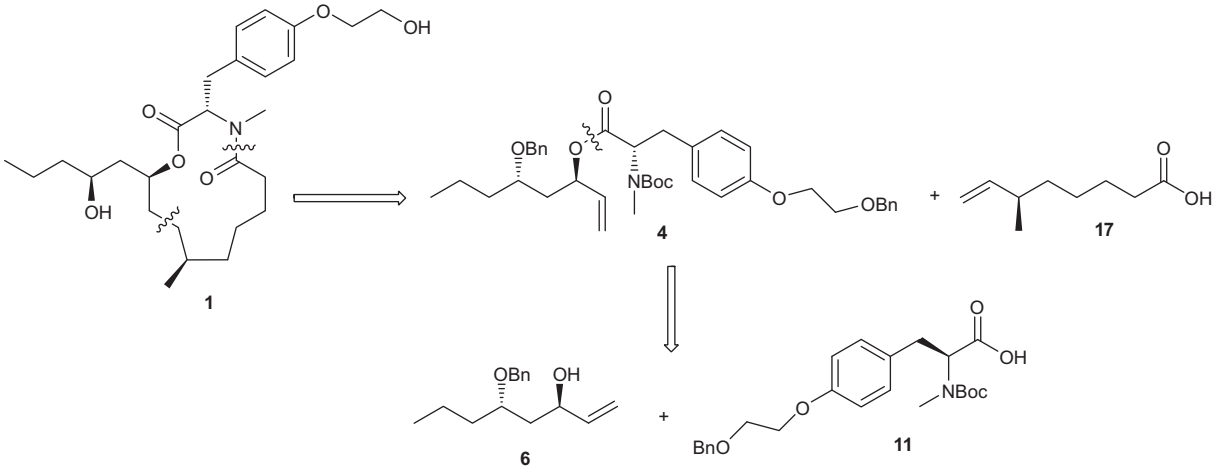
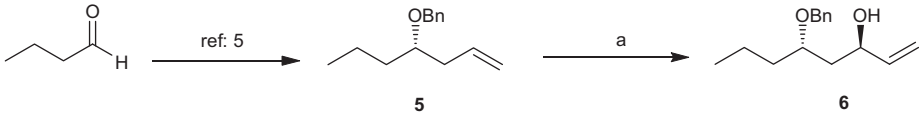


Scheme 1. Retrosynthetic analysis.



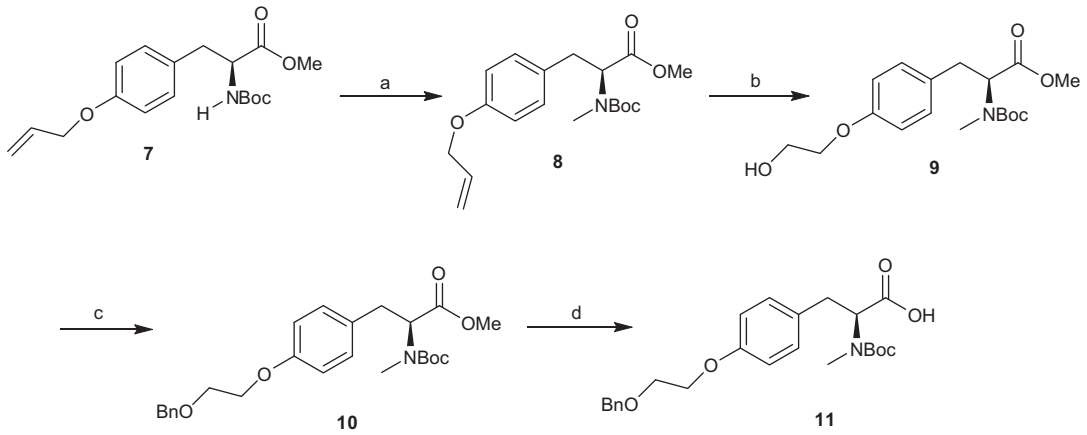
Scheme 2. Reagents and conditions. (a) (i) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane:H_2O (3:1), rt, 4.5 h; (ii) vinyl magnesium bromide, dry THF, −20 °C, 1 h, 75%; (iii) (+)-DIPT, $Ti(O^iPr)_4$, CHP, 4 Å MS, dry CH_2Cl_2, −20 °C, 12 h, 45%.

eventually lead to olefin **15**. Deprotection of the TBDPS protecting group in **15** would give the primary alcohol **16**, which upon oxidation under TEMPO and BIAB conditions would furnish the requisite carboxylic acid **17**.

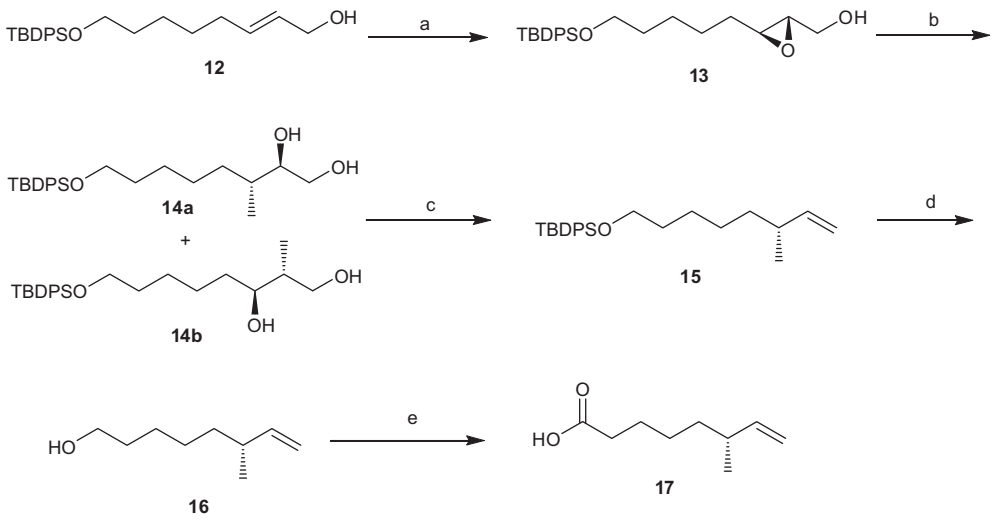
Thus, our initial focus was on the synthesis of fragment **6** (Scheme 2), from commercially available *n*-butyraldehyde. Transformation of *n*-butyraldehyde into benzyl protected homoallyl alcohol **5**[5] (its ee was found to be 95%) was previously reported on during the synthesis of some piperidine alkaloids. Oxidative cleavage[8] {$NaIO_4$/OsO_4/2,6-lutidine/1,4-dioxane:H_2O (3:1)/rt/4.5 h} of the terminal double bond in **5** afforded the aldehyde, which upon vinylation (vinyl magnesium bromide/dry THF/−20 °C/1 h) gave a 1:1 diastereomeric mixture of allylic alcohols **6** (75% combined yield). Alternatively, diastereomerically pure compound **6** could be obtained by Sharpless kinetic resolution[9] {(+)-DIPT/$Ti(O^iPr)_4$/CHP/4 Å MS/dry CH_2Cl_2/−20 °C/12 h/45%}.

The synthesis of amino acid fragment **11** (Scheme 3) started from the known compound *O*-allyl *N*-Boc-L-tyrosine **7**.[6] N-Methylation (CH_3I/Ag_2O/DMF/rt/9 h) of compound **7** afforded **8** (85%). Oxidative cleavage[8] {$NaIO_4$/OsO_4/2,6 lutidine/1,4-dioxane:H_2O (3:1)/ rt/4 h} of the olefin in compound **8** afforded the aldehyde, which without further purification was subjected to reduction ($NaBH_4$/MeOH/0 °C to rt/1 h) to afford **9** (80%, over two steps). The thus obtained primary alcohol **9** was protected as its benzyl ether (BnBr/Ag_2O/DMF/rt/12 h) to furnish **10** (83%). Finally, saponification of the compound **10** {LiOH/THF:MeOH:H_2O (3:1:1)/0 °C to rt/6 h} gave **11** (84%). The spectroscopic data of **10** and **11** were in agreement with the reported values.[10]

The synthesis of fragment **17** (Scheme 4) started from the known allylic alcohol **12**.[7] Accordingly, Sharpless epoxidation[11] {(+)-DIPT/$Ti(O^iPr)_4$/CHP/4 Å MS/dry CH_2Cl_2/−20 °C/6 h/90%} of **12** afforded **13** and its ee was evaluated by HPLC as 88.76%. The 2,3-epoxy alcohol **13** upon a regioselective[12] ring-opening reaction by the methyl nucleophile generated in situ from Me_3Al (Me_3Al/hexane/0 °C/1 h) in an S_N2 fashion gave a mixture of 1,2- and 1,3-diols (C3:C2, in an 8:2 ratio, 86% combined yield). This mixture



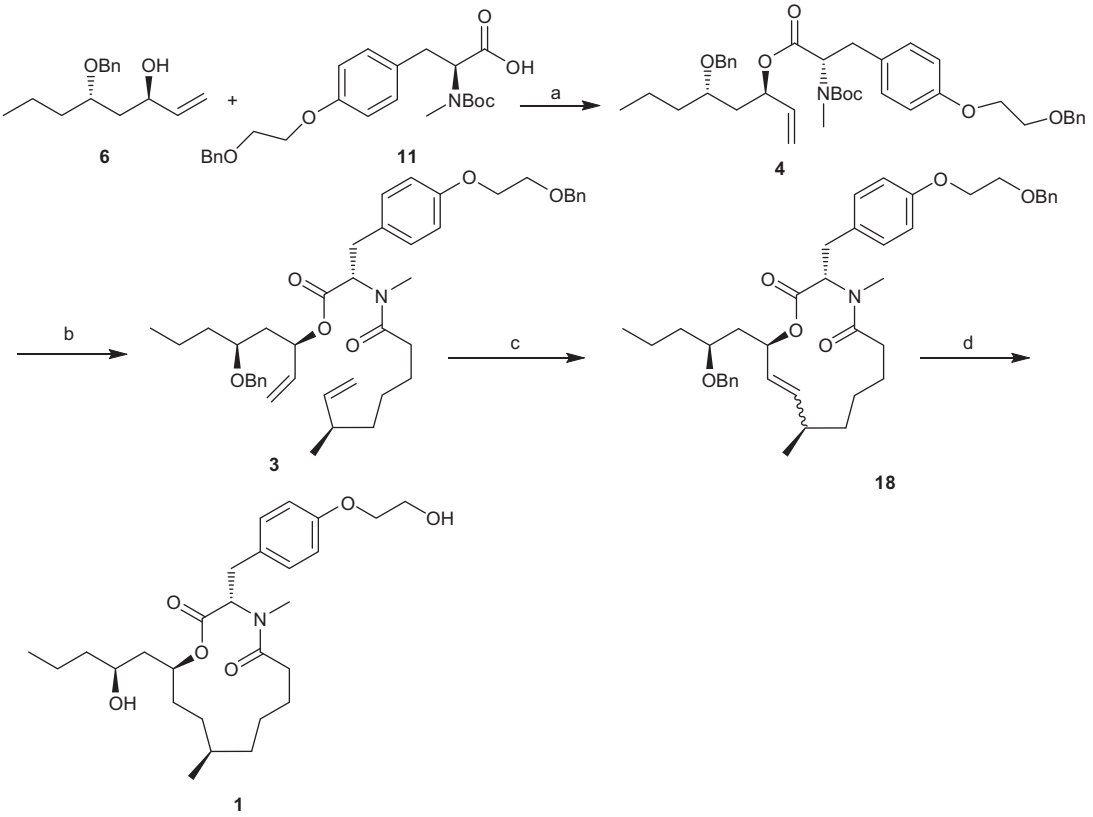
Scheme 3. Reagents and conditions. (a) MeI, Ag_2O, DMF, rt, 9 h, 85%; (b) (i) $NaIO_4$, OsO_4, 2,6-lutidine, 1,4-dioxane:H_2O (3:1), rt, 4 h; (ii) $NaBH_4$, MeOH, 0 °C to rt, 1 h, 80% (over two steps); (c) Benzyl bromide, Ag_2O, DMF, rt, 12 h, 83% (d) LiOH, THF:MeOH:H_2O (3:1:1), 0 °C to rt, 6 h, 84%.



Scheme 4. Reagents and conditions. (a) (+)-DIPT, $Ti(O^iPr)_4$, CHP, 4 Å MS, dry CH_2Cl_2, −20 °C, 6 h, 90%; (b) Me_3Al, hexane, 0 °C, 1 h, 86%; (c) I_2, TPP, imidazole, dry CH_2Cl_2, 0 °C to rt, 2 h, 70%; (d) TBAF, dry THF, 0 °C to rt, 1 h, 90%; (e) TEMPO, BIAB, CH_2Cl_2:H_2O (3:1), 0 °C to rt, 12 h, 82%.

was subjected to iodination (I_2/TPP/imidazole/dry CH_2Cl_2/0 °C to rt/2 h), wherein only the 1,2-diol was consumed to afford terminal olefin **15** (70%). The isomeric diols were thus purified. Olefin **15** was characterised from its spectroscopic data. Next, desilylation (TBAF/dry THF/0 °C to rt/1 h) of **15** furnished the corresponding primary alcohol **16** (90%). The thus obtained primary alcohol **16** was subjected to oxidation {TEMPO/BIAB/CH_2Cl_2:H_2O (3:1)/0 °C to rt/12 h} to afford carboxylic acid **17** (82%) whose formation was confirmed by the appearance of α-methylene protons in the ^{1}H NMR spectrum resonating at δ 2.35 ppm (J = 7.5 Hz) as a triplet and the carbonyl signal in ^{13}C NMR appearing at δ 180.1 ppm in addition to other spectroscopic evidence.

Next, esterification of **11** with alcohol **6** (Scheme 5) under DCC conditions (DCC/DMAP/dry CH_2Cl_2/0 °C to rt/12 h) afforded ester **4** (85%). The deprotection of the Boc group (TFA/dry CH_2Cl_2/0 °C to rt/2 h) in ester **4** resulted in the corresponding *sec*-amine, which without further purification was acylated with carboxylic acid **17** (EDCI/HOBT/DIPEA/dry CH_2Cl_2/0 °C to rt/12 h) to provide diene **3** (78% over two steps). Ring-closing metathesis[13a, b] of diene **3** (10 mol % G-II/dry CH_2Cl_2/12 h/reflux) afforded **18** (83%) as '*E*'



Scheme 5. Reagents and conditions. (a) DCC, DMAP, dry CH_2Cl_2, 0 °C to rt, 12 h, 85%; (b) (i) TFA, dry CH_2Cl_2, 0 °C to rt, 2 h; (ii) 17, EDCI, HOBT, DIPEA, dry CH_2Cl_2, 0 °C to rt, 12 h, 78% (over two steps); (c) 10 mol % G-II, dry CH_2Cl_2, 12 h, reflux, 83%; (d) H_2, Pd-C, EtOAc, rt, 12 h, 80%.

and 'Z' diastereomers (in a 2:1 ratio, respectively). No attempts were made to separate the *E*- and *Z*-isomers since the isomeric status was irrelevant because of the ensuing olefinic reduction step. Accordingly, the saturation of the double bond and hydrogenolysis of the benzyl groups (H_2/Pd-C/EtOAc/rt/12 h) occurred in a single step providing the target compound **1** (80%) as a colourless oil with $[\alpha]_D^{25} = -89.3$ (*c* 0.5, MeOH) {lit.[3a] $[\alpha]_D^{25} = -91.0$ (*c* 0.73, MeOH), lit.[3b] $[\alpha]_D^{25} = -88.5$ (*c* 1.0, MeOH)}. The spectroscopic data of **1** were identical to the reported values.[3a, b]

3. Conclusion

In conclusion, the total synthesis of a novel antifungal antibiotic **1** has been accomplished wherein Keck asymmetric allylation, Sharpless kinetic resolution, regioselective epoxide-ring opening, esterification and ring-closing metathesis were the key reactions.

4. Experimental

4.1. General

Column chromatography was performed on silica gel, Acme grade 60–120 mesh. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenoneketyl. Unless stated otherwise, optical rotations were measured with a JASCO P-1020 instrument at 25 °C. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker 300 or Varian VXR 400 or Varian VXR 500 in $CDCl_3$ as the solvent with TMS as the reference unless otherwise indicated. Unless stated otherwise, HRMS spectra were recorded on a QTOF analyser (QSTAR XL, Applied Biosystems/MDS Sciex) at NCMS-IICT, Hyderabad. Unless stated otherwise, elemental analysis was carried on a Vario Micro Cube Elementar at Analytical Chemistry Division IICT, Hyderabad. The software ACD/Name Version 1.0, developed by M/s Advanced Chemistry Development Inc., Toronto, Canada, assisted nomenclature was used in the experimental section. Unless stated otherwise, all reactions were performed under an inert atmosphere.

4.1.1. (3*R*,5*S*)-5-(Benzyloxy)oct-1-en-3-ol 6

To a stirred solution of **5** (0.4 g, 1.96 mmol) in 1,4-dioxane:H_2O (3:1, 5.0 mL) was added OsO_4 (0.4 mL, 0.5 M in toluene) dropwise. After 5 min., 2,6-lutidine (0.45 mL, 3.92 mmol) and $NaIO_4$ (0.83 g, 3.92 mmol) were added and stirred for 4.5 h at room temperature. The reaction mixture was quenched with Na_2SO_3 (1.5 g) and extracted with EtOAc (2 × 50.0 mL). The combined organic layers were washed with water (30.0 mL), brine (30.0 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude aldehyde obtained was used directly for the next reaction.

To a solution of the aldehyde (0.33 g, 1.6 mmol) in dry THF (5.0 mL) was added a 1.0 M solution of vinyl magnesium bromide (3.2 mL, 3.2 mmol) at −20 °C and stirred for 1 h. After completion of the reaction, the reaction mixture was quenched with a saturated aq NH_4Cl (10.0 mL) solution and extracted with EtOAc (2 × 50.0 mL). The combined organic layers were washed with water (30.0 mL), brine (30.0 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (Silica gel, 60–120 mesh, EtOAc:*n*-hexane, 1:19) to afford 1:1 diastereomeric mixture of allylic alcohols (0.28 g, 75%) as a yellow oily liquid.

To a suspension of activated molecular sieves 4 Å (1.0 g) in dry CH_2Cl_2 (3.0 mL) was added (+)-DIPT (0.15 g, 0.64 mmol) in dry CH_2Cl_2 (1.0 mL) followed by the slow addition of $Ti(O^iPr)_4$ (0.16 mL, 0.53 mmol) at −20 °C. After stirring for 20 min cumene hydroperoxide (0.1 mL, 0.64 mmol) was added at −20 °C, and stirred for a further 20 min. Allylic alcohol (0.25 g, 1.06 mmol) in dry CH_2Cl_2 (1.0 mL) was added and the reaction mixture was stirred at −20 °C for 12 h, then warmed up to 0 °C and quenched with an aq basic solution (3 M NaOH: brine 3:7, 5.0 mL). After stirring for 1 h, the reaction mixture was filtered through a pad of celite using EtOAc. The filtrate was concentrated and purified by column chromatography (silica gel 60–120 mesh, EtOAc:*n*-hexane 1:19) to afford allylic alcohol **6** (0.114 g, 45%) as a yellow oily liquid. $[\alpha]_D^{25} = +62.2$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.24 (m, 5H), 5.96–5.80 (m, 1H), 5.27 (d, *J* = 18.6 Hz, 1H), 5.09 (d, *J* = 10.4 Hz, 1H), 4.59 (d, AB pattern, *J* = 11.3 Hz, 1H), 4.50 (d, AB pattern, *J* = 11.3 Hz, 1H), 4.41 (q, *J* = 4.5 Hz, 1H), 3.74 (p, *J* = 6.2 Hz, 1H), 2.93–2.84 (br s, 1H), 1.82–1.46 (m, 6H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.9, 128.4, 127.8, 127.7, 113.8, 76.7, 71.0, 69.8, 39.8, 35.6, 18.4, 14.3; HRMS (*m/z*) $[M+Na]^+$ Calcd 257.1512. Found 257.1510 for $C_{15}H_{22}O_2Na$.

4.1.2. (*S*)-Methyl 3-[4-(allyloxy)phenyl]-2-[*tert*-butoxycarbonyl(methyl)amino]propanoate 8

To a stirred solution of **7** (0.5 g, 1.49 mmol) in dry DMF (6.0 mL) was added Ag_2O (0.689 g, 2.98 mmol). After 5 min, MeI (0.55 mL, 8.95 mmol) was added and allowed to stir at room temperature for 9 h. The reaction mixture was quenched with a saturated aq NH_4Cl solution (10.0 mL) and extracted with EtOAc (2 × 50.0 mL). The combined organic layers were washed with water (30.0 mL), brine (30.0 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 60–120 mesh, EtOAc:*n*-hexane 1:9) to afford **8** (0.44 g, 85%) as a yellow oil. $[\alpha]_D^{25} = -173.9$ (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15–7.05 (m, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 6.11–5.98 (m, 1H), 5.46–5.35 (m,1H), 5.32–5.24 (m, 1H), 4.94–4.85 (m, 0.5H), 4.51 (d, *J* = 5.2 Hz, 2H), 4.49–4.43 (m, 0.5H), 3.74 (s, 3H), 3.31–3.17 (m, 1H), 3.00–2.89 (m, 1H), 2.71 (s, 3H), 1.43–1.31 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 157.4, 133.4, 130.0, 129.5, 117.6, 114.8, 114.6, 68.7, 61.8, 59.4, 52.1, 32.6, 31.7, 28.1; HRMS (*m/z*) $[M+Na]^+$ calcd. 372.1781. Found 372.1780 for $C_{19}H_{27}NO_5Na$.

4.1.3. (*S*)-Methyl 2-[*tert*-butoxycarbonyl(methyl)amino]-3-[4-(2-hydroxyethoxy)phenyl]propanoate 9

To a stirred solution of **8** (0.44 g, 1.26 mmol) in 1,4-dioxane:H_2O (3:1, 5.0 mL), was added OsO_4 (0.4 mL, 0.5 M in toluene) dropwise. After 5 min., 2,6-lutidine (0.3 mL, 2.52 mmol) and $NaIO_4$ (0.54 g, 2.52 mmol) were added and stirred for 4 h at room temperature. After completion of the reaction, the reaction mixture was quenched with Na_2SO_3 (1.5 g) and extracted with EtOAc (2 × 50.0 mL). The combined organic layers were washed with water (30.0 mL), brine (30.0 mL), dried (Na_2SO_4) and evaporated. The crude aldehyde obtained was used directly for the next reaction.

To a stirred solution of the aldehyde (0.4 g, 1.13 mmol) in MeOH (5.0 mL) was added $NaBH_4$ (0.043 g, 1.13 mmol) at 0 °C and allowed to stir at room temperature for 1 h. Methanol was evaporated and extracted with EtOAc (2 × 50.0 mL). The combined organic layers were washed with water (30.0 mL), brine (30.0 mL), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (silica gel 60–120 mesh, EtOAc:*n*-hexane 2:8) to afford alcohol **9** (0.35 g, 80%, over two steps) as a yellow oil. $[\alpha]_D^{25} = -93.6$ (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16–7.04 (m, 2H), 6.85 (d, *J* = 7.9 Hz, 2H), 4.94–4.84 (m, 0.5H), 4.51–4.41 (m, 0.5H), 4.08–4.02 (m, 2H), 4.00–3.91 (m, 2H), 3.77–3.70 (m, 3H), 3.29–3.17 (m, 1H), 3.02–2.91 (m, 1H), 2.71 (s, 3H), 2.07–1.97 (br s, 1H), 1.56 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 157.5, 130.0, 114.6, 114.5, 69.1, 61.8, 61.4, 59.5, 52.1, 34.5, 34.2, 28.2; HRMS (*m/z*) $[M+Na]^+$ Calcd 376.1730. Found 376.1728 for $C_{18}H_{27}NO_6Na$.

4.1.4. {(2*S*,3*S*)-3-[5-(*tert*-Butyldiphenylsilyloxy)pentyl]oxiran-2-yl}methanol 13

To a suspension of activated molecular sieves 4 Å (3.0 g) in dry CH_2Cl_2 (5.0 mL) was added (+)-DIPT (0.26 g, 1.09 mmol) in dry

CH_2Cl_2 (2.0 mL) followed by the slow addition of $Ti(O^iPr)_4$ (0.27 mL, 0.91 mmol) at −20 °C. After stirring for 20 min cumene hydroperoxide (0.33 mL, 2.2 mmol) was added at −20 °C and stirred for a further 20 min. Allylic alcohol **12** (0.7 g, 1.83 mmol) in dry CH_2Cl_2 (3.0 mL) was added and the reaction mixture was stirred at −20 °C for 6 h, then warmed up to 0 °C and quenched with an aq basic solution (3 M NaOH: brine 3:7, 15.0 mL). After stirring for 1 h, the reaction mixture was filtered through a pad of Celite using EtOAc. The filtrate was concentrated and purified by column chromatography (silica gel 60–120 mesh, EtOAc:*n*-hexane 1:9) to afford **13** (0.65, 90%) as a colourless oily liquid. The ee was found to be 88.76% as determined by chiral HPLC analysis {(Chiral cel-IC: 250 × 4.6 mm, 5u, 3% ^{i}PrOH/hexane, flow rate 1 mL/min, 210 nm)}: t_R (minor) 17.115 min, t_R (major) 19.727 min. $[\alpha]_D^{25} = -32.4$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.62 (m, 4H), 7.46–7.34 (m, 6H), 3.90 (d, *J* = 12.0 Hz, 1H), 3.66 (t, *J* = 6.0 Hz, 2H), 3.67–3.57 (m, 1H), 2.96–2.88 (m, 2H), 1.67–1.51 (m, 8H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.4 (6C), 134.0, 129.4, 127.4 (4C), 63.7, 61.6, 58.4, 55.8, 32.5, 31.4, 26.5 (3C), 25.5 (2C), 19.0; HRMS (*m/z*) $[M+Na]^+$ Calcd 421.2169. Found 421.2163 for $C_{24}H_{34}O_3NaSi$.

4.1.5. (*R*)-*tert*-Butyl(6-methyloct-7-enyloxy)diphenylsilane 15

To stirred solution of **14a** and **14b** (0.44 g, 1.06 mmol) in dry CH_2Cl_2 (7.0 mL) were added I_2 (0.54 g, 2.12 mmol), TPP (0.55 g, 2.12 mmol) and imidazole (0.21 g, 3.18 mmol) successively at 0 °C and allowed to stir at room temperature for 2 h. After the reaction was complete, the solvent was evaporated and adsorbed onto silica and purified by column chromatography (silica gel 60–120 mesh, EtOAc:*n*-hexane 0.5:9.5) to give **15** (70%, 0.28 g) as a colourless oil. $[\alpha]_D^{25} = -9.7$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67–7.62 (m, 4H), 7.41–7.32 (m, 6H), 5.69–5.59 (m, 1H), 4.95–4.85 (m, 2H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.14–2.01 (m, 1H), 1.40–1.22 (m, 8H), 1.05 (s, 9H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.0, 135.5, 134.2, 129.5, 127.6, 112.4, 64.0, 37.6, 36.5, 32.6, 26.8, 25.8, 20.2, 19.2; HRMS (*m/z*) $[M+Na]^+$ Calcd 403.1168. Found 403.1166 for $C_{25}H_{36}ONaSi$.

4.1.6. (*R*)-6-Methyloct-7-en-1-ol 16

To a stirred solution of **15** (0.2 g, 0.52 mmol) in dry THF (3.0 mL) was added a 1.0 M solution of TBAF (0.6 mL, 0.6 mmol) at 0 °C and allowed to stir at room temperature for 1 h. Next, the THF solvent was evaporated and adsorbed onto silica and purified by column chromatography (silica gel 60–120 mesh, EtOAc:*n*-hexane 1:9) to give **16** (0.07 g, 90%) as a yellow oil. $[\alpha]_D^{25} = -17.3$ (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.70–5.58 (m, 1H), 4.96–4.85 (m, 2H), 3.61 (t, *J* = 6.7 Hz, 2H), 2.15–2.04 (m, 1H), 1.60–1.48 (m, 2H), 1.39–1.23 (m, 6H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.8, 112.4, 62.9, 37.6, 36.5, 32.6, 26.8, 25.7, 20.2; LCMS: 165 $[M+Na]^+$. Anal. Calcd for $C_9H_{18}O$: C, 75.66; H, 12.40. Found: C, 75.42; H, 12.33.

4.1.7. (*R*)-6-Methyloct-7-enoic acid 17

To stirred solution of **16** (0.07 g, 0.5 mmol) in CH_2Cl_2:H_2O (3:1, 2.0 mL) were added TEMPO (cat) and BIAB (0.24 g, 0.73 mmol) successively at 0 °C and allowed to stir at room temperature for 12 h. Later, the reaction mixture was quenched with saturated aq $Na_2S_2O_3$ (10.0 mL) and extracted with CH_2Cl_2 (2 × 15.0 mL). The combined organic layers were washed with water (10.0 mL), brine (10.0 mL), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (silica gel 60–120 mesh, EtOAc:*n*-hexane 1:9) to give **17** (0.06 g, 82%) as a yellow oil. $[\alpha]_D^{25} = -35.9$ (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5–74–5.59 (m, 1H), 4.98–4.88 (m, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.16–2.05 (m, 1H), 1.70–1.57 (m, 2H), 1.38–1.24 (m, 4H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.1, 144.7, 112.7, 37.6, 36.1, 34.0, 26.7, 24.6, 20.3; LCMS: 179 $[M+Na]^+$. Anal. Calcd for $C_9H_{16}O_2$: C, 68.90; H, 10.22. Found: C, 69.11; H, 10.55.

4.1.8. (*S*)-[(3*R*,5*S*)-5-(Benzyloxy)oct-1-en-3-yl] 3-[4-(2-(benzyloxy)ethoxy)phenyl]-2-[*tert*-butoxycarbonyl(methyl) amino]propanoate 4

To a stirred solution of **6** (0.1 g, 0.43 mmol) in dry CH_2Cl_2 (2.0 mL) were added DCC (0.1 g, 0.51 mmol) and DMAP (cat) followed by **11** (0.2 g, 0.46 mmol) in dry CH_2Cl_2 (2.0 mL) at 0 °C and allowed to stir at room temperature for 12 h. The solvent was evaporated off and the residue adsorbed on to the silica and purified by column chromatography (silica gel 60–120 mesh, EtOAc:*n*-hexane 1:9) to give **4** (0.23 g, 85%) as a yellow oil. $[\alpha]_D^{25} = -50.2$ (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.30 (m, 10H), 7.14–7.02 (m, 2H), 6.87–6.79 (m, 2H), 5.85–5.73 (m, 1H), 5.58–5.47 (m, 1H), 5.33–5.11 (m, 2H), 4.87–4.78 (m, 1H), 4.63 (s, 2H), 4.55–4.27 (m, 2H), 4.16–4.05 (m, 2H), 3.84–3.77 (m, 2H), 3.45–3.33 (m, 1H), 3.28–3.12 (m, 1H), 2.97–2.80 (m, 1H), 2.74–2.64 (m, 3H), 1.58 (s, 9H), 1.41–1.30 (m, 6H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.7, 129.8, 128.4, 128.1, 128.0, 127.7, 127.6, 127.5, 114.6, 114.5, 73.3, 72.8, 72.5, 71.4, 71.1, 68.4, 67.4, 29.7, 29.3, 18.1, 14.1; HRMS (*m/z*) $[M+Na]^+$ Calcd 668.3557. Found 668.3558 for $C_{39}H_{51}NO_7Na$.

4.1.9. (*S*)-[(3*R*,5*S*)-5-(Benzyloxy)oct-1-en-3-yl] 3-[4-(2-(benzyloxy)ethoxy)phenyl]-2-[(*R*)-*N*,6-dimethyloct-7-enamido] propanoate 3

To a stirred solution of **4** (0.21 g, 0.32 mmol) in dry CH_2Cl_2 (2.0 mL) was added TFA (0.1 mL) at 0 °C and allowed to stir at room temperature for 2 h. After the reaction was completed, TFA was removed under vacuum. Later DIPEA (0.17 mL, 0.97 mmol) was added to the reaction mixture. After 5 min, a solution of carboxylic acid **17** (0.05 g, 0.32 mmol) in dry CH_2Cl_2 (1.0 mL) was added to the amine followed by EDCI (0.074 g, 0.48 mmol) and HOBT (0.064 g, 0.48 mmol) at 0 °C and allowed to stir at room temperature for 12 h. The reaction mixture was quenched with saturated aq NH_4Cl (10.0 mL) solution and extracted with $CHCl_3$ (2 × 15.0 mL). The combined organic layers were washed with 1 M HCl (15.0 mL), water (15.0 mL), saturated aq $NaHCO_3$ (15.0 mL) solution and brine (15.0 mL), dried (Na_2SO_4) and evaporated. The crude residue was purified by column chromatography (silica gel 60–120 mesh, EtOAc:*n*-hexane 1:9) to give **3** (0. 16 g, 78%, over two steps) as a colourless oil. $[\alpha]_D^{25} = -32.4$ (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.28 (m, 10H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.87–6.76 (m, 2H), 5.85–5.59 (m, 2H), 5.57–5.46 (m, 1H), 5.35–5.10 (m, 2H), 5.25–5.19 (m, 1H), 5.00–4.84 (m, 2H), 4.62 (s, 2H), 4.54–4.42 (m, 1H), 4.37–4.28 (m, 1H), 4.15–4.04 (m, 2H), 3.85–3.77 (m, 2H), 3.46–3.33 (m, 1H), 3.30–3.17 (m, 1H), 2.94–2.73 (m, 4H), 2.22–2.11 (m, 1H), 1.76 (t, *J* = 6.6 Hz, 2H), 1.70–1.42 (m, 6H), 1.41–1.11 (m, 6H), 0.98 (d, *J* = 7.9 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 170.4, 157.5, 144.6, 136.4, 135.9, 129.9, 129.7, 129.2, 128.4, 128.3, 128.0, 127.7, 127.6, 127.5, 116.6, 114.8, 114.5, 112.3, 74.9, 73.3, 72.7, 71.2, 68.4, 67.2, 57.8, 39.4, 37.5, 36.3, 36.0, 33.4, 33.8, 29.6, 26.9, 24.9, 20.1, 18.1, 14.2; HRMS (*m/z*) $[M+Na]^+$ Calcd 706.4078. Found 706.4076 for $C_{43}H_{57}NO_6Na$.

4.1.10. (3*S*,10*R*,13*S*)-3-[4-(2-Hydroxyethoxy)benzyl]-13-[(*S*)-2-hydroxypentyl]-4,10-dimethyl-1-oxa-4-azacyclotridecane-2,5-dione 1 (PF1163A)

To a solution of compound **18** (0.022 g 0.044 mmol) in EtOAc (1.0 mL) was added Pd/C (0.005 g, 10 mol%) and stirred under H_2 atmosphere for 12 h. After completion of the reaction, the mixture was filtered through a Celite pad, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 60–120 mesh, EtOAc:*n*-hexane 4:6) to

give **1** (0.011 g, 80%) as a colourless oil. $[\alpha]_D^{25} = -89.3$ (*c* 0.5, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.02 (m, 2H), 6.81 (d, J = 8.3 Hz, 2H), 5.83–5.69 (m, 1H), 5.11–4.93 (m, 1H), 4.02 (s, 2H), 3.91 (s, 2H), 3.52–3.27 (m, 1H), 3.26–3.10 (m, 1H), 3.04–2.86 (m, 3H), 2.85–2.54 (m, 1H), 2.38–2.26 (m, 1H), 1.75–1.04 (m, 19H), 0.88 (t, J = 7.2 Hz, 3H), 0.83 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 171.6, 157.6, 130.4, 128.9, 114.3, 73.1, 69.0, 66.5, 61.4, 55.8, 49.2, 42.0, 39.2, 33.8, 33.3, 29.7, 24.2, 20.6, 18.9, 14.2; HRMS (*m*/*z*) $[M+Na]^+$ Calcd 500.29826. Found 500.29825 for $C_{27}H_{43}NO_6Na$.

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