Stereoselective Synthesis of (–)-PF1163A via Prins Cyclization

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Abstract: A highly stereoselective and convergent total synthesis of PF1163 A is described while proving the versatility of Prins cyclization in natural product synthesis. The Prins cyclization, Yamaguchi esterification, and ring-closing metathesis reactions are the key steps utilized in the synthesis of macrolactone.

Keywords: (–)-PF1163A, 13-membered macrolactone, Prins cyclization, ring-closing metathesis

PF1163A (**1**) and PF1163B (**2**) were isolated as new antifungal antibiotics from a fermentation broth of *Penicillium sp.*[1a] and subsequently shown to be the first known inhibitors of ERG25p, a C-4 methyl oxidase. The antifungal activity of **1** is four times higher than that of **2** with IC_{50} values of 12 ng/mL and 34 ng/mL, respectively. PF1163A and B are structurally identical in every respect except for the presence of an extra hydroxyl group in the side chain of **1**. Sasaki[1b] and co-workers elucidated the structures after rigorous analysis of spectral and comparative data. Tatsuta et al.[2] realized a synthesis via asymmetric allyl titanations thereby providing an absolute proof for the stereostructures of the natural products **1** and **2**. Inspired by the biological properties and structural similarity to other biologically active natural products, such as spongidepsin (**3**), doliculide (**4**), and the geodiamolides (**5**, Figure 1) and in continuation of our interest in the synthesis of bioactive naturally occurring lactones,[4j,k] we have investigated the synthesis of (–)-PF1163A via Prins cyclization.[3]

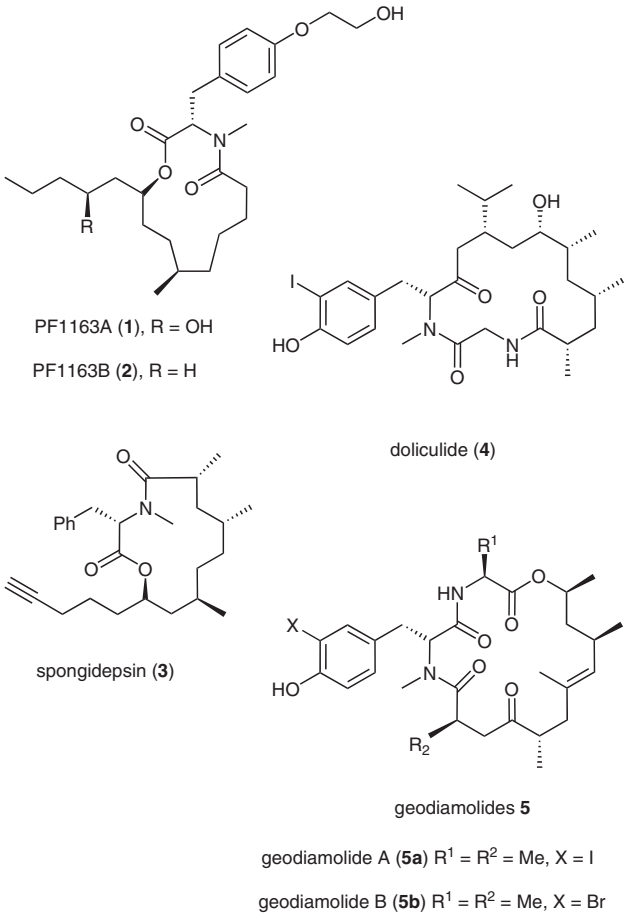

Figure 1

Our retrosynthetic analysis (Scheme 1) revealed two key synthons **16** and **17**. With our initial focus on the synthesis of synthon **16**, we envisaged that the synthon **16** could be achieved via Prins cyclization between known homoallylic alcohol **8**[4c] and aldehyde **9**[5] (Scheme 1) whereas the synthon **17** could be drawn from L-tyrosine.

Our synthetic efforts began with the precurser building block **6**, which has been synthesized and utilized to make several natural products in our group.[4] Prins cyclization of compound **6** with aldehyde **7**[5] in the presence of TFA followed by hydrolysis of the resulting trifluoroacetate gave trisubstituted pyran **8** in 52% yield (Scheme 2). Though the stereochemical aspects of such Prins cyclizations and structurally similar compounds to **8** have been discussed in detail previously,[3,4] we decided to analyze the product in this approach. The primary hydroxyl group in **8** was transformed to tosylate **9** using TsCl and triethylamine in anhydrous CH_2Cl_2. The secondary hydroxyl group was protected as its MOM ether **10** using MOMCl and Hünig's base in anhydrous CH_2Cl_2. Substitution of tosylate in **10** using NaI in acetone followed by reductive opening of the iodomethyl pyran produced alcohol **12** in 91% overall yield (2 steps).[4b,h] The resulting secondary hydroxyl group was protected as its TBS ether **13** using TBSCl, DMAP, and imidazole. Treating **13** with Pd/C in EtOAc furnished alcohol **14** accomplishing two reactions, benzyl ether deprotection and the reduction of the double bond in one pot. Oxidation of primary alcohol of **14** with DMP in CH_2Cl_2 afforded the aldehyde, which was treated without purification with methylene triphenylphosphorane to furnish olefin **15** in 88% overall yield. Finally deprotection of the silyl protecting group using TBAF furnished the key fragment **16** in 83% yield.

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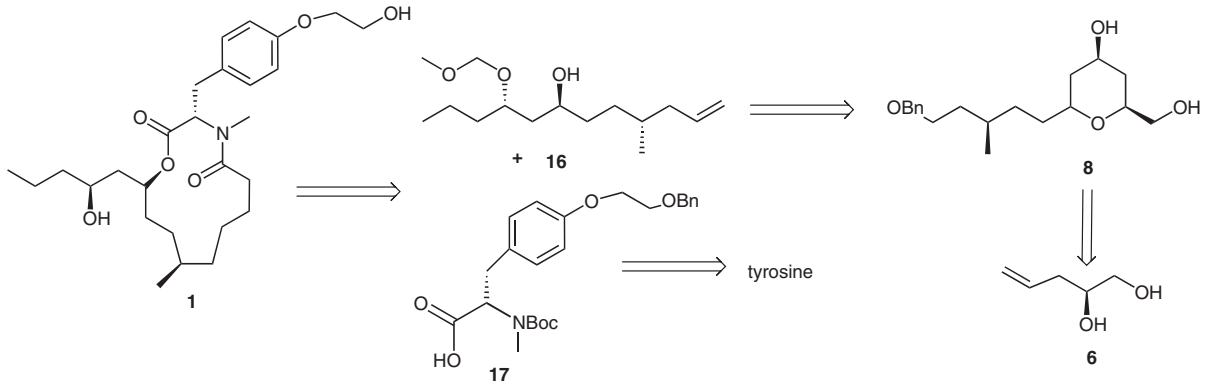
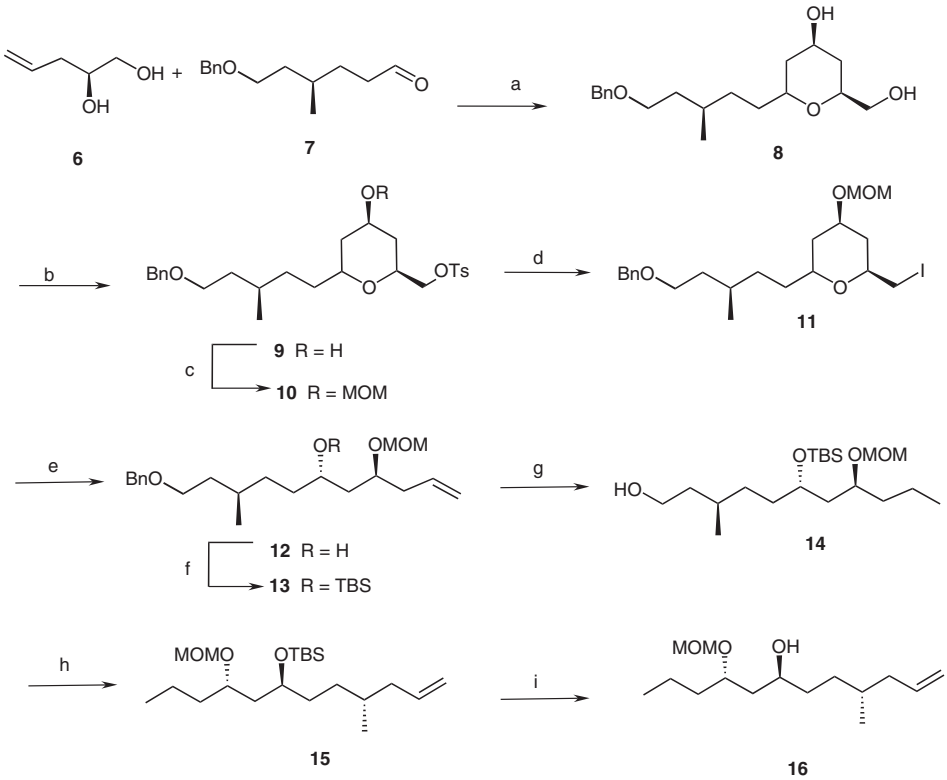


Scheme 1 Retrosynthesis of (–)-PF1163A

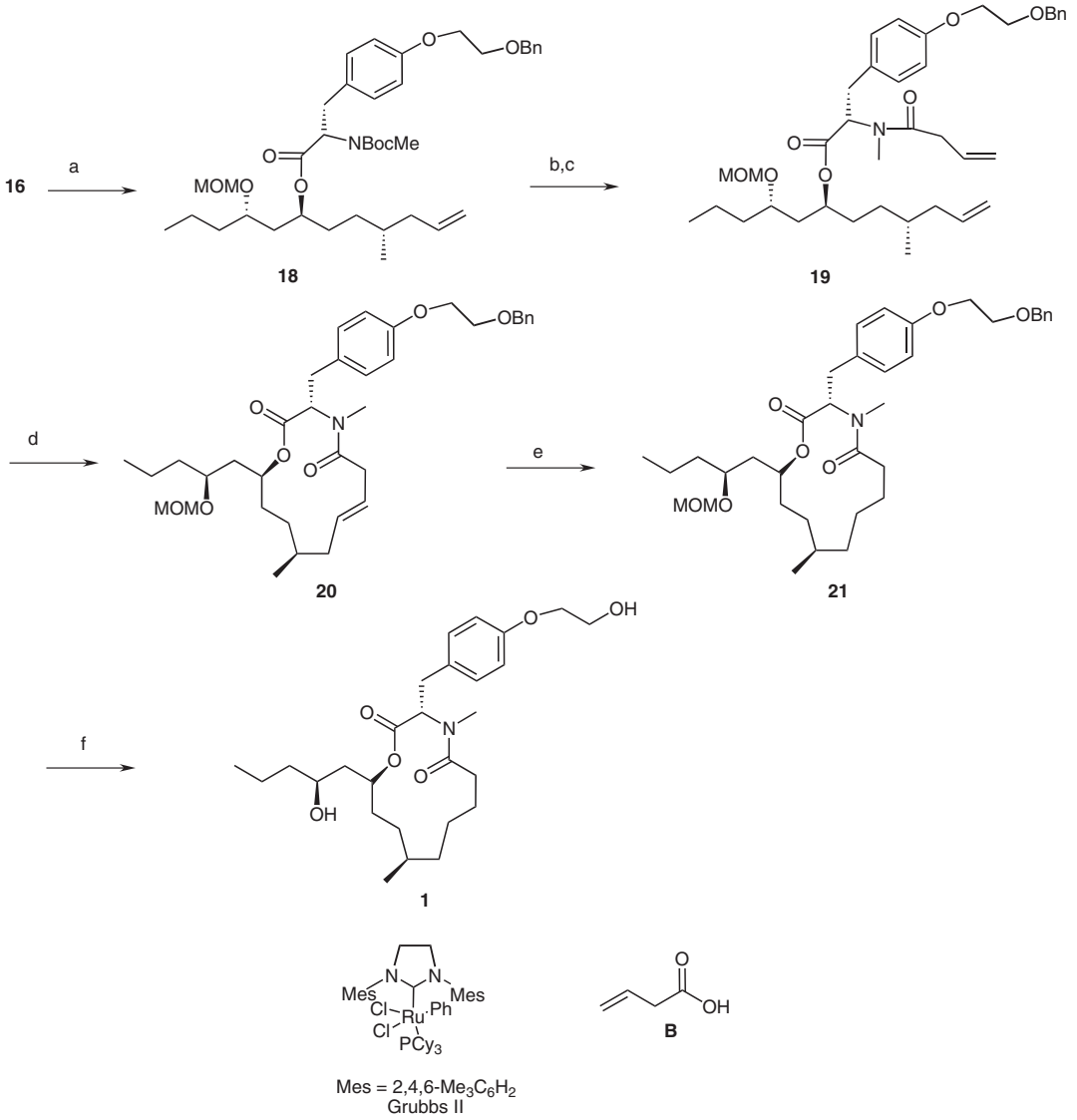


Scheme 2 *Reagents and conditions*: (a) aldehyde, TFA, CH_2Cl_2, 0 °C to r.t., 3 h then K_2CO_3, MeOH, r.t., 30 min, 52%; (b) (i) TsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 3 h, 85%; (c) MOMCl, DIPEA, CH_2Cl_2, 0 °C to r.t., 2 h, 92%; (d) NaI, acetone, reflux, 24 h, 90%; (e) Zn, EtOH, reflux, 2 h, 92%; (f) TBDMSCl, imidazole, DMAP, CH_2Cl_2, 0 °C to r.t., 2 h, 92%; (g) Pd/C, EtOAc, 8 h, 85%; (h) DMP, CH_2Cl_2, 2 h, 91%; then $Ph_3P{=}CH_2$, THF; (i) TBAF, THF, 0 °C, 83%.

Fragment **17** was synthesized from L-tyrosine by a known route.[6,7] The synthesis of the target compound was successfully completed by combining the fragments **16** and **17** in a six-step sequence as shown in Scheme 3.

Fragment **16** was esterified with acid **17** under Yamaguchi conditions[8] to obtain ester **18** in 83% yield. Selective deprotection of the NBoc group using TBSOTf, 2,6-lutidine, and TBAF[9] gave the corresponding amine, which was acylated with commercially available vinylacetic acid using a combination of EDCI and HOBt to provide the desired diene fragment **19** in 75% yield over the two steps. The ring-closing metathesis of diene **19** using 5 mol% Grubbs second-generation catalyst[10] followed by a palladium-catalyzed hydrogenation (Pd/C, EtOAc, H_2, 8 h) provided the macrolactone **21**[11] in 75% yield over the two steps. Cleavage of the MOM ether was achieved using TFA in anhydrous CH_2Cl_2 at ambient temperature to furnish PF1163A (**1**) in 75% yield. The synthetic compound showed spectroscopic and analytical data {^{1}H NMR, ^{13}C NMR, IR, R_f and $[\alpha]_D$} identical with those of the natural compound.[1]

In summary, we have accomplished a highly convergent and stereoselective synthesis of PF1163A (**1**), thus proving the versatility of the Prins cyclization in natural product synthesis.



Scheme 3 *Reagents and conditions*: (a) $Cl_3C_6H_2COCl$, DIPEA, **17**, DMAP, toluene, 83%; (b) TBSOTf, 2,6-lutidine, TBAF, THF, r.t., 88%; (c) EDCI, HOBt, CH_2Cl_2, then B; 75% (d) Grubbs II cat., CH_2Cl_2, reflux, 12 h, 65%; (e) Pd/C, H_2, EtOAc, 8 h, 85%; (f) TFA–CH_2Cl_2 (1:5), 0 °C to r.t., 2 h, 75%.

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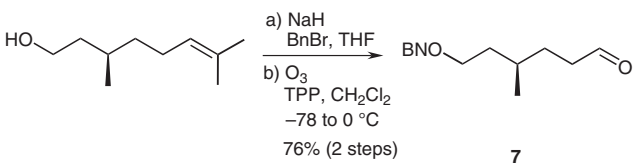
(5) Aldehyde **9** was prepared from (*R*)-citronellol in two steps in 76% overall yield as shown in Scheme 4.



Scheme 4

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(11) **{(2*S*,4*R*)-6-[(*R*)-5-(Benzyloxy)-3-methylpentyl]-tetrahydro-4-(methoxymethoxy)-2*H*-pyran-2-yl} Methyl 4-Methylbenzenesulfonate (10)**

To a stirred solution of alcohol **9** (1.8 g, 3.78 mmol) in anhyd CH_2Cl_2 (20 mL) at 0 °C were added DIPEA (1.31 mL, 7.56 mmol), DMAP (cat.) and MOMCl (0.91 g, 11.34 mmol) successively, the resulting mixture was stirred for 3 h at r.t. and then quenched by adding H_2O (10 mL) and extracted with CH_2Cl_2 (3 ´ 20 mL). The organic extracts were washed with brine (10 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure to remove the solvent, and the crude residue was purified by column chromatography to afford the pure product **10** as a liquid (1.80 g, 92%). R_f = 0.7 (SiO_2, 10% EtOAc in hexane); clear oil; R_f = 0.5 (EtOAc–hexane, 3:7). $[\alpha]_D^{20}$ –2.6 (*c* 1.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82–7.76 (m, 2 H), 7.38–7.22 (m, 7 H), 4.66 (s, 2 H), 4.49 (s, 2 H), 4.14–3.92 (m, 2 H), 3.73–3.61 (m, 1 H), 3.59–3.43 (m, 3 H), 3.35 (s, 3 H), 3.25–3.14 (m, 1 H), 2.43 (s, 3 H), 1.98–1.88 (dd, 2 H, *J* = 9.4, 2.8 Hz), 1.78–1.01 (m, 10 H), 0.87 (d, 3 H, *J* = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6, 138.6, 132.9, 129.7, 128.3, 127.9, 127.5, 127.4, 94.3, 76.1, 72.8, 72.5, 72.4, 72.0, 68.5, 55.2, 38.0, 36.6, 34.4, 33.1, 32.5, 29.8, 21.5, 19.5. IR (KBr): ν_{max} = 2922, 2852, 1456, 1362, 1037, 979 cm^{-1}. ESI-MS: *m/z* = 521 [M$^+$ + H], 543 [M$^+$ + Na].

(4*S*,6*S*,9*R*)-4-(Methoxymethoxy)-9-methyldodec-11-en-6-ol (16)

To a stirred soln of **15** (0.8 g, 2.15 mmol) in anhyd THF (8 mL), TBAF (4.3 mL, 4.3 mmol) was added, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (2 × 5 mL), and the combined organic layers washed with brine (10 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure to remove the solvent. The crude residue was then purified by column chromatography on silica gel (EtOAc–hexane, 1:9) to afford **16** as a white solid; yield 0.46 g (83%); clear oil; R_f = 0.4 (EtOAc–hexane, 2:8); $[\alpha]_D^{20}$ +12.1 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85–5.70 (m, 1 H), 5.05–4.94 (m, 2 H), 4.76–4.62 (m, 2 H), 3.90–3.76 (m, 2 H), 3.40 (s, 2 H), 2.13–2.02 (m, 1 H), 1.96–1.84 (m, 1 H), 1.68–1.08 (m, 10 H), 0.99–0.84 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.5, 115.5, 96.2, 75.9, 68.2, 55.8, 41.2, 41.1, 37.0, 34.9, 32.9, 32.4, 19.4, 18.7, 14.1. IR (KBr): ν_{max} = 3453, 2930, 1459, 1376, 1038, 911 cm^{-1}. ESI-MS: *m/z* = 281 [M$^+$ + Na].

(2*S*)-(4*S*,6*S*,9*R*)-4-(Methoxymethoxy)-9-methyldodec-11-en-6-yl 3-{4-[2-(benzyloxy)ethoxy]phenyl}-2-(*N*-Methylbut-3-enamido) Propanoate (19)

To a stirred solution of *N*-Boc-deprotected amine (200 mg, 0.35 mmol) in anhyd CH_2Cl_2 (12 mL) was added carboxylic acid fragment **B** (33 mg, 0.38 mmol) and then HOBt (4 mg, 0.035 mmol) followed by EDCI (201 mg, 1.05 mmol). The reaction was stirred for 6 h at r.t., quenched with HCl (1 N, 15 mL), and diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (20 mL), and the resulting solution washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc–hexane, 3:7) to afford diene **2** as a colorless oil (160 mg, 75%). R_f = 0.4 (EtOAc–hexane, 3:7); $[\alpha]_D^{20}$ –9.3 (*c* 0.5,$CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 5 H), 7.11–7.01 (m, 2 H), 6.86–6.77 (m, 2 H), 5.85–5.65 (m, 2 H), 5.35–5.27 (m, 1 H), 5.11–4.90 (m, 4 H), 4.64–4.44 (m, 4 H), 4.13–4.06 (m, 2 H), 3.82–3.76 (m, 2 H), 3.51–3.39 (m, 1 H), 3.36–3.18 (m, 4 H), 3.14–2.86 (m, 4 H), 2.82 (s, 3 H), 2.10–1.96 (m, 1 H), 1.94–1.80 (m, 1 H), 1.67–1.19 (m, 11 H), 0.95–0.82 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 169.5, 157.6, 137.1, 131.0, 129.8, 129.1, 128.4, 127.7, 117.7, 115.9, 114.9, 114.6, 96.2, 74.5, 73.4, 72.8, 68.5, 67.3, 57.8, 55.8, 41.3, 39.2, 38.9, 37.4, 33.9, 32.7, 32.3, 31.6, 29.8, 19.4, 18.2, 14.3. IR (KBr): ν_{max} = 2924, 2856, 1650, 1243, 1046 cm^{-1}. ESI-MS: *m/z* = 660 [M$^+$ + Na].

(3*S*,10*R*,13*S*)-3-[4-(2-hydroxyethoxy)benzyl]-13-*S*-2-(methoxymethoxy)pentyl-4,10-dimethyl-1-oxa-4-azacyclotridecane-2,5-dione (21)

To solution of compound **20** (0.200 g, 0.328 mmol) in EtOAc (10 mL) was added Pd/C 10% (50 mg) and the mixture stirred under H_2 atmosphere for 7 h. After completion, the reaction mass was filtered through Celite, and the solvent was removed under reduced pressure to give crude product **21**. Purification using column chromatography on silica gel (hexane–EtOAc, 4:1) gave pure product as a colorless solid (0.145 g, 85% yield); $[\alpha]_D^{25}$ –48.5 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.07 (m, 2 H), 6.83 (d, 2 H, *J* = 8.5 Hz), 5.13–5.02 (m, 1 H), 4.66–4.39 (m, 2 H), 4.08–4.02 (m, 2 H), 3.97–3.90 (m, 2 H), 3.35 (s, 3 H), 3.23–3.11 (t, 1 H, *J* = 11.1 Hz), 3.07–2.91 (m, 3 H), 2.88–2.57 (m, 1 H), 2.26–2.07 (m, 1 H), 1.72–1.08 (m, 19 H), 0.92–0.89 (m, 2 H), 0.85 (t, 3 H, *J* = 6.8 Hz), 0.81 (d, 3

H, *J* = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 130.2, 129.9, 114.8, 114.5, 75.4, 72.2, 69.0, 61.45, 55.7, 55.5, 39.0, 38.7, 37.3, 33.5, 33.3, 31.5, 30.1, 29.6, 25.1, 24.1, 20.5, 17.9, 14.2. IR (film): ν = 3437 (OH), 2926, 2869, 1728, 1636, 1512, 1247, 1038 cm^{-1}. ESI-MS: *m/z* = 544 $[M + Na]^+$.

(3*S*,10*R*,13*S*)-3-[4-(2-hydroxyethoxy)benzyl]-13-[(*S*)-2-hydroxy pentyl]-4,10-dimethyl-1-oxa-4-azacyclotridecane-2,5-dione [PF1163 A(1)]

To a stirred solution of **21** (0.02 g, 0.03 mmol) in anhyd TFA–CH_2Cl_2 (1:5, 2 mL) was added at 0 °C, and the reaction mixture was stirred for 2 h at r.t. The reaction mixture was quenched with $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2 (2 × 2 mL), and the combined organic layers were washed with brine (2 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc–hexane, 3:7) to afford **1** as a colorless oil (13 mg, 75%). R_f = 0.4 (EtOAc–hexane, 7:3); $[\alpha]_D^{20}$ –88.5 (*c* 1.0, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20–7.03 (m, 2 H), 6.84–6.75 (m, 2 H), 5.82–5.66 (m, 1 H), 5.14–4.91 (m, 1 H), 4.01 (s, 1 H), 3.90 (s, 1 H), 3.53–3.27 (m, 2 H), 3.01–2.80 (m, 3 H), 2.78–2.52 (m, 1 H), 2.38–2.24 (m, 1 H), 1.76–1.02 (m, 22 H), 0.91 (t, *J* = 7.8 Hz, 3 H), 0.82 (d, *J* = 7.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 171.7, 157.4, 130.3, 128.8, 114.5, 73.2, 69.1, 66.6, 61.3, 56.0, 49.4, 42.1, 39.0, 33.9, 33.2, 29.7, 24.1, 20.7, 19.0, 14.0. IR (KBr): ν_{max} = 3429, 2924, 2856, 1728, 1632, 1511, 1459, 1247 cm^{-1}. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{27}H_{43}O_6NNa$: 500.2988; found: 500.2979.