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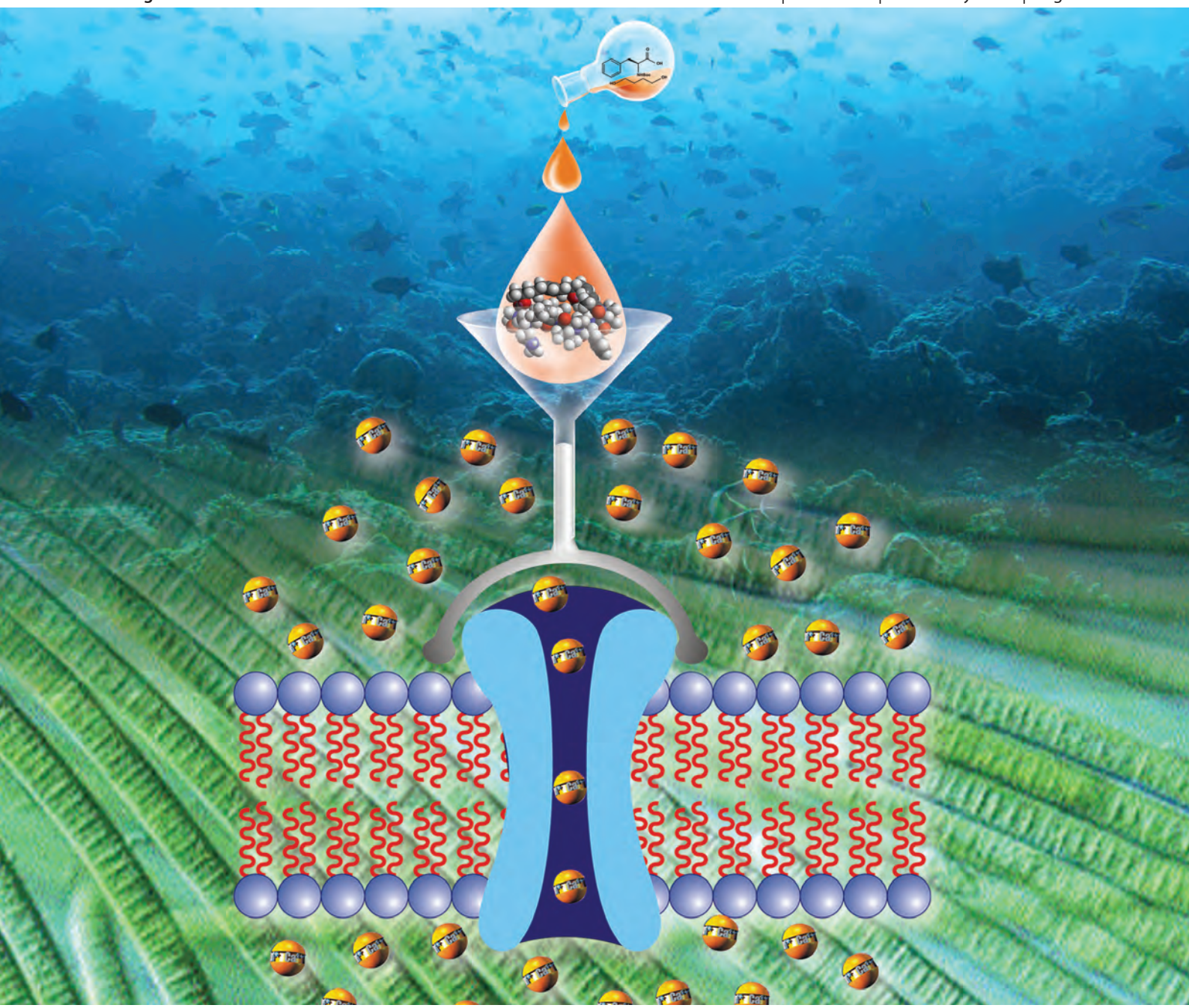

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Total synthesis of (29*S*,37*S*)-isomer of malevamide E, a potent ion-channel inhibitor†‡

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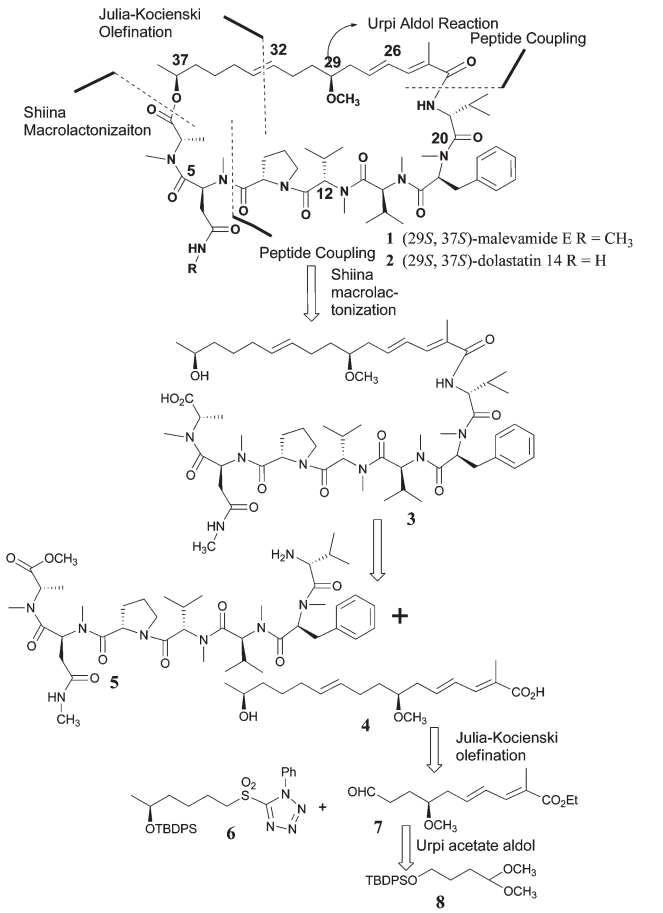
The first total synthesis of (29*S*,37*S*)-malevamide E (1), a potent ion channel inhibitor, has been achieved in a convergent fashion involving Julia–Kocienski olefination, Urpi acetal aldol and Shiina macrolactonization reactions as the key steps. The strategy developed herein is amenable for the synthesis of the other possible isomers in search for the correct stereoisomer of the naturally occurring molecule.

Introduction

Extracts of cyanobacteria belonging to the genus *Symploca* (Oscillatoriaceae) have given rise to scores of biologically active natural products with interesting structures.[1] One such example is a new depsipeptide, malevamide E, an *N*-methylated analogue of dolastatin 14, isolated from field-collected colonies of the filamentous cyanobacterium *Symploca laete-Viridis*.[2] Dolastatin 14 was previously reported by Pettit and co-workers[3] in exceptionally low yield from *D.auricularia*. Malevamide E demonstrated a dose-dependent (2–45 μM) inhibition of store-operated Ca^{2+} entry in thapsigargin-treated human embryonic kidney (HEK) cells indicating an inhibitory effect on Ca^{2+} release-activated Ca^{2+} (CRAC) channels.

Although, there has been considerable interest in the total synthesis of dolastatin 14, to date, neither the total synthesis nor the stereochemical configuration of dolastatin 14 or malevamide E has been reported. All four diastereomers of its polyketide-derived subunit, dolatrienoic acid were earlier synthesized as part of the effort toward the full synthesis of dolastatin 14 by two independent groups.[4] Encouraged by the properties and coupled with our interest in total synthesis of marine natural products,[5] we embarked on the challenge of taking up a simple approach to make all possible diastereomers of the polyketide subunit. Herein, we report the first total synthesis of (29*S*,37*S*)-isomer of malevamide E (**1**).

Retrosynthetically (Scheme 1), (29*S*,37*S*)-malevamide E (**1**) can be obtained by macrolactonization of acyclic hydroxy acid **3**, which, in turn, could be prepared by coupling the two key intermediates **4** and **5**, the former with the long chain fatty



Scheme 1 Retrosynthetic analysis.

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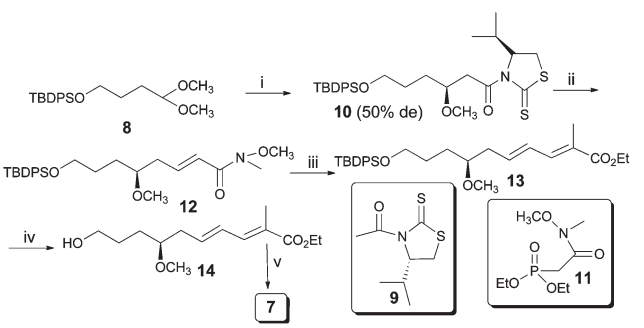
acid moiety and the latter possessing the heptapeptide component. The salient feature of our synthesis is the stereoselective construction of the aliphatic fragment involving two key steps: (i) enantioselective addition of a titanium enolate derived from a chiral thiazolidinethione which was expected to fix the **C29** stereocenter; and (ii) construction of **C32–C33** bond using Julia–Kocienski olefination of the subunits **6** and **7**.

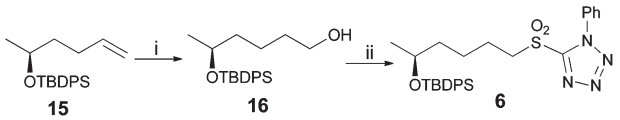
Results and discussion

Our synthetic endeavour began with the synthesis of aldehyde **7** (Scheme 2) which started with the preparation of 4-(*tert*-butyldiphenylsiloxy)butanal dimethyl acetal **8** from butanediol according to the reported procedure.[6] An acetal aldol reaction between the resultant dimethyl acetal **8** and (*S*)-*N*-acetyl-4-isopropyl-1,3-thiozolidine-2-thione (**9**), according to the conditions described by Urpi,[7] provided the aldol product **10** in 72% yield in 3 : 1 dr in favour of the required isomer. The diastereomerically pure products could be easily separated using simple column chromatography.[8] Reductive cleavage of the chiral auxiliary of the major isomer (the minor isomer can be used for the synthesis of another diastereomer of the molecule) afforded aldehyde, which was subjected to a Wittig–Horner reaction with *N*-methyldiethylphosphoacetamide (**11**) at −40 °C in presence of NaH to obtain the *α*,*β*-unsaturated amide **12** in 78% yield exclusively as an *E*-isomer.[9] The amide **12** was reduced with DIBAL-H to the corresponding aldehyde followed by Wittig homologation with $Ph_3P{=}CH(CH_3)CO_2Et$ in benzene under reflux conditions to provide the *α*,*β*-unsaturated ester **13** in 80% yield. Desilylation of **13** with TBAF in THF gave a primary alcohol **14** in 75% yield, which on oxidation under Parikh–Doering conditions gave the aldehyde **7**.

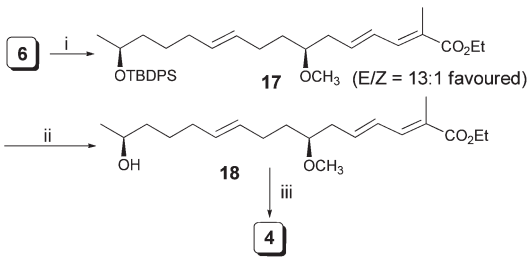
On the other hand, sulfone **6** was synthesized (Scheme 3) starting from a known compound **15**,[4] which was prepared by silyl protection of the corresponding alcohol. Hydroboration and oxidation of the terminal olefin moiety of **15** afforded primary alcohol **16** in 80% yield, which was further converted into the desired sulfone **6** in 85% yield *via* Mitsunobu reaction using 1-phenyl-1*H*-tetrazol-5-thiol (PT-SH) and diisopropyl azodicarboxylate (DIAD) and oxidation in one pot using catalytic amounts of ammonium molybdate and H_2O_2.



Scheme 2 Synthesis of compound **7**. (i) 9, $TiCl_4$, DIPEA, $SnCl_4$, CH_2Cl_2, −78 °C, 1 h, 72%; (ii) (a) DIBAL, CH_2Cl_2, −78 °C, 15 min, 96%; (b) 11, NaH, THF, −40 °C,1 h, 78%; (iii) (a) DIBAL, CH_2Cl_2, −78 °C, 15 min, 97%; (b) $Ph_3P{=}C(CH_3)COOEt$, benzene, reflux, 3 h, 80%; (iv) TBAF, THF, 0 °C, rt, 1 h, 85%; (v) $SO_3{\cdot}Py$, Et_3N, DCM : DMSO (2 : 1), 0 °C, rt, 30 min, 96%.



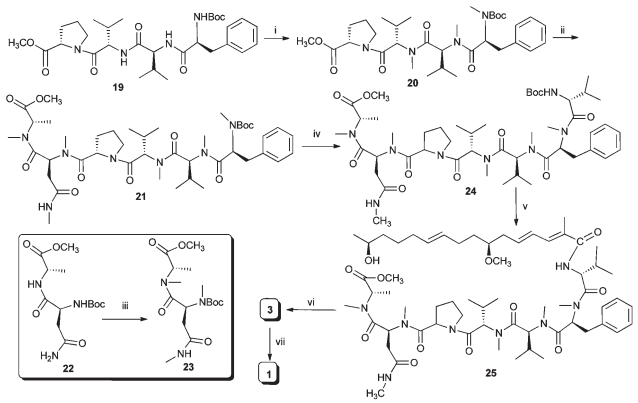
Scheme 3 Synthesis of sulphone **6**. (i) (a) $BH_3\,SMe_2$, THF, 0 °C, rt, 2 h, (b) H_2O_2, NaOH, 80%; (ii) (a) PTSH, DIAD, PPh_3, THF, rt, 30 min, (b) $(NH_4)_6Mo_7O_{24}H_2O$, H_2O_2, EtOH, rt, 15 min, 85%.



Scheme 4 Synthesis of compound **4**. (i) LiHMDS, THF : HMPA, −78 °C, aldehyde 7, −78 °C, 3 h, 72%; (ii) TBAF : AcOH (1 : 1), H_2O, DMF, 50 °C, 12 h, 85%; (iii) LiOH, THF : MeOH : H_2O (3 : 1 : 1), 0 °C, rt, 1 h, 74%.

Synthesis of compound **17**, as depicted in Scheme 4, was performed through crucial Julia–Kocienski olefination.[10] Accordingly, sulfone **6** was treated with LiHMDS in dry THF : HMPA (4 : 1) at −78 °C followed by slow addition of aldehyde **7**, over a period of 10 min and the same temperature was maintained for 3 h to furnish the desired *E*-olefinic compound **17** in 72% yield along with 7% of the *Z*-isomer. An attempt to accomplish the deprotection of silyl group with TBAF in THF was ineffective and no desired product was obtained even at higher temperatures. Alternatively, desilylation of **17** using TBAF and AcOH (1 : 1) in presence of H_2O in DMF for 12 h gave deprotected **18** in 85% yield.[11] Saponification of **18** with LiOH in THF : MeOH : H_2O (3 : 1 : 1) at 0 °C afforded corresponding hydroxy acid **4**, which was used directly in the next step without further characterization.

The synthesis of the peptide segment, depicted in Scheme 5, started from the tetrapeptide **19**, which was synthesized from commercially available protected amino acids by standard solution phase peptide synthesis conditions using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole hydrate (HOBt) as coupling agents and dry CH_2Cl_2 as solvent. For synthesis of **24**, *N*-methylation of dipeptide **22** and tetrapeptide **19** was carried out using silver oxide and MeI in DMF to provide the corresponding *N*-methylated dipeptide **23** and tetrapeptide **20**, respectively. From the 2D-TOCSY and ROESY spectrum of **20**, at least 4 conformations were present in the NMR time scale out of which conformations 1A, 1B and 2A, 2B showed exchange peaks with each other (see ESI, Fig. 1‡). For 1A,1B strong nOes between ^{4}Pro Hδ → ^{3}Val Hα confirmed *trans* configuration and absence of such nOes for 2A, 2B suggests *cis*



Scheme 5 Synthesis of peptide fragment and completion of the total synthesis. (i) Ag_2O, MeI, DMF, 0 °C, rt, 12 h, 72%; (ii) (a) LiOH, THF : MeOH : H_2O (3 : 1 : 1) 0 °C, rt, 1 h; (b) TFA salt of Boc-deprotected **23**, BOP-Cl, DIPEA, CH_2Cl_2, 0 °C, rt, 12 h, 76%; (iii) Ag_2O, MeI, DMF, 0 °C, rt, 12 h, 68%; (iv) (a) TFA, CH_2Cl_2, 0 °C, rt, 1 h; (b) Boc-D-Val-OH, BOP-Cl, DIPEA, CH_2Cl_2, 0 °C, rt, 12 h, 79%; (v) (a) TFA, CH_2Cl_2, 0 °C, rt, 1 h; (b) **4**, EDCI, HOBt, CH_2Cl_2, 0 °C, rt, 15 min, then added amine from step (a), DIPEA, CH_2Cl_2, rt, 12 h, 75%; (vi) LiOH, THF : MeOH : H_2O (3 : 1 : 1), 0 °C, rt, 1 h, 96%; (vii) MNBA, DMAP, CH_2Cl_2, rt, 12 h, 62%.

configuration around proline peptide bond. Other two conformations may be attributed to the *cis*/*trans* isomerism of the one of the tertiary amides of **20** as these classes of peptides are prone to exhibit *cis*/*trans* conformations.[12] Coupling of the *N*-methylated tetrapeptide **20** with *N*-methylated dipeptide **23** using BOP-Cl gave the hexapeptide **21** in 76% yield.

Finally, Boc deprotection of **21** using TFA in CH_2Cl_2 followed by coupling with Boc-D-Val-OH using BOP-Cl as a coupling reagent gave the heptapeptide component **24**. NMR studies on hexapeptide **21** and heptapeptide **24** suggested presence of at least 8 conformations and may be attributed again to the *cis*/*trans* isomerisation of the tertiary amides (see ESI, Fig. 2 and 3‡).

With both the halves of the molecule now ready to be coupled, the heptapeptide **24** was treated with 30% TFA in CH_2Cl_2 at 0 °C to effect Boc deprotection and coupled with the hydroxy acid **4** following the EDCI/HOBt protocol to obtain the coupled product **25** in 75% yield. The hydroxy ester **25** on saponification with LiOH in THF : MeOH : H_2O (3 : 1 : 1) at 0 °C afforded corresponding hydroxy acid **3**, which was used directly in the next step without further characterization. The stage was now set to carry out the crucial macrolactonization reaction. Lactonization was successfully carried out using Shiina anhydride protocol[13] using 2-methyl-6-nitrobenzoic anhydride (MNBA) in presence of DMAP in CH_2Cl_2 at room temperature to afford the target molecule **1** in 62% yield.

NMR spectral data, both ^1H and ^{13}C, and specific rotation of the synthetic **1** were entirely not in agreement with the data reported for the isolated natural compounds. However, the detailed 2D-NMR analysis of **1** showed similar chemical shifts for the aliphatic region and deviated for certain residues of the peptoid portion.[14] From the assigned major conformation, it is worth noting that chemical shifts of the Ala, Asn and Phe match well with the natural product.

In conclusion, we have developed a method for the total syntheses of (29*S*,37*S*)-isomer of malevamide E (**1**) in a convergent fashion involving Julia–Kocienski olefination, Urpi acetal aldol and Shiina macrolactonization as the key steps. Our strategy is amenable for the synthesis of other possible diastereomers whose synthesis is under progress and will be reported in due course.

Experimental section

Compound 25

To a solution of **18** (50 mg, 0.15 mmol) in THF : MeOH : H_2O (3 : 1 : 1, 3 mL) at 0 °C, LiOH·H_2O (18.5 mg, 0.44 mmol) was added and stirred from 0 °C to room temperature for 1 h. The reaction mixture was then acidified to pH ~ 2 with 1 N HCl. It was diluted with EtOAc, washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to obtain the crude acid **4**, which was used directly in the next step without further characterization.

In round bottom flask, a solution of **24** (99.8 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was taken. To this solution, trifluoroacetic acid (1 mL) was added at 0 °C and slowly warmed to room temperature and stirred for 1 h. The reaction mixture was then concentrated *in vacuo* and azeotroped with CH_2Cl_2 3 times (3 × 10 mL) to give the Boc-deprotected compound **5**.

The above prepared acid **4** was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. It was then sequentially treated with HOBt (29.7 mg, 0.22 mmol) and EDCI (42.0 mg, 0.22 mmol). After 10 min, compound **5**, prepared above and dissolved in CH_2Cl_2 (2 mL), was added to the reaction mixture followed by the addition of DIPEA (0.08 mL, 0.44 mmol). After stirring for 12 h at room temperature, the reaction mixture was diluted with $CHCl_3$, washed with saturated NH_4Cl solution, 1 N HCl, saturated $NaHCO_3$ solution, water, brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel, 2% to 3% MeOH in $CHCl_3$ as eluent) afforded **25** (100 mg, 75%) as a white solid. R_f = 0.3 (SiO_2, 10% MeOH in $CHCl_3$); specific rotation $[\alpha]_D^{25}$ = −66.6 (*c* 0.15, $CHCl_3$); IR (neat): ν_{max} 3404, 2361, 2111, 1637, 1445, 1218, 1020, 769, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ see Table 6;‡ ^{13}C NMR (400 MHz, $CDCl_3$): δ 173.09, 171.82, 170.66, 170.21, 170.04, 169.55, 169.14, 168.32, 137.62, 137.16, 133.89, 130.68, 130.24, 130.14, 129.98, 129.54, 129.04, 128.59, 127.89, 79.97, 68.08, 60.04, 58.73, 56.92, 56.73, 55.47, 54.97, 53.72, 52.44, 52.27, 49.85, 47.36, 39.04, 38.89, 37.32, 35.73, 33.73, 32.60, 32.08, 31.88, 30.97, 30.06, 29.81, 29.46, 28.60, 28.30, 27.06, 26.47, 25.94, 25.07, 23.63, 22.79, 19.95, 19.81, 19.52, 19.44, 19.23, 18.09, 16.98, 14.26, 12.98; MS (ESIMS): *m*/*z* (%): 1157 (100) $[M + Na]^+$; HRMS (ESIMS): calcd for $C_{61}H_{99}N_8O_{12}$ $[M + H]^+$: 1135.7282, found: 1135.7255.

Compound 1

To a solution of **25** (55 mg, 0.05 mmol) in THF : MeOH : H_2O (3 : 1 : 1, 3 mL) at 0 °C, LiOH·H_2O (6.11 mg, 0.14 mmol) was added and stirred from 0 °C to room temperature for 1 h. The reaction mixture was then acidified to pH ~ 2 with 1 N HCl. It

was diluted with EtOAc, washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The hydroxy acid **3**, thus obtained, after flash chromatography (52 mg, 96%), was directly used in the next step without further characterization.

To a stirred solution of 2-methyl-6-nitrobenzoic anhydride (MNBA, 18.98 mg, 0.06 mmol) and DMAP (13.48 mg, 0.11 mmol) in CH_2Cl_2 (16 mL) was added a solution of hydroxy acid **3** (52 mg, 0.05) in CH_2Cl_2 (10 mL) over a period of 12 h at room temperature using a syringe pump. Thereafter, saturated $NaHCO_3$ solution (20 mL) was added and the aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel, 2% to 3% MeOH in $CHCl_3$ as eluent) afforded **1** (31 mg, 62%) as a colorless oil. R_f = 0.3 (SiO_2, 10% MeOH in $CHCl_3$); specific rotation $[\alpha]_D^{25} = -22.6$ (*c* 0.09, CH_2Cl_2); IR (neat): ν_{max} 3703, 3572, 3332, 2926, 2567, 2361, 1635, 1445, 1219, 1096, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ see Table 8 in ESI;‡ ^{13}C NMR (150 MHz, $CDCl_3$): δ see Table 8 in the ESI;‡ MS (ESIMS): *m*/*z* (%): 1103 (100) $[M + H]^+$; HRMS (ESIMS): calcd for $C_{60}H_{95}N_8O_{11}$ $[M + H]^+$: 1103.7120, found: 1103.7085.

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14 For δ values see ESI Table 8.‡

