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Total synthesis of the polyenoyltetramic acid polycephalin C

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Dedicated to K. C. Nicolaou in recognition of his receipt of the Tetrahedron Prize and his enormous contribution to the art and craft of Organic Synthesis

Abstract—The total synthesis of the polyenoyltetramic acid polycephalin C is described. Key steps of the synthesis include a double Swern oxidation, double Takai reaction and a double Stille reaction. In addition, the absolute stereochemistry of the ring junction has been determined by synthesis of both isomers and comparison of their CD spectra with natural polycephalin C.

1. Introduction

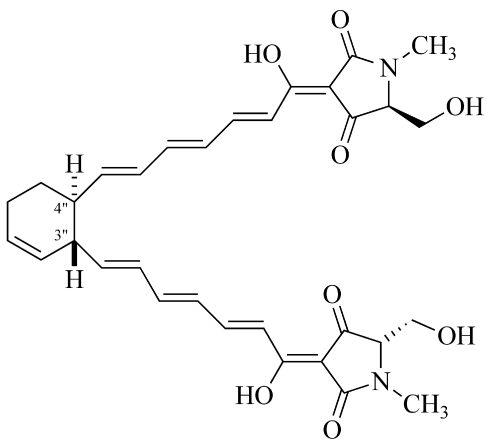
The tetramic acid (pyrrolidine-2,4-dione) ring system is a key structural unit in many natural products.[1] The spectrum of biological activity displayed by these natural products is remarkable in its diversity; it includes potent antibiotic, antiviral and antiulcerative properties, cytotoxicity and mycotoxicity, the inhibition of tumors as well as fungicidal acitivity. In addition, other members of this class are responsible for pigmentation of certain sponges and molds.[1]

A recently isolated member of this class of compounds is polycephalin C **1**.[2] This fungal metabolite isolated from the extracts of *Physarum polycephalum* is a bis(trienoyl)tetramic acid linked by an unusual asymmetric cyclohexene ring (Fig. 1). The tetramic acid unit of each terminus is derived from (*S*)-*N*-methyl serine and is linked by a fully conjugated *all-E*-triene chain to the cyclohexene ring (Fig. 1). This unusual tetramic acid is thought to be one of several metabolites responsible for the yellow colour of the wild-type plasmodia *P. polycephalum*.[2] Although the structure elucidation paper had established that the relative configuration at the 3″,4″ ring junction was *trans* the absolute stereochemistry at these positions had not been established. Hence, we initiated a total synthesis programme towards this challenging molecule, with the goal of defining the absolute structure of this molecule. We now wish to report in full the details of this study.[3]

1.1. Retrosynthetic analysis

As the 3″,4″ ring junction configuration of polycephalin C **1** could be *R*,*R* or *S*,*S* we arbitrarily selected the *S*,*S* isomer as the initial target. Disconnection between carbons C-5′ and C-6′ and also C-2‴ and C-3‴ led to two main fragments, the stannylated dienoyltetramic acid **2** and the bis-iodide intermediate **3**. It was envisaged that stannane **2** would be prepared from readily available thioester **4** and amino ester **5**, fragments which had been utilised previously in our syntheses of physarorubinic acid[4a] and erythroskyrine.[4b]

To synthesise the bis-iodide **3** it was envisaged that starting from cyclohexene diol **6**, 1,4-dioxidation and a double Takai reaction would provide this fragment rapidly. It was expected that diol **6** would be prepared from Diels–Alder adduct **7** via double bond manipulation and exhaustive reduction (Scheme 1). With both fragments in hand a double Stille coupling followed by TBS deprotection would then give (3″*S*,4″*S*)-**1** in a concise fashion.



Polycephalin C **1**

Figure 1. Polycephalin C.

Keywords: natural product synthesis; tetramic acids; lactams; Takai reaction; Swern oxidation.

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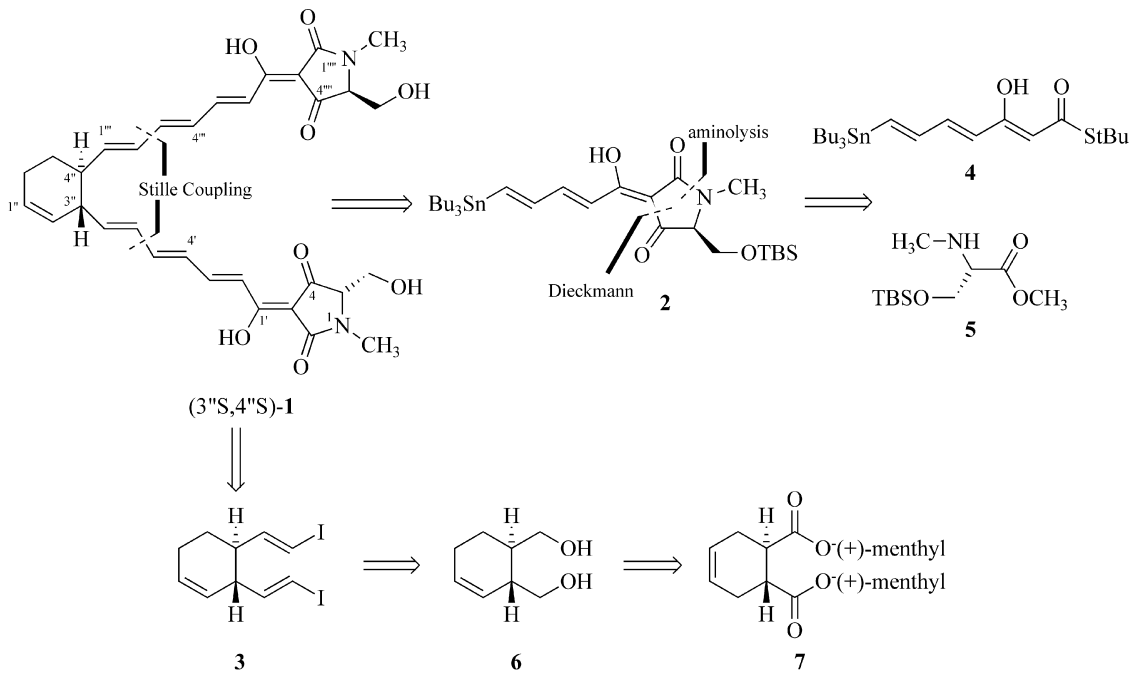


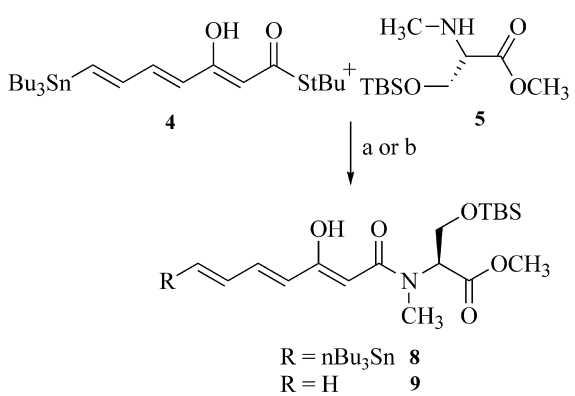
Scheme 1. Retrosynthetic analysis.

2. Results and discussion

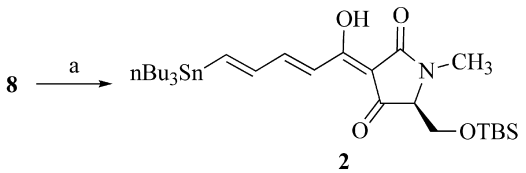
2.1. Synthesis of dienoyltetramic acid 2

The two step sequence which leads to the formation of dienoyltetramic acid **2** begins with a silver mediated aminolysis reaction.[5] This mild and selective reaction for the formation of β-ketoamides had been applied successfully in our synthesis of physarorubinic acid[4a] and erythroskyrine[4b] and accordingly we did not envisage any difficulty with the synthesis of ketoamide **8** from thioester **4** and amino ester **5**. However, to our surprise initial attempts at the reaction gave only small amounts (30–40%) of destannylated product **9** (Scheme 2) following column chromatography on florisil.

The reaction conditions were therefore investigated, since the only perceptible reason for destannylation to occur was the presence of acid. Indeed, on increasing the amount of triethylamine and reducing the amount of silver trifluoroacetate and purification of the reaction mixture on silica not florosil† resulted in a clean and high yielding synthesis of ketoamide **8**.



Scheme 2. *Reagents and conditions*: (a) 2 equiv. CF_3CO_2Ag, 2.5 equiv. NEt_3, THF, 0°C, 2 h, 45% yield of **9**, (b) 1 equiv. CF_3CO_2Ag, 5 equiv. NEt_3, THF, 0°C, 20 min, 81% yield of **8**.



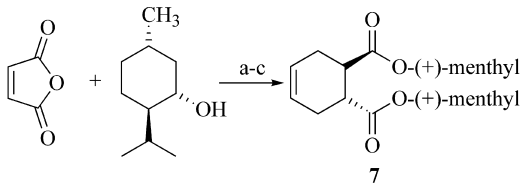
Scheme 3. *Reagents and conditions*: (a) NaOMe, MeOH, 25°C, 2 min, 90%.

The Dieckmann cyclisation of ketoamide **8** utilising sodium methoxide in methanol proceeded as expected revealing the dienoyltetramic acid **2** in an excellent 90% yield (Scheme 3). With the tetramic acid portion in hand attention was turned to the synthesis of bis-iodide **3**.

2.2. Synthesis of bis-iodide 3

The starting point for the synthesis of bis-iodide **3** was a chiral auxillary mediated Diels–Alder reaction, whereby the two stereocentres would be created with high diastereocontrol in a single step. The asymmetric Diels–Alder reaction employed in this case combines the dienophile, (+)-dimenthyl fumarate **10**, with 1,3-butadiene to yield a *trans* disubstituted cyclohexene **7**. This asymmetric reaction, pioneered by Walborsky and perfected by Yamamoto is reported to occur with excellent diastereoselectivity.[6] Although (+)-Dimenthyl fumarate **10** is commercially available, due to the large quantities required for the

† Florosil is composed of silica, magnesium oxide and sodium sulfate, it is thought that the aminolysis product may have been coordinating metal ions and being lost in this way.



Scheme 4. *Reagents and conditions*: (a) *p*-toluenesulfonic acid·H_2O, toluene, reflux, 17 h, 90%, (b) morpholine, toluene, 100°C, 81%, (c) Et_2AlCl, butadiene, −60°C, 36 h, 73%.

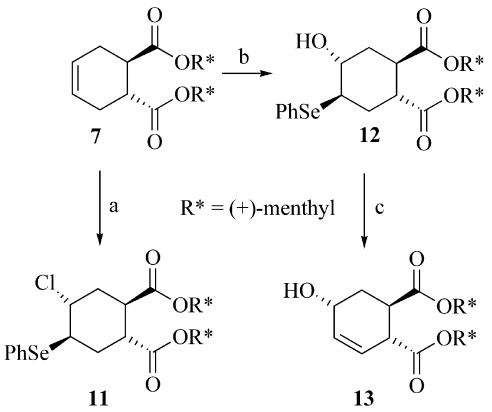
proposed route, the dienophile was synthesised in two steps from maleic anhydride (Scheme 4).[7] (see Experimental) With the dienophile in hand the low temperature Lewis acid mediated Diels–Alder reaction was carried out to afford exclusively the desired Diels–Alder adduct (*R*,*R*)-**7** (d.e. >95% by NMR) in a 73% yield (Scheme 4).

Having set the stereochemistry at the ring junction, double bond transposition was then required. It was envisaged that overall addition of selenic acid across the double bond and a subsequent oxidation–elimination sequence would affect the desired process.[8]

Initial attempts at this reaction utilising phenylselenium chloride in a 13:1 MeCN/H_2O mixture resulted only in formation of the unwanted chloride **11**. Unfortunately, this material was not useful in the synthesis, as the subsequent oxidation–elmination sequence would have given a mixture of both desired and undesired alkenes.[8a] Therefore, the reaction was repeated but this time utilising phenylselenium bromide at elevated temperatures (50°C). Pleasingly, it was found that utilising these reaction conditions resulted in clean conversion of alkene **7** to the desired hydroxyselenide **12** in good yield (Scheme 5). Subsequent oxidation with *m*-CPBA at −30°C followed by heating to 50°C in the presence of Hünigs base gave the desired allylic alcohol **13** in an excellent 92% overall yield (Scheme 5).

Having transposed the double bond, removal of the hydroxyl group and reduction of the two ester functionalities was required. Obviously, the most efficient design of the synthesis would carry out both of these transformations simultaneously. To that end it was proposed that conversion of the hydroxyl group to a leaving group and then carrying out an exhaustive reduction would achieve this goal.

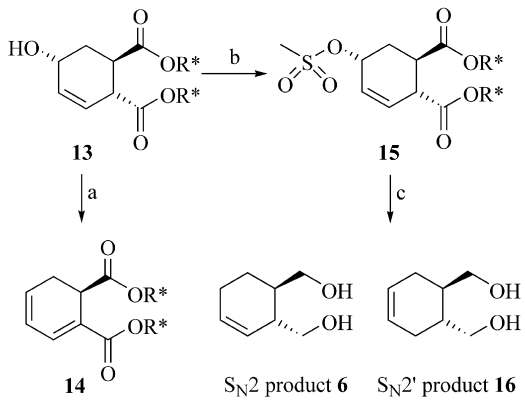
In the first instance the tosylate leaving group was selected for this reaction. However, low temperature tosylation proved ineffective and tosylation at elevated temperature occurred but was followed by elimination to form diene **14** (Scheme 6). It was thought that the steric bulk of the tosylate group was prohibiting the desired bond formation at low temperature and that low temperature was key to preventing elimination. Therefore, formation of the less bulky mesylate **15** was undertaken. However, at 0°C, this attempted mesylation also gave only diene **14** with only a small amount of desired product. On the other hand, when the reaction was carried out at lower temperature (−78°C to −15°C) and quenched at low temperature the mesylate **15** could be formed in an excellent 87% yield (Scheme 6). At this point crystals of suitable quality were grown for X-ray crystallography and proved the absolute configuration of mesylate **15**.[9]



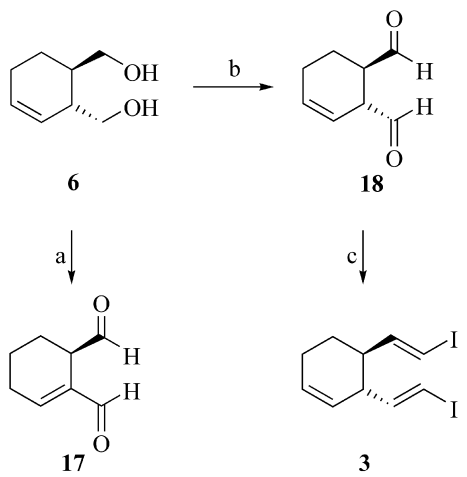
Scheme 5. *Reagents and conditions*: (a) PhSeCl, MeCN/H_2O (13:1), room temperature, 30 min, (b) PhSeBr, MeCN/H_2O (15:1), 50°C, 12 h, 75%, (c) *m*-CPBA, CH_2Cl_2, −30°C, 5 min then Hünigs base, 50°C, 14 h, 92% over 2 steps.

With mesylate **15** in hand, exhaustive reduction conditions were then examined to prepare diol **6**. Initial attempts at carrying out this transformation using lithium aluminium hydride were promising. Carrying out the reaction at 0°C in THF resulted in high yields (83–100%) and a pleasing 3:1 ratio of S_N2/S_N2' attack. A variety of other solvents were then examined including ether, dimethoxyethane and dioxane, but none of which increased the ratio of desired diol **6** to undesired diol **16**. Alternative reducing agents were therefore tried and these included Super hydride, lithium borohydride and K-selectride. All attempts utilising these reagents either failed to increase the ratio of desired to undesired or gave multicomponent reaction mixtures.

It is known that sodium borohydride in refluxing DMSO can reduce esters and can also reduce sulfonate derivatives.[10] Interestingly, it was found that the reduction of the esters did not take place, even at elevated temperatures but that mesylate reduction did occur in an encouraging 30:1 S_N2/S_N2' ratio. In order to further improve this ratio a DMSO/THF (1:1) solvent mixture was utilised thus permitting a lowering of the reaction temperature. Utilising this system a 40:1 ratio in favour of S_N2 attack could be achieved. Unfortunately, on scale up of the reaction, yields were greatly decreased from the initial 61% on a small scale



Scheme 6. *Reagents and conditions*: (a) *p*-toluenesulfonyl chloride, pyridine, 40°C, 6 h, 67%, (b) methanesulfonyl chloride, Et_3N, CH_2Cl_2, −78°C to −15°C, 87%, (c) $LiAlH_4$, THF, −78°C to room temperature, 85% overall yield (5:1 **6**/**16**), 64% **6**.



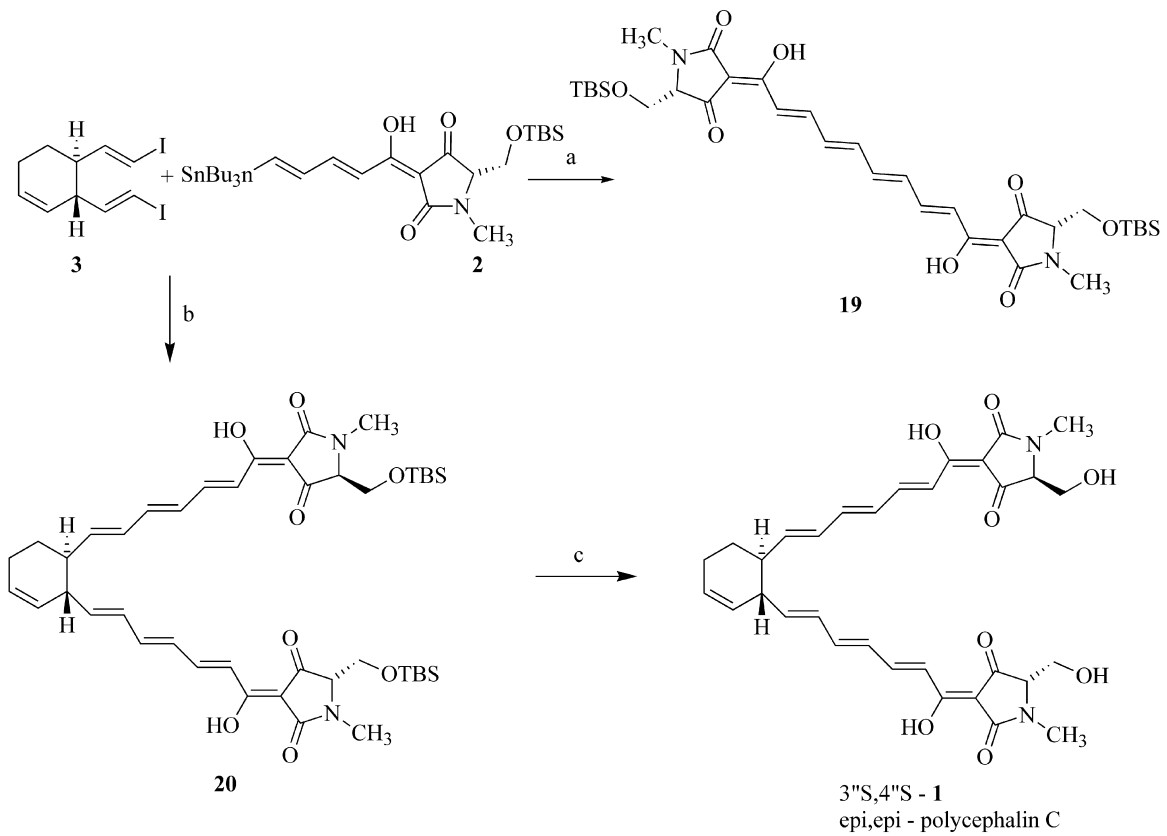
Scheme 7. *Reagents and conditions*: (a) $(COCl)_2$, DMSO, −78°C, 2 h then NEt_3, −78°C to −10°C, (b) $(COCl)_2$, DMSO, −78°C, 1 h then iPr$_2$NEt, −78°C to 0°C, 15 min, 87%, (c) $CrCl_2$, CHI_3, 0°C to room temperature, 2 h, 40%.

(50 mg) to only 43% when the reaction was carried out on gram scale. Hence these reaction conditions were abandoned.

Indeed, the best result obtained after these reaction conditions had been investigated was a modification of the initial reduction, using lithium aluminium hydride in THF. By carrying out the reaction from −78°C to room temperature, the S_N2/S_N2' ratio was increased to an acceptable 5:1 of separable diols in a combined 85% yield and furnishing a 64% isolated yield of desired diol **6** (Scheme 6). Utilising this reaction sequence gram quantities of diol **6** could be prepared.

At this point, the 1,4-oxidation of diol **6** was then investigated and the Swern[11] reaction selected as the optimum method. However, initial attempts at the double Swern oxidation were disappointing resulting in the formation of α,β-unsaturated dialdehyde **17**. However, this problem could be overcome by replacement of triethylamine with a more hindered base.[12] Thus, Swern oxidation with Hünigs base, followed by a cold acidic workup and washing with pH 7 buffer solution provided the desired dialdehyde **18** in high yield and purity (Scheme 7). The unstable nature of this compound meant that it was freshly prepared for immediate use in the subsequent step, formation of the Stille coupling partner **3**.

It was envisaged that a double Takai[13] olefination reaction could be used to install the required *trans*-double bond geometry in the formation of bis-iodide **3**. Upon reacting the dialdehyde **18** under standard Takai reaction conditions we were delighted to find that the desired bis-iodide **3** was the major product of the reaction (>90% bis-*trans* product by NMR) in a reasonable 40% yield. Thus bis-iodide **3** was prepared from (+)-dimenthyl fumarate in 7 steps in an overall 9.8% yield. Having prepared the two fragments required to construct (3″*S*,4″*S*)-**1** we then examined the reaction required to join the two fragments, a double Stille[14] coupling.



Scheme 8. *Reagents and conditions*: (a) 20 mol% $[Pd(Pfur_3)_2Cl_2]$, DMF, room temperature, 2 h, (b) 15 mol% $[Pd(MeCN)_2Cl_2]$, DMF, room temperature, 1 h, 53%, (c) TFA/H_2O, (9:1)×3, room temperature, 64%.

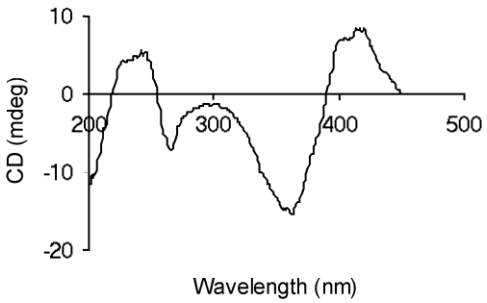


Figure 2. CD spectrum of (3″*S*,4″*S*)-**1**.

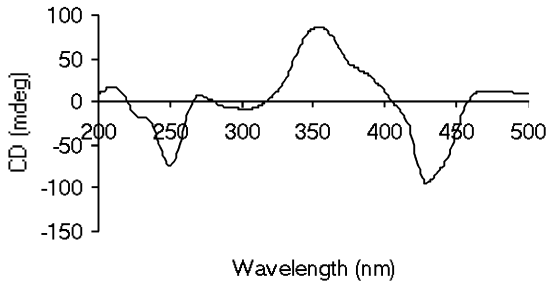


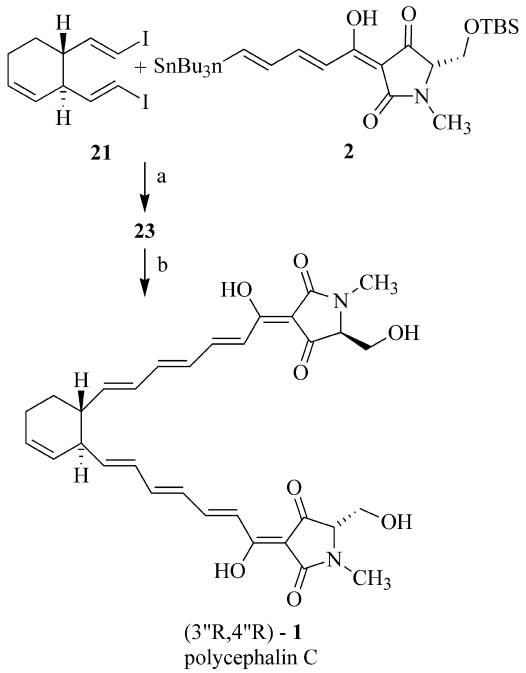
Figure 3. CD spectrum of (3″*R*,4″*R*)-**1**.

2.3. Synthesis of 3″*S*,4″*S*-1

Initial attempts at union of the two fragments bis-iodide **3** and dienoyltetramic acid **2** utilised the palladium catalyst bis-(trifurylphosphine)palladium dichloride which had been utilised to great success in our syntheses of erythroskyrine[4b] and physarorubinic acid.[4a] Disappointingly, utilising this catalyst did not lead to the desired double Stille coupling but gave the homo-coupled polyenoyl-bis-tetramic acid **19** as the major product, with only small amounts of the desired double Stille product **20** being isolated. Following optimisation studies the double Stille product **20** could be isolated in a good 53% yield utilising palladium bis(acetonitrile) dichloride as the catalyst after size exclusion chromatography (Scheme 8). The final step of the synthesis removal of the TBS ethers was carried out with trifluoroacetic acid (TFA)/water (9:1) which facilitated smooth deprotection when added and immediately removed under reduced pressure (three times). Purification by reverse-phase HPLC then gave (3″*S*,4″*S*)-**1** in 64% yield and overall 3.3% yield from dimenthyl fumarate (Scheme 8).

The spectroscopic data (^{1}H and ^{13}C NMR, MS, IR) of this synthetic material were in excellent agreement with that published in the literature and coupling constants from the polyene chain indicate the all (*E*)-double bond geometry. However, despite being of the correct sign, the optical rotation was found to differ from that given in the structure elucidation paper. In addition the CD spectrum (Fig. 2) in the range from 300 to 450 nm was also different and from this it was concluded that the 3″*S*,4″*S*-configured compound was in fact *epi*,*epi*-(3″*S*,4″*S*)-polycephalin C and that the isolated natural product had the *R*,*R* configuration about the ring junction.

To prove that this was correct the synthesis was repeated starting from (−)-dimenthyl fumarate to create the opposite configuration at the 3″,4″ ring junction. As the reaction sequence for preparation of the bis-iodide **3** had already been elaborated synthesis of the bis-iodide **21** proceeded uneventfully. Following Stille coupling with stannane **2**, deprotection with TFA/H_2O gave polycephalin C **1** with 3″*R*,4″*R* stereochemistry at the ring junction (Scheme 9).



Scheme 9. *Reagents and conditions*: (a) 5 mol% [Pd(MeCN)$_2$Cl$_2$], DMF, room temperature, 1 h, 56%, (b) TFA/H_2O (9:1)×3, room temperature, 74%.

The spectroscopic data (^{1}H and ^{13}C NMR, MS, IR) of this synthetic material were again in excellent agreement with that published in the literature. However, and importantly, in this case the optical rotation and CD spectrum (Fig. 3), crucial for confirmation of configuration, were also in excellent agreement with the published data.

Thus, the total synthesis of this unusual bistetramic acid, polycephalin C **1** has been completed in a short and efficient fashion and the goal of defining the absolute stereochemistry of the ring junction achieved.

3. Experimental

3.1. General

All reactions were carried out under an atmosphere of argon, and those not involving aqueous reagents were carried out in oven-dried glassware, cooled under vacuum. Diethyl ether (Et_2O) and tetrahydrofuran were distilled over sodium benzophenone ketyl; dichloromethane, methanol and toluene were distilled over calcium hydride; pentane was distilled over sodium and triethylamine from potassium hydroxide. All other reagents and solvents were used as supplied. Aqueous solutions are saturated unless otherwise specified. Phosphate buffer refers to potassium dihydrogen phosphate and sodium hydroxide in distilled water. Petrol refers to petroleum ether bp 40–60°C, which was distilled prior to use and ether (Et_2O) refers to diethyl ether.

Flash column chromatography was carried out using Merck Kieselgel (230–400 mesh) under pressure unless otherwise indicated. Analytical thin layer chromatography (TLC) was performed using precoated glass-backed plates (Merck Kieselgel 60 F254) and visualised by ultra-violet irradiation (254 nm) or by staining with aqueous acidic ammonium molybdate(IV) or potassium permanganate solutions as appropriate.

^{1}H NMR spectra were recorded in $CDCl_3$ (unless otherwise stated) on Bruker DPX-400, Bruker DRX-500 or Bruker DRX-600 spectrometers and are reported as follows: chemical shift, δ_H (in parts per million, ppm), (number of protons, multiplicity, coupling constant, *J*, in Hertz, and assignment). For spectra recorded in $CDCl_3$, residual protic solvent $CHCl_3$ (δ_H=7.26 ppm) was used as an internal reference. ^{13}C NMR spectra were recorded on the same spectrometers at 100 or 125 or 150 MHz, using the central resonance of $CDCl_3$ (δ_C=77.0 ppm) as the internal reference unless otherwise stated.

DEPT-135 and two-dimensional (COSY, HMQC, HMBC) NMR spectroscopy were used where appropriate, to aid in the assignment of signals in the ^{1}H and ^{13}C NMR spectra. Where coincident coupling constants have been observed in the NMR spectrum, the apparent multiplicity of the proton resonance concerned has been reported.

Some compounds exist as a mixture of keto and enol tautomers, abbreviated as k and e, respectively.

Mass spectra and accurate mass data were obtained on a Micromass Platform LC–MS, Kratos MS890MS or Bruker BIOAPEX 4.7 T FTICR spectrometer by electrospray ionisation (ESI), electron impact (EI), chemical ionisation (CI) or fast atom/ion bombardment (FAB) techniques at the Department of Chemistry, Lensfield Road, Cambridge and are reported as follows: signal (relative intensity, assignment).

Optical rotations were measured on an Optical Activity AA-1000 Polarimeter or a Perkin Elmer 343 Polarimeter and $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}; concentration (*c*) is in g 100 ml^{-1}.

Infra-red spectra were recorded either as solutions (CH_2Cl_2/MeOH) or a KBr disk on a Perkin Elmer 1600 FTIR spectrometer; alternatively as a film on a Perkin Elmer Spectrum One FT-IR spectrometer.

Melting points were measured on a Reichert hot stage apparatus, and are uncorrected. Microanalyses were performed using a CE-440 Elemental Analyser in the microanalytical laboratories at the Department of Chemistry, Lensfield Road, Cambridge.

CD spectra were recorded on a Jasco-810 spectropolarimeter themostated at 20°C using 0.1 cm cuvettes. Samples were dissolved in methanol and spectra were subtracted by the appropriate background.

Preparative HPLC was carried out on a Gilson Autoprep system using a Supelco, Supelcosil™ ABZ+PLUS column (10 cm, 2.12 cm Φ, 5 μm). Method: Eluent A: water, 0.1% TFA. B: acetonitrile 95%, water 5%, TFA 0.05%. Method: 3:1 A/B to 19:1 B/A over 35 min, flowrate 6 ml min^{-1}, detection at 254 nm.

3.1.1. (2′*S*,2*Z*,4*E*,6*E*)-3′-(*tert*-Butyldimethylsilyloxy)-2′-[(3-hydroxy-7-tri-*n*-butylstannylhepta-2,4,6-trienoyl)-methylamino]-propionic acid methyl ester 8

Amino ester **5** (260 mg, 1.05 mmol) in THF (4 ml) was added to thioester **4** (500 mg, 1.0 mmol) in THF (1.0 ml). Triethylamine (700 μl, 5.0 mmol) was then added and the reaction mixture cooled to 0°C. Silver trifluoroacetate (270 mg, 1.22 mmol) was then added in one portion and the reaction mixture stirred at 0°C for 20 min. Petrol (3 ml) was then added and the reaction mixture filtered through a pad of celite (×2, washing with petrol/ether 10:1). The solvent was then removed under reduced pressure and the residue immediately purified by flash column chromatography (petrol/ether 10:1 then 3:1] affording **8** (528 mg, 81%) as a yellow oil, R_F 0.58 [petrol/ether 1:1]; $[\alpha]_D^{25}$=−15.6 (*c* 0.16, CH_2Cl_2); ν_{max} (CH_2Cl_2, cm^{-1}) 2952, 2928, 2856 (CH), 1745, 1632, 1591 (C=O, C=C); δ_H (600 MHz, $CDCl_3$) (k/e 25:75, major rotamer assigned) 7.15 (1H-k, dd, *J*=15.5, 10.3 Hz, H-5), 7.00–6.93 (1H-k, 1H-e, m, H-6 (k), H-5 (e)), 6.70–6.58 (1H-k, 2H-e, m, H-7 (k), H-7, H-6 (e)), 6.20 (1H-k, d, *J*=15.3 Hz, H-4), 5.88 (1H-e, d, *J*=15.2 Hz, H-4), 5.27 (1H-e, s, H-2), 5.11 (1H-e, app q, *J*=3.5 Hz, H-2′), 5.07 (1H-k, app q, *J*=3.5 Hz, H-2′), 4.16–4.11 (1H-k, 1H-e, m, H_a-3′), 4.01–3.97 (1H-k, 1H-e, m, H_b-3′), 3.73 (3H-e, s, OCH_3), 3.72 (3H-k, s, OCH_3), 3.70 (2H-k, s, H-2), 3.13 (3H-k, s, NCH_3), 3.11 (3H-e, s, NCH_3), 1.59–1.43 (6H-k, 6H-e, m, CH_2-2 Bu_3Sn), 1.31 (6H-k, 6H-e, app sextet, *J*=7.4 Hz, CH_2-3 Bu_3Sn), 0.94 (6H-k, 6H-e, app q, *J*=9.0, 7.9, 8.4 Hz, CH_2-1 Bu_3Sn), 0.89 (9H-k, 9H-e, t, *J*=7.3 Hz, CH_3 Bu_3Sn), 0.86 (9H-k, 9H-e, s, SiC(CH_3)$_3$), [0.05 (s, 6H-k, 6H-e) and 0.04 (6H-k, 6H-e), Si(CH_3)$_2$]; δ_C (150 MHz, $CDCl_3$) 193.7, 172.5, 170.0, 169.8, 169.6, 167.9 (k/e, C-3, C-1, C-1′), 150.6 (e, C-5), 145.9 (k, C-5), 145.3, 144.6, 142.8 (1C-k, 2C-e, C-7, C-6 (e), C-7 (k)), 138.3 (k, C-6), 127.0 (k, C-4), 125.2 (e, C-4), 89.5 (e, C-2), 62.0, 61.8 (k/e, C-3′), 59.4 (k, C-2′), 58.6 (e, C-2′), 52.0 (k/e, OCH_3), 48.0 (k, C-2), 34.6 (k, NCH_3), 33.9 (e, NCH_3), 29.1, 29.0 (k/e, CH_2-2 Bu_3Sn), 27.4, 27.2 (k/e, CH_2-3 Bu_3Sn), 25.7, 25.6 (k/e, SiC(CH_3)$_3$), 18.0 (k/e, SiC(CH$_3$)$_3$), 13.6 (k/e, CH_3 Bu_3Sn), 9.7, 9.6 (k/e, CH_2-1 Bu_3Sn), −5.6, −5.7, −5.8 (k/e, Si(CH_3)$_2$); *m/z* (ESI) (Found: [M+Na]$^+$, 682.2926. $C_{30}H_{57}NO_5SiSn$ requires [M+Na]$^+$, 682.2903).

3.1.2. (2′*S*,2*Z*,4*E*)-3′-(*tert*-Butyldimethylsilyloxy)-2′-[(3-hydroxyhepta-2,4,6-trienoyl)-methylamino]-propionic acid methyl ester 9

Thioester **4** (200 mg, 0.4 mmol) was dissolved in THF (3 ml) and amino ester **5** (297 mg, 1.2 mmol) was added as a solution in THF (2 ml). Triethylamine (139 μl, 1.0 mmol) was then added and the reaction mixture cooled to 0°C. Silver trifluoroacetate (177 mg, 0.8 mmol) was then added in one portion and the reaction stirred for 2 h at 0°C. The reaction mixture was filtered through a florisil pad [ether/petrol 2:1] and the solvent removed under reduced pressure. Flash column chromatography on florisil [petrol/ether 2:1 to 1:2] afforded **9** (61 mg, 45%) as a colourless oil, R_F 0.41

[petrol/ether 1:1]; δ_H (600 MHz, $CDCl_3$) (k/e 20:80, major rotamer assigned) 7.30–7.20 (1H-k, m, H-5), 7.02 (1H-e, dd, J=15.1, 11.0 Hz, H-5), [6.49–6.25 (2H-k, 1H-e, m), 5.94 (1H-e, d, J=15.2 Hz), 5.67 (1H-k, d, J=16.9 Hz), 5.55 (1H-k, d, J=10.0 Hz), 5.45 (1H-e, d, J=16.9 Hz) and 5.32 (1H-e, d, J=10.1 Hz), H-4, H-6, H_a-7, H_b-7], 5.30 (1H-e, s, H-2), 5.09 (1H-e, q, J=3.5 Hz, H-2′), 5.04 (1H-k, q, J=3.5 Hz, H-2′), 4.14–4.08 (1H-k, 1H-e, m, H_a-3′), 4.01–3.91 (1H-k, 1H-e, m, H_b-3′), 3.70 (3H-k, 3H-e, s, OCH_3), 3.69 (2H-k, s, H-2), 3.11 (3H-k, s, NCH_3), 3.09 (3H-e, s, NCH_3), 0.84 (9H-k, 9H-e, SiC(CH_3)$_3$), 0.03 (6H-k, 6H-e, Si(CH_3)$_2$),; δ_C (150 MHz, $CDCl_3$) 193.5, 172.9, 170.3, 169.9, 169.6, 168.1 (k/e, C-3, C-1, C-1′), 144.7, 136.7, 136.1, 135.5, 129.6, 127.6 (k/e C-4, C-5, C-6), 122.7 (k/e C-7), 90.1 (e, C-2), 62.4, 62.1 (k/e, C-3′), 59.8, 59.1 (k/e, C-2′), 52.4 (k/e, OCH_3), 48.4 (k, C-2), 35.0, 34.3 (k/e, NCH_3), 26.1 (k/e, SiC(CH_3)$_3$), 18.4 (k/e, SiC(CH$_3$)$_3$), −5.2, −5.3 (k/e, Si(CH_3)$_2$).

3.1.3. (3*Z*,5*S*,2′*E*,4′*E*)-5-(*tert*-Butyl-dimethyl-silyloxy-methyl)-3-(1′-hydroxy-5′-tri-*n*-butyl-stannyl-penta-2′,4′-dienylene)-*N*-methyl-pyrrolidine-2,4-dione 2

Freshly prepared sodium methoxide in methanol (8.0 ml, 4.0 mmol, 0.5 M) was added rapidly to a stirred solution of **8** (528 mg, 0.80 mmol) in methanol (10 ml) at 25°C. After 2 min, saturated aqueous NH_4Cl (5 ml) and ether (5 ml) were added and the aqueous layer separated. The aqueous layer was extracted into ether (2×5 ml) and the combined organic phase was decanted to remove water prior to removal of the solvent under reduced pressure, affording tetramic acid **2** (13 mg, 90%) as a dark yellow oil, $[\alpha]_D^{25}$=−116.4 (*c* 0.14, CH_2Cl_2); ν_{max} (CH_2Cl_2, cm^{-1}) 2956, 2928, 2855 (CH), 1706, 1623, 1587, 1541 (C=O, C=C); δ_H (600 MHz, $CDCl_3$) (major tautomer assigned) 7.32 (1H, dd, J=15.2, 10.5 Hz, H-3′), 7.06 (1H, d, J=15.2 Hz, H-2′), 6.99 (1H, d, J=18.6 Hz, H-5′), 6.83 (1H, dd, J=18.6, 10.4 Hz, H-4′), 3.98–3.93 (2H, m, H_a-1″, H_b-1″), 3.68 (1H, app s, H-5), 3.04 (3H, s, NCH_3), 1.55–1.47 (6H, m, CH_2-2 Bu$_3$Sn), 1.35–1.29 (6H, m, CH_2-3 Bu$_3$Sn), 0.96 (6H, t, J=8.0 Hz, CH_2-1 Bu$_3$Sn), 0.90 (9H, t, J=7.3 Hz, CH_3 Bu$_3$Sn), 0.82 (9H, s, SiC(CH_3)$_3$), [0.04 (3H, s) and 0.01 (3H, s), Si(CH_3)$_2$]; δ_C (150 MHz, $CDCl_3$) 192.6, 174.1, 173.1 (C-4, C-2, C-1′), 151.0 (C-5′), 145.29, 145.26 (C-3′, C-4′), 120.2 (C-2′), 101.4 (C-3), 68.6 (C-5), 60.8 (C-1″), 29.0 (*C*H$_2$-2 Bu$_3$Sn), 27.2 (*C*H$_2$-3 Bu$_3$Sn), 26.9 (NCH_3), 25.6 (SiC(CH_3)$_3$), 17.95 (SiC(CH$_3$)$_3$), 13.6 (*C*H$_3$ Bu$_3$Sn), 9.7 (*C*H$_2$-1 Bu$_3$Sn), −5.7 (Si(CH_3)$_2$); *m*/*z* (ESI) (Found: [M+Na]$^+$, 650.2664. $C_{29}H_{53}NO_4SiSn$ requires [M+Na]$^+$, 650.2664).

3.1.4. (2*Z*,1′*S*,2′*R*,5′*S*)-But-2-enedioic acid bis-(2′-isopropyl-5′-methyl-cyclohexyl) ester 22[7]

Maleic anhydride (10.0 g, 102 mmol), (+)-menthol (31.2 g, 200 mmol) and *p*-toluenesulfonic acid hydrate (0.58 g, 6.12 mmol) were dissolved in toluene (120 ml). The flask was fitted with a Dean–*S*tark head and the reaction heated at reflux for 17 h. The solution was allowed to cool and was then washed with saturated aqueous $NaHCO_3$ (100 ml). The organic portion was washed further with water (100 ml) and brine (100 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The pink residue was passed through a pad of silica [petrol to 1% ether in petrol] which afforded maleate **22** (36.0 g, 90%) as a white amorphous solid, R_F 0.43 [petrol/ether 20:1]; $[\alpha]_D^{25}$=+102.5 (*c* 0.12, CH_2Cl_2); (Found: C, 73.50; H, 10.30%. $C_{24}H_{40}O_4$ requires C, 73.43; H, 10.27%); mp 78–81°C; ν_{max} (CH_2Cl_2, cm^{-1}) 2954, 2927, 2865 (CH), 1729, 1711 (C=O); δ_H (600 MHz, $CDCl_3$) 6.18 (2H, s, C*H*=C*H*), 4.79 (2H, td, J=10.9, 4.3 Hz, H-1′, H-1″), 2.12–2.10 (2H, m, H_a-6′, H_a-6″), 1.90 (2H, sept d, J=6.9, 2.4 Hz, CH$_3$′C*H*′CH$_3$′, CH$_3$″C*H*″CH$_3$″), 1.70–1.68 (4H, m, H_a-3′, H_a-3″, H_a-4′, H_a-4″), 1.53–1.47 (2H, m, H-5′, H-5″), 1.47–1.38 (2H, m, H-2′, H-2″), 1.10–0.98 (4H, m, H_b-3′, H_b-3″, H_b-6′, H_b-6″), [0.92 (6H, d, J=6.5 Hz) and 0.89 (6H, d, J=7.0 Hz), CH′CH_3′, CH″CH_3″, CH_3′CH′CH$_3$′, CH_3″CH″CH$_3$″], 0.92–0.84 (2H, m, H_b-4′, H_b-4″), 0.78 (6H, J=6.9 Hz, CH$_3$′CH′CH_3′, CH$_3$″CH″CH_3″); δ_C (150 MHz, $CDCl_3$) 164.7 (C=O), 129.8 (HC=CH), 75.3 (C-1′, C-1″), 47.0 (C-2′, C-2″), 40.6 (C-6′, C-6″), 34.3 (C-4′, C-4″), 31.4 (C-5′, C-5″), 26.1 (CH$_3$′*C*H′CH$_3$′, CH$_3$″*C*H″CH$_3$″), 23.4 (C-3′, C-3″), 22.0, 20.8 (*C*H$_3$′CH′CH$_3$′, *C*H$_3$″CH″CH$_3$″, CH′*C*H$_3$′, CH″*C*H$_3$″), 16.3 (CH$_3$′CH′*C*H$_3$′, CH$_3$″CH″*C*H$_3$″); *m*/*z* (ESI) (Found: [M+Na]$^+$, 415.2824. $C_{24}H_{40}O_4$ requires [M+Na]$^+$, 415.2829).

3.1.5. (2*E*,1′*S*,2′*R*,5′*S*)-But-2-enedioic acid bis-(2′-isopropyl-5′-methyl-cyclohexyl) ester 10[7]

Morpholine (1.33 g, 15.3 mmol) in toluene (20 ml) was added to a solution of di-(+)-menthyl maleate **22** (45 g, 153 mmol) in toluene (180 ml) and the solution was heated at 100°C for 10 h. The solution was cooled and diluted with ether (200 ml). It was then washed sequentially with 3N HCl (150 ml), saturated aqueous $NaHCO_3$ (150 ml), water (150 ml), and brine (150 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting oil was passed through a pad of silica [petrol/ether 20:1] and afforded fumarate **10** (36.6 g, 81%) as a white crystalline solid, R_F 0.54 [petrol/ether 20:1]; $[\alpha]_D^{25}$=+102.0 (*c* 0.15, CH_2Cl_2); (Found: C, 73.54; H, 10.36%. $C_{24}H_{40}O_4$ requires C, 73.43; H, 10.27%) mp 52–54°C; ν_{max} (CH_2Cl_2, cm^{-1}) 2955, 2870 (CH), 1718 (C=O); δ_H (600 MHz, $CDCl_3$) 6.82 (2H, s, C*H*=C*H*), 4.79 (2H, td, J=10.9, 4.4 Hz, H-1′, H-1″), 2.02 (2H, d, J=11.9 Hz, H_a-6′, H_a-6″), 1.87 (2H, septd, J=6.9, 2.6 Hz, CH$_3$′C*H*′CH$_3$′, CH$_3$″C*H*″CH$_3$″), 1.71–1.68 (4H, m, H_a-3′, H_a-3″, H_a-4′, H_a-4″), 1.53–1.48 (2H, m, H-5′, H-5″), 1.46–1.41 (2H, m, H-2′, H-2″), 1.11–0.98 (4H, m, H_b-3′, H_b-3″, H_b-6′, H_b-6″), [0.91 (6H, d, J=6.8 Hz) and 0.90 (6H, d, J=7.1 Hz), CH′CH_3′, CH″CH_3″, CH_3′CH′CH$_3$′, CH_3″CH″CH$_3$″], 0.91–0.89 (2H, m, H_b-4′, H_b-4″), 0.76 (6H, d, J=7.0 Hz, CH$_3$′CH′CH_3′, CH$_3$″CH″CH_3″); δ_C (150 MHz, $CDCl_3$) 164.6 (C=O), 133.8 (HC=CH), 75.3 (C-1′, C-1″), 47.0 (C-2′, C-2″), 40.7 (C-6′, C-6″), 34.2 (C-4′, C-4″), 31.4 (C-5′, C-5″), 26.3 (CH$_3$′*C*H′CH$_3$′, CH$_3$″*C*H″CH$_3$″), 23.4 (C-3′, C-3″) 22.0, 20.7 (*C*H$_3$′CH′CH$_3$′, *C*H$_3$″CH″CH$_3$″, CH′*C*H$_3$′, CH″*C*H$_3$″), 16.3 (CH$_3$′CH′*C*H$_3$′, CH$_3$″CH″*C*H$_3$″); *m*/*z* (ESI) (Found: [M+Na]$^+$, 415.2824. $C_{24}H_{40}O_4$ requires [M+Na]$^+$, 415.2829).

3.1.6. (1*R*,2*R*,1′*S*,2′*R*,5′*S*)-Cyclohex-4-ene-1,2-dicarboxylic acid bis-(2′-isopropyl-5′-methyl-cyclohexyl) ester 7[6c]

Diethylaluminium chloride (140 ml, 140 mmol, 1.0 M in

hexanes) was added to a stirred solution of (+)-dimenthyl-fumarate **10** (27.5 g, 70 mmol) in dry toluene (400 ml) at −60°C. The deep red solution was stirred for 40 min, at which point, butadiene (24 ml, 280 mmol) was condensed separately and transferred via cannula to the reaction mixture. After 36 h at −60°C the reaction mixture was allowed to warm to −10°C, at which point water (250 ml) was added in small portions (NOTE: CAUTION REQUIRED) until the colour of the solution was discharged. Once warmed to room temperature, the solution was allowed to stand for 4 h in order to allow as much butadiene polymerisation to occur as possible. Filtration through celite was then carried out to remove polymeric material. The aqueous layer was then extracted into ether (2×200 ml) and the combined organic extracts were washed sequentially with 3N HCl (300 ml), water (300 ml) and brine (300 ml). The organic layer was then dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was left under vacuum until a gel formed, at which point ether (200 ml) was added and the gel filtered through celite to remove the remaining polymeric material. The solvent was removed in vacuo and the residue passed through a short pad of silica [petrol/ether 20:1], affording the Diels–Alder adduct **7** (22.92 g, 73%) as a white crystalline solid, R_F 0.32 [petrol/ether 20:1]; $[\alpha]_D^{25}=+25.7$ (*c* 0.18, CH_2Cl_2); (Found: C, 75.29; H, 10.33%. $C_{28}H_{46}O_4$ requires C, 75.29; H, 10.38%); mp 42–44°C; ν_{max} (CH_2Cl_2, cm^{-1}) 2954, 2869 (CH), 1728 (C=O); δ_H (600 MHz, $CDCl_3$) 5.70–5.65 (2H, m, H-4, H-5), 4.66 (2H, td, *J*=10.9, 4.3 Hz, H-1′, H-1″), 2.89–2.84 (2H, m, H-1, H-2), 2.43–2.40 (2H, m, H_a-3, H_a-6), 2.18–2.14 (2H, m, H_b-3, H_b-6), 2.01–1.98 (2H, m, H_a-6′, H_a-6″), 1.87 (2H, septd, *J*=6.9, 2.7 Hz, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), 1.69–1.65 (4H, m H_a-3′, H_a-3″, H_a-4′, H_a-4″), 1.52–1.43 (2H, m, H-5′, H-5″), 1.42–1.37 (2H, m, H-2′, H-2″), 1.08–0.98 (4H, m, H_b-3′, H_b-3″, H_b-6′, H_b-6″), [0.90 (6H, d, *J*=6.8 Hz) and 0.89 (6H, d, *J*=7.1 Hz), $CH'CH_3'$, $CH''CH_3''$, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$], 0.95–0.84 (2H, m, H_b-4′, H_b-4″), 0.73 (6H, d, *J*=6.9 Hz, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$); δ_C (150 MHz, $CDCl_3$) 174.9 (C=O), 125.4 (C-4, C-5), 74.7 (C-1′, C-1″), 47.4 (C-2′, C-2″), 41.6 (C-1, C-2), 41.1 (C-6′, C-6″), 34.7 (C-4′, C-4″), 31.8 (C-5′, C-5″), 28.3 (C-3, C-6), 26.4 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), 23.6 (C-3′, C-3″), 22.4, 21.3 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$, $CH'CH_3'$, $CH''CH_3''$), 16.4 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$); *m/z* (ESI) (Found: $[M+Na]^+$, 469.3294. $C_{28}H_{46}O_4$ requires $[M+Na]^+$ 469.3294).

3.1.7. (1*R*,2*R*,4*R*,5*R*,1′*S*,2′*R*,5′*S*)-4-Chloro-5-phenylselanyl-cyclohexane-1,2-dicarboxylic acid bis-(2′-isopropyl-5′-methyl-cyclohexyl) ester 11

Benzeneselenyl chloride (88 mg, 0.46 mmol) was added portionwise to a stirred solution of Diels–Alder adduct **7** (200 mg, 0.42 mmol) in MeCN/H_2O (14 ml, 13:1) at room temperature. After 30 min, saturated aqueous $NaHCO_3$ (20 ml) was added. The aqueous layer was removed and re-extracted into CH_2Cl_2 (2×20 ml). The combined organic phase was then washed with water (30 ml) and brine (30 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure affording chloride **11** as a yellow solid which was characterised without further purification, R_F 0.8 [CH_2Cl_2]; ν_{max} (CH_2Cl_2, cm^{-1}) 2954, 2869 (CH), 1726 (C=O); δ_H (600 MHz, $CDCl_3$) 7.52–7.49 (2H, m, 2×*m*-C*H*), 7.26–7.21 (3H, m, 2×*o*-C*H*, *p*-C*H*), 4.64–4.56 (2H, m, H-1′, H-1″), 4.40 (1H, app d, *J*=2.8 Hz, H-4), 3.65 (1H, app d, *J*=2.5 Hz, H-5), 3.09 (1H, td, *J*=11.5, 3.7 Hz, H-1), 2.93 (1H, app td, *J*=12.0, 11.1, 3.7 Hz, H-2), 2.40–2.29 (2H, m, H_a-3, H_a-6), 2.17–2.06 (2H, m, H_a-6′, H_a-6″), 1.94–1.90 (2H, m, H_b-3, H_b-6), 1.81–1.68 (2H, m, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), 1.60 (4H, app d, *J*=11.8 Hz, H_a-3′, H_a-3″, H_a-4′, H_a-4″), 1.46–1.30 (4H, m, H-2′, H-2″, H-5′, H-5″), 1.01–0.75 (18H, m, H_b-3′, H_b-3″, H_b-4′, H_b-4″, H_b-6′, H_b-6″, $CH'CH_3'$, $CH''CH_3''$, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), [0.67 (3H, d, *J*=7.0 Hz) and 0.64 (3H, d, *J*=7.0 Hz), $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$]; δ_C (150 MHz, $CDCl_3$) 171.6, 171.5 (C=O), 132.9 (*m*-C*H*), 127.7, 126.5 (*p*-C*H*, 2×*o*-C*H*), 125.9 (*ipso*-C*S*e), 72.9, 72.8 (C-1′, C-1″), 57.7 (C-4), 45.10, 45.06 (C-2′, C-2″), 44.2 (C-5), 39.00, 38.88, 38.85 (C-2, C-6′, C-6″), 37.5 (C-1), 32.5, 32.4 (C-3′, C-3″), 30.1 (C-6), 29.6 (C-5′, C-5″), 26.8 (C-3), 24.2 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), 21.3 (C-4′, C-4″), 20.2, 19.08, 19.07 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$, $CH'CH_3'$, $CH''CH_3''$), 14.13, 14.08 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$); *m/z* (ES) 661 (98, $[M+Na]^+$), 639 (100, $[M+H]^+$).

3.1.8. (1*R*,2*R*,4*R*,5*R*,1′*S*,2′*R*,5′*S*)-4-Hydroxy-5-phenylselanyl-cyclohexane-1,2-dicarboxylic acid bis-(2′-isopropyl-5′-methyl-cyclohexyl) ester 12

Water (37 ml, 2.05 mol) was added slowly to a stirred solution of Diels–Alder adduct **7** (7.5 g, 15.7 mmol) in acetonitrile (500 ml). Phenylselenium bromide (5.0 g, 21.2 mmol) was then added portionwise and the solution heated at 50°C for 12 h. Saturated aqueous $NaHCO_3$ (400 ml) was added and the aqueous layer extracted into ether (3×150 ml). The combined organic phase was sequentially washed with saturated aqueous $NaHCO_3$ (500 ml), water (500 ml) and brine (500 ml). It was then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Flash column chromatography [petrol/ether 9:1 to 1:1] and trituration of the resulting yellow solid furnished alcohol **12** (6.4 g, 75%) as a white amorphous solid, R_F 0.48 [petrol/ether 1:1]; $[\alpha]_D^{25}=+30.2$ (*c* 0.22, CH_2Cl_2); (Found: C, 65.96; H, 8.49%. $C_{34}H_{52}O_5Se$ requires C, 65.89; H, 8.46%); mp 130–131°C; ν_{max} (CH_2Cl_2, cm^{-1}) 3650–3300 (br, OH), 2955, 2926, 2870 (CH), 1727 (C=O); δ_H (600 MHz, $CDCl_3$) 7.58–7.57 (2H, m, 2×*m*-C*H*), 7.32–7.26 (3H, m, *p*-C*H*, 2×*o*-C*H*), [4.67 (1H, td, *J*=10.9, 4.4 Hz) and 4.62 (1H, td, *J*=10.9, 4.3 Hz), H-1′, H-1″], 3.77 (1H, br s, H-4), 3.26–3.23 (1H, m, H-5), 3.18 (1H, dd, *J*=11.6, 6.4 Hz, H-1), 3.06 (1H, dd, *J*=11.2, 6.6 Hz, H-2), 2.46 (1H, ddd, *J*=14.1, 7.1, 4.1 Hz, H_a-3), 2.35–2.31 (2H, m, CHO*H*, H_a-6), [2.00–1.97 (1H, m) and 1.94–1.88 (1H, m), H_a-6′, H_a-6″], 1.94–1.88 (1H, m, H_b-3), 1.86–1.78 (3H, m, H_b-6, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), 1.67–1.65 (4H, m, H_a-3′, H_a-3″, H_a-4′, H_a-4″), 1.51–1.44 (2H, m, H-5′, H-5″), 1.41–1.35 (2H, m, H-2′, H-2″), 1.07–0.84 (18H, m, H_b-3′, H_b-3″, H_b-4′, H_b-4″, H_b-6′, H_b-6″, $CH'CH_3'$, $CH''CH_3''$, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), [0.71 (3H, d, *J*=7.2 Hz) and 0.70 (3H, d, *J*=7.2 Hz) $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$]; δ_C (150 MHz, $CDCl_3$) 173.2, 173.1 (C=O), 135.3 (*m*-C*H*), 129.2, 128.1 (*p*-C*H*, 2×*o*-C*H*), 127.2 (*ipso*-C*S*e), 74.8, 74.7 (C-1′, C-1″), 68.7 (C-4), 47.4 (C-5), 46.90, 46.87 (C-2′, C-2″), 41.3 (C-2), 40.7, 40.6 (C-6′, C-6″), 40.4 (C-1), 34.23, 34.20 (C-3′, C-3″), 31.6 (C-6), 31.4, 31.3 (C-5′, C-5″), 29.9 (C-3),

26.11, 26.09 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), 23.2, 23.1 (C-4′, C-4″), 21.98, 21.97, 20.80, 20.77 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$, $CH'CH_3'$, $CH''CH_3''$), 16.0 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$); *m/z* (ESI) (Found: $[M+Na]^+$, 643.2878. $C_{34}H_{52}O_5Se$ requires $[M+Na]^+$, 643.2853).

3.1.9. (1*R*,2*R*,3*Z*,5*R*,1′*S*,2′*R*,5′*S*)-5-Hydroxy-cyclohex-3-ene-1,2-dicarboxylic acid bis-(2′-isopropyl-5′-methyl-cyclohexyl) ester 13

A solution of *m*-CPBA (57%, 3.14 g, 10.4 mmol) in dichloromethane (60 ml) was added dropwise to a stirred solution of **12** (5.86 g, 9.45 mmol) in dichloromethane at −30°C. After 5 min, diisopropylamine (5.3 ml, 37.5 mmol) was added and the reaction mixture was heated at 50°C for 14 h. Saturated aqueous $NaHCO_3$ (100 ml) was added and the aqueous phase re-extracted into dichloromethane (2×50 ml). The combined organic phase was washed with saturated aqueous $Na_2S_2O_3$ (150 ml), saturated aqueous $NaHCO_3$ (150 ml) and brine (150 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography [CH_2Cl_2 to 0.5% MeOH in CH_2Cl_2] then furnished allylic alcohol **13** (4.01 g, 92%) as a pale yellow oil, R_F 0.5 [3% MeOH in CH_2Cl_2]; $[\alpha]_D^{25}=+43.9$ (*c* 0.1, CH_2Cl_2); ν_{max} (CH_2Cl_2, cm^{-1}) 3600–3100 (br, OH), 2955, 2869 (CH), 1728 (C=O); δ_H (600 MHz, $CDCl_3$) 5.26–5.91 (2H, m, H-3, H-4), [4.70 (1H, td, *J*=10.8, 4.3 Hz) and 4.69 (1H, td, *J*=10.8, 4.3 Hz), H-1′, H-1″], 4.23 (1H, br s, H-5), 3.48–3.46 (1H, m, H-2), 3.10 (1H, ddd, *J*=12.5, 9.9, 3.3 Hz, H-1), 2.18–2.13 (1H, m, H_a-6), 2.01–1.99 (2H, m, H_a-6′, H_a-6″), 1.90–1.80 (3H, m, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$, H_b-6), 1.69–1.66 (5H, m, H_a-3′, H_a-3″, H_a-4′, H_a-4″, CHO*H*), 1.55–1.48 (2H, m, H-5′, H-5″), 1.44–1.40 (2H, m, H-2′, H-2″), 1.10–0.97 (4H, m, H_b-3′, H_b-3″, H_b-6′, H_b-6″), 0.91–0.76 (14H, m, H_b-4′, H_b-4″, $CH'CH_3'$, $CH''CH_3''$, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), 0.74 (6H, d, *J*=7.0 Hz, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$); δ_C (150 MHz, $CDCl_3$) 174.5, 172.1 (C=O), 129.7, 128.2 (C-3, C-4), 75.5, 75.1 (C-1′, C-1″), 63.1 (C-5), 47.4 (C-2′, C-2″), 44.9 (C-2), 41.20, 41.15 (C-6′, C-6″), 37.5 (C-1), 34.7, 34.6 (C-4′, C-4″), 33.5 (C-6), 31.82, 31.80 (C-5′, C-5″), 26.4 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), 23.5 (C-3′, C-3″), 22.41, 22.39 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), 21.3 ($CH'CH_3'$, $CH''CH_3''$), 16.4, 16.3 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$); *m/z* (ESI) (Found: $[M+Na]^+$, 485.3243. $C_{28}H_{46}O_5$ requires $[M+Na]^+$, 485.3259).

3.1.10. (1*R*,2*E*,4*Z*,1′*S*,2′*R*,5′*S*)-Cyclohexa-2,4-diene-1,2-dicarboxylic acid bis-(2′-isopropyl-5′-methyl-cyclohexyl) ester 14

p-Toluenesulfonyl chloride (57 mg, 0.3 mmol) was added in one portion to a stirred solution of allylic alcohol **13** (93 mg, 0.3 mmol) in pyridine (0.25 ml) at room temperature. The reaction was heated at 40°C for 6 h at which point the reaction mixture was poured onto copper sulfate solution (5 ml). It was then extracted into ether (3×5 ml) and washed sequentially with copper sulfate (3×5 ml), water (5 ml) and brine (5 ml). The organic phase was then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure, furnishing diene **14** (60 mg, 67%) as a white crystalline solid, R_F 0.35 [petrol/ether 10:1]; $[\alpha]_D^{25}=+144.6$ (*c* 0.09, CH_2Cl_2); (Found: C, 75.40; H, 9.81%. $C_{28}H_{44}O_4$ requires C, 75.63; H, 9.97%); mp 54–55°C; ν_{max} (CH_2Cl_2, cm^{-1}) 2953, 2930, 2869 (CH), 1729, 1702, (C=O), 1642 (C=C); δ_H (600 MHz, $CDCl_3$) 7.09–7.08 (1H, m, H-3), 6.11–6.06 (2H, m, H-4, H-5), 4.77–4.73 (1H, td, *J*=10.9, 4.4 Hz, H-1′), 4.65–4.61 (1H, td, *J*=10.9, 4.3 Hz, H-1″), 3.66 (1H, dd, *J*=9.8, 2.6 Hz, H-1), 2.93–2.89 (1H, m, H_a-6), 2.52 (1H, app dd, *J*=18.6, 9.8 Hz, H_b-6), 2.09–2.07 (1H, m, H_a-6′), 1.95–1.89 (2H, m, H_a-6″, $CH_3'CH'CH_3'$), 1.84 (1H, app quintd, *J*=7.0, 2.8 Hz, $CH_3''CH''CH_3''$), 1.70–1.63 (4H, m, H_a-3′, H_a-3″, H_a-4′, H_a-4″), 1.55–1.49 (1H, m, H-5′), 1.48–1.42 (2H, m, H-5″, H-2′), 1.35–1.30 (1H, m, H-2″), 1.12–1.05 (1H, m, H_b-3′), 1.04–0.98 (2H, m, H_b-3″, H_b-6′), 0.94–0.79 (15H, m, H_b-4′, H_b-4″, H_b-6″, $CH'CH_3'$, $CH''CH_3''$, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), 0.75 (3H, d, *J*=6.9 Hz, $CH_3'CH'CH_3'$), 0.71 (3H, d, *J*=6.9 Hz, $CH_3''CH''CH_3''$); δ_C (150 MHz, $CDCl_3$) 172.8, 166.6 (C=O), 133.3 (C-3), 131.8 (C-5), 126.8 (C-2), 124.2 (C-4), 75.2 (C-1′), 74.8 (C-1″), 47.6 (C-2′), 47.4 (C-2″), 41.4 (C-6′), 41.0 (C-6″), 37.2 (C-1), 34.8, 34.7 (C-4′, C-4″), 31.80, 31.76 (C-5′, C-5″), 26.9 (C-6), 26.6, 26.2 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), 23.4 (C-3′), 23.1 (C-3″), 22.44, 22.39, 21.3, 21.2 ($CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$, $CH'CH_3'$, $CH''CH_3''$), 16.8 ($CH_3'CH'CH_3'$), 16.2 ($CH_3''CH''CH_3''$); *m/z* (ESI) (Found: $[M+Na]^+$ 467.3137. $C_{28}H_{44}O_4$ requires $[M+Na]^+$, 467.3140).

3.1.11. (1*R*,2*R*,3*Z*,5*R*,1′*S*,2′*R*,5′*S*)-5-Methanesulfonyloxy-cyclohex-3-ene-1,2-dicarboxylic acid bis-(2′-isopropyl-5′-methyl-cyclohexyl) ester 15

Triethylamine (9.67 ml, 69.4 mmol) was added to a solution of allylic alcohol **13** (24.2 g, 52.2 mmol) in dichloromethane (240 ml) and the solution was cooled to −78°C. Methanesulfonyl chloride (4.73 ml, 61.1 mmol) was added and the solution allowed to warm to −15°C (Note: TLC appears dirty due to decomposition of desired product on silica). Saturated aqueous $NaHCO_3$ (2 ml) was then added and the organic layer separated. The aqueous layer was further extracted into dichloromethane (2×200 ml) and the combined organic phase washed with saturated aqueous $NaHCO_3$ (300 ml) and brine (300 ml). It was then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure giving crude mesylate **15** (25.7 g, 87%) as a pale yellow solid. A small amount was triturated with petrol for full characterisation, $[\alpha]_D^{25}=+73.3$ (*c* 0.09, CH_2Cl_2); mp 93–94°C; ν_{max} (CH_2Cl_2, cm^{-1}) 2955, 2870 (CH), 1729 (C=O), 1361, 1175 (SO_2O); δ_H (600 MHz, $CDCl_3$) 6.16 (1H, dd, *J*=10.0, 2.4 Hz, H-3), 5.99–5.96 (1H, m, H-4), 5.19–5.18 (1H, m, H-5), 4.74–4.68 (2H, m, H-1′, H-1″), 3.51 (1H, d, *J*=9.5 Hz, H-2), 3.17–3.13 (1H, m, H-1), 3.04 (3H, s, $CHOSO_2CH_3$), 2.42 (1H, d, *J*=14.4 Hz, H_a-6), 2.00–1.98 (2H, m, H_a-6′, H_a-6″), 1.95–1.93 (1H, m, H_b-6), 1.84 (2H, app td, *J*=6.7 Hz, 2.2, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), 1.68 (4H, app d, *J*=11.8 Hz, H_a-3′, H_a-3″, H_a-4′, H_a-4″), 1.49–1.39 (4H, m, H-5′, H-5″, H-2′, H-2″), 1.07–0.97 (4H, m, H_b-3′, H_b-3″, H_b-6′, H_b-6″), 0.91–0.89 (14H, m, H_b-4′, H_b-4″, $CH'CH_3'$, $CH''CH_3''$, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$), 0.75–0.74 (6H, m, $CH_3'CH'CH_3'$, $CH_3''CH''CH_3''$); δ_C (150 MHz, $CDCl_3$) 173.4, 171.1 (C=O), 132.2 (C-3), 124.8 (C-4), 75.8, 75.4 (C-1′, C-1″), 72.6 (C-5), 47.34, 47.29 (C-2′, C-2″), 44.6 (C-2), 41.13, 41.12 (C-6′, C-6″), 39.4 ($CHOSO_2CH_3$), 37.5 (C-1), 34.6 (C-4′, C-4″), 31.79, 31.77 (C-5′, C-5″), 31.5 (C-6), 26.5, 26.4 (CH_3'

*C*H′CH$_3$′, CH$_3$″*C*H″CH$_3$″), 23.5 (C-3′, C-3″), 22.3, 21.22, 21.18 (*C*H$_3$′CH′CH$_3$′, *C*H$_3$″CH″CH$_3$″, CH′*C*H$_3$′, CH″*C*H$_3$″), 16.3 (CH$_3$′CH′*C*H$_3$′, CH$_3$″CH″*C*H$_3$″); *m/z* (ESI) (Found: [M+Na]$^+$ 563.3021. $C_{29}H_{48}O_7S$ requires [M+Na]$^+$, 563.3013).

3.1.12. (1*R*,2*Z*,6*R*)-(6-Hydroxymethyl-cyclohex-2-enyl)-methanol 6

$LiAlH_4$ (14.2 ml, 14.2 mmol, 1.0 M in THF) was added dropwise to a stirred solution of mesylate **15** (1.0 g, 1.78 mmol) in THF (25 ml) at −78°C. The reaction mixture was allowed to warm to room temperature overnight at which point ethyl acetate (10 ml) was added dropwise. Ground sodium sulfate decahydrate was then added portionwise and the reaction mixture stirred for 10 h. Filtration and evaporation gave a colourless oil (273 mg, 85%, S_N2/S_N2' 5:1) and flash column chromatography [EtOAc] afforded diol **6** (159 mg, 64%) as a pale brown oil, R_F 0.33 [ether/MeOH 19:1]; $[\alpha]_D^{25}=-46.0$ (*c* 0.15, CH_2Cl_2); ν_{max} (CH_2Cl_2, cm^{-1}) 3600–3100 (br, OH), 3019 (alkene C–H), 2921, 2876 (CH); δ_H (600 MHz, $CDCl_3$) 5.80 (1H, ddd, *J*=9.9, 6.2, 3.5 Hz, H-3), 5.45 (1H, dd, *J*=9.9, 2.2 Hz, H-2), 3.81 (2H, s, 2×O*H*), 3.66 (1H, dd, *J*=10.8, 3.9 Hz, H$_a$-1′), 3.61 (1H, dd, *J*=10.8, 4.6 Hz, H$_a$-2′), 3.56 (1H, dd, *J*=10.8, 7.3 Hz, H$_b$-2′), 3.49 (1H, dd, *J*=10.8, 7.8 Hz, H$_b$-1′), 2.15 (1H, m, H-1), 2.06–2.02 (2H, m, H$_a$-4, H$_b$-4), 1.71–1.64 (2H, m, H$_a$-5, H-6), 1.40–1.33 (1H, m, H$_b$-5); δ_C (150 MHz, $CDCl_3$) 129.2 (C-3), 127.3 (C-2), 67.2 (C-2′), 66.6 (C-1′), 42.7 (C-1), 39.9 (C-6), 24.5 (C-5), 24.2 (C-4); *m/z* (ESI) (Found: [M+Na]$^+$, 165.0894. $C_8H_{14}O_2$ requires [M+Na]$^+$, 165.0891).

3.1.13. (1*R*,3*Z*,6*R*)-(6-Hydroxymethyl-cyclohex-3-enyl)-methanol 16

A small amount (20 mg) of diol **16** was isolated for full characterisation, R_F 0.39 [ether/MeOH 19:1]; $[\alpha]_D^{25}=-69.0$ (*c* 0.20, CH_2Cl_2); (Found: C, 67.56; H, 9.91%. $C_8H_{14}O_2$ requires C, 67.57; H, 9.92%); ν_{max} (CH_2Cl_2, cm^{-1}) 3600–3050 (br, OH), 3024, 2890, 2801 (CH); δ_H (600 MHz, $CDCl_3$) 5.65 (2H, d, *J*=5.7 Hz, H-3, H-4), [3.75–3.72 (2H, m) and 3.62–3.58 (2H, m), H$_a$-1′, H$_b$-1′, H$_a$-2′, H$_b$-2′], 2.78 (2H, t, *J*=5.5 Hz, 2×CH$_2$O*H*), 2.04–2.01 (2H, m, H$_a$-2, H$_a$-5), 1.90–1.85 (2H, m, H$_b$-2, H$_b$-5), 1.72–1.67 (2H, m, H-1, H-6); δ_C (150 MHz, $CDCl_3$) 126.0 (C-3, C-4), 66.3 (C-1′, C-2′), 39.7 (C-1, C-6), 28.5 (C-2, C-5); *m/z* (ESI) (Found: [M+Na]$^+$, 165.0884. $C_8H_{14}O_2$ requires [M+Na]$^+$, 165.0891).

3.1.14. (1*R*,2*R*,3*Z*)-Cyclohex-3-ene-1,2-dicarbaldehyde 18

Oxalyl chloride (609 μl, 7.0 mmol) in CH_2Cl_2 (12.5 ml) was cooled to −78°C and DMSO (1.24 ml, 17.5 mmol) in CH_2Cl_2 (12.5 ml) was added *via* cannula. The reaction mixture was stirred at −78°C for 1 h before a solution of the diol **6** (250 mg, 1.75 mmol) in CH_2Cl_2 (12.5 ml) was added dropwise *via* cannula. The reaction mixture was stirred for 30 min at which point DIPEA (2.42 ml, 14.0 mmol) was added dropwise over 5 min. The reaction mixture was stirred at −78°C for 15 min and then warmed to 0°C. It was stirred for 5 min at 0°C and then washed with cold 1N HCl (3×40 ml) and pH 7 buffer (2×40 ml) before being dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. This provided 1,4-dialdehyde **18** (215 mg, 87%) as a pale yellow liquid, R_F 0.28 [CH_2Cl_2]; $[\alpha]_D^{25}=-40.0$ (*c* 0.08, CH_2Cl_2); ν_{max} (CH_2Cl_2, cm^{-1}) 2925, 2839, 2722 (CH), 1714 (C=O); δ_H (600 MHz, $CDCl_3$) 9.74 (1H, s, H-1′), 9.67 (1H, s, H-2′), 5.98–5.93 (1H, m, H-4), 5.83 (1H, dd, *J*=10.0, 1.6 Hz, H-3), 3.50–3.49 (1H, m, H-2), 2.99–2.96 (1H, m, H-1), 2.12–2.06 (2H, m, H$_a$-5, H$_b$-5), 2.00–1.95 (1H, m, H$_a$-6), 1.79–1.73 (1H, m, H$_b$-6); δ_C (150 MHz, $CDCl_3$) 201.9 (C-1′), 199.1 (C-2′), 130.6 (C-4), 119.6 (C-3), 48.2 (C-2), 45.1 (C-1), 23.2 (C-5), 20.3 (C-6); *m/z* (EI) (Found: [M]$^+$, 138.0688. $C_8H_{10}O_2$ requires [M]$^+$, 138.0681).

3.1.15. (1*Z*,3*R*,4*R*,1′*E*)-3,4-Bis-(2′-iodo-vinyl)-cyclohexene 3

A solution of dialdehyde **18** (100 mg, 0.72 mmol) and CHI_3 (638 mg, 1.62 mmol) in THF (10 ml) was added to a rapidly stirred slurry of $CrCl_2$ (885 mg, 7.2 mmol) in THF (5 ml) at 0°C. After 30 min, the ice bath was removed and the reaction was allowed to warm to room temperature. After 2 h, ether (100 ml) and water (100 ml) were added. The organic layer was separated and the aqueous further extracted into ether (2×50 ml). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (2×100 ml), saturated aqueous $Na_2S_2O_3$ (1×100 ml), water (2×100 ml) and brine (1×100 ml). This was then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure, providing divinyl iodide **3** (110 mg, 40%) as a pale yellow oil, R_F 0.35 [petrol]; ν_{max} (CH_2Cl_2, cm^{-1}) 3021, 2920, 2854 (CH), 1650, 1601 (C=C); δ_H (600 MHz, $CDCl_3$) 6.48 (1H, dd, *J*=14.4, 8.1 Hz, H-1′), 6.40 (1H, dd, *J*=14.4, 8.1 Hz, H-1″), 6.08 (1H, d, *J*=14.4 Hz, H-2′), 6.07 (1H, d, *J*=14.4 Hz, H-2″), 5.82–5.79 (1H, m, H-1), 5.48 (1H, dd, *J*=7.9, 2.2 Hz, H-2), 2.67–2.64 (1H, m, H-3), 2.27–2.03 (3H, m, H-4, H$_a$-6, H$_b$-6), 1.80–1.76 (1H, m, H$_a$-5), 1.53–1.43 (1H, m, H$_b$-5); δ_C (150 MHz, $CDCl_3$) 148.6 (C-1″), 147.9 (C-1′), 128.6 (C-1), 126.4 (C-2), 76.6 (C-2″), 75.5 (C-2′), 46.9 (C-3), 45.2 (C-4), 26.1 (C-5), 23.7 (C-6); *m/z* (ESI) 132 (100, [M−I$_2$]$^+$).

3.1.16. (3*Z*,5*S*,2′*E*,4′*E*,6′*E*,3″*S*,4″*S*,1‴*E*,3‴*E*,5‴*E*,7‴*Z*,5⁗*S*)-5-*tert*-butyldimethylsilyloxymethyl-3-{7′-{4″-[7‴-(5⁗-*tert*-butyldimethylsilyloxymethyl-1⁗-methyl-2⁗,4⁗-dioxo-pyrrolidin-3⁗-ylidene)-7‴-hydroxy-hepta-1‴,3‴,5‴-trienyl]cyclohexen-3″-yl}-1′hydroxy-hepta-2′,4′,6′-trien-1′-ylene}-1-methylpyrrolidine-2,4-dione 20.

A solution of bis-(acetonitrile) dichloropalladium (7.0 mg, 0.03 mmol) in DMF (1 ml) was added to a stirred solution of divinyl iodide **3** (70 mg, 0.18 mmol) and stannane **2** (284 mg, 0.45 mmol) in DMF (2 ml) at room temperature. The reaction was stirred for 1 h at which point ethyl acetate (50 ml) and water (50 ml) were added. The organic layer was separated, washed with water (6×50 ml) and the solvent removed under reduced pressure. Size exclusion chromatography on Sephadex LH-20 [CH_2Cl_2/MeOH 1:1] then afforded **20** (77 mg, 53%) as an orange amorphous solid, R_F 0.45 [3% MeOH in CH_2Cl_2]; mp 75–77°C; ν_{max} (CH_2Cl_2, cm^{-1}) 3600–3100 (br, OH), 2929, 2857 (CH), 1701, 1611, 1598, 1556 (C=O, C=C); δ_H (600 MHz, $CDCl_3$) 7.45 (2H, dd,

J=15.0, 11.5 Hz, H-3′, H-5‴), 7.12 (2H, d, J=15.0 Hz, H-2′, H-6‴), 6.61 (2H, dd, J=14.0, 11.3 Hz, H-5′, H-3‴), [6.40 (1H, dd, J=14.8, 11.5 Hz) and 6.39 (1H, dd, J=14.6, 11.4 Hz), H-4′, H-4‴], 6.21 (1H, dd, J=15.2, 10.3 Hz, H-2‴), 6.20 (1H, dd, J=15.1, 10.6 Hz, H-6′), 5.96 (1H, dd, J=15.2, 7.9 Hz, H-1‴), 5.87 (1H, dd, J=15.1, 8.1 Hz, H-7′), 5.83–5.81 (1H, m, H-1″), 5.52 (1H, dd, J=10.1, 1.8 Hz, H-2″), 3.96 (2H, dd, J=10.9, 2.4 Hz, H_a-6, H_a-6‴), 3.92 (2H, dd, J=10.9, 3.9 Hz, H_b-6, H_b-6‴), 3.67 (2H, m, H-5, H-5‴), 3.03 (6H, s, NCH_3, NCH_3‴), 2.77 (1H, br s, H-3″), 2.22 (1H, app dd, J=15.6, 7.9 Hz, H-4″), 2.09 (2H, br s, H_a-6″, H_b-6″), 1.82–1.73 (1H, m, H_a-5″), 1.62–1.41 (1H, m, H_b-5″), 0.80 (18H, s, SiC(CH_3)$_3$, SiC(CH_3‴)$_3$), [0.03 (6H, s) and −0.01 (6H, s) Si(CH_3)$_2$, Si(CH_3‴)$_2$]; δ_C (150 MHz, $CDCl_3$) 192.47 (C-4, C-4‴), 174.06 (C-2, C-2‴), 172.24 (C-1′, C-7‴), 144.21, 144.15 (C-3′, C-5‴), 143.39 (C-7′, C-1‴), 142.80, 142.60 (C-5′, C-3‴), 130.62 (C-6′), 129.99, 129.87, 129.83 (C-4′, C-4‴, C-2‴), 128.22 (C-1″), 127.56 (C-2″), 120.96, 120.87 (C-2′, C-6‴), 100.84, 100.82 (C-3, C-3‴), 68.61 (C-5, C-5‴), 60.95 (C-6, C-6‴), 44.51 (C-3″), 43.07 (C-4″), 27.06, 26.98 (C-5″, NCH_3, NCH_3‴), 25.56 (SiC(CH_3)$_3$, SiC(CH_3‴)$_3$), 24.02 (C-6″), 17.95 (SiC(CH$_3$)$_3$, SiC(CH$_3$‴)$_3$), −5.66, −5.71 (Si(CH_3)$_2$, Si(CH_3‴)$_2$); m/z (ESI) (Found: [M+Na]$^+$, 827.4079. $C_{44}H_{64}N_2O_8Si$ requires [M+Na]$^+$, 827.4099).

3.1.17. (3*Z*,5*S*,2′*E*,4′*E*,6′*E*,8′*E*,10′*Z*,5″*S*)-5-*tert*-butyldimethylsilyloxymethyl-3-[10′-(5″-*tert*-butyldimethylsilyloxymethyl-1″-methyl-2″,4″-dioxo-pyrrolidine-3-ylidene)-1′,10′-dihydroxydeca-2′,4′,6′,8′-tetraen-1′-ylene]-1-methylpyrrolidine-2,4-dione 19.

A small amount of side product **19** was isolated for characterisation purposes, R_F 0.28 [3% MeOH in CH_2Cl_2]; ν_{max}(CH_2Cl_2, cm^{-1}) 3600–3000 (br, OH), 2928, 2857 (CH), 1701, 1611, 1541 (C═O, C═C); δ_H(600 MHz, $CDCl_3$) 7.48 (2H, dd, J=15.1, 11.1 Hz, H-8′, H-3′), 7.25 (2H, d, J=15.1 Hz, H-9′, H-2′), 6.74 (2H, m, J=11.3 Hz, H-6′, H-5′), 6.68 (2H, m, J=11.3 Hz, H-7′, H-4′), 3.97 (2H, dd, J=10.9, 2.8 Hz, H_a-6, H_a-6″), 3.95 (2H, dd, J=10.9, 4.2 Hz, H_b-6, H_b-6″), 3.68 (2H, m, H-5, H-5″), 3.05 (6H, s, NCH_3, NCH_3″), 0.81 (18H, s, SiC(CH_3)$_3$, SiC(CH_3″)$_3$), [0.04 (6H, s) and 0.00 (6H, s) Si(CH_3)$_2$, Si(CH_3″)$_2$]; δ_C(150 MHz, $CDCl_3$) 192.6 (C-4, C-4″), 173.7 (C-2, C-2″), 171.3 (C1′, C-10′), 142.5 (C-8′, C-3′), 140.6 (C-6′, C-5′), 135.5 (C-7′, C-4′), 123.7 (C-9′, C-2′), 101.7 (C-3, C-3″), 68.6 (C-5, C-5″), 60.7 (C-6, C-6″), 27.0 (NCH$_3$, NCH$_3$″), 25.5 (SiC(CH$_3$)$_3$, SiC(CH$_3$″)$_3$), 17.95 (SiC(CH$_3$)$_3$, SiC(CH$_3$″)$_3$), −0.5 (Si(CH$_3$)$_2$, Si(CH$_3$″)$_2$); m/z (ESI) (Found: [M+Na]$^+$, 695.3160. $C_{34}H_{52}N_2O_8Si_2$ requires [M+Na]$^+$, 695.3137).

3.1.18. (3*Z*,5*S*,2′*E*,4′*E*,6′*E*,3″*S*,4″*S*,1‴*E*,3‴*E*,5‴*E*,7‴*Z*,5⁗*S*)-5-hydroxymethyl-3-{7′-{4″-[7‴-(5⁗-hydroxymethyl-1⁗-methyl-2⁗,4⁗-dioxo-pyrrolidin-3⁗-ylidene)-7‴-hydroxy-hepta-1‴,3‴,5‴-trienyl]cyclohexen-3″-yl}-1′-hydroxy-hepta-2′,4′,6′-trien-1′-ylene}-1-methylpyrrolidine-2,4-dione (*epi*,*epi*-polycephalin C) 1.

A mixture of TFA/water (9:1, 1 ml) was added to **20** (20 mg, 24 μmol) and immediately removed under reduced pressure. The process was repeated twice and afforded crude *epi*,*epi*-polycephalin C. Purification by preparative HPLC then afforded *epi*,*epi*-polycephalin C **1** (10.6 mg, 64%) as an orange amorphous solid, t_{ret} 24.5 min, R_F 0.57 [$CHCl_3$/MeOH/H_2O 60:40:9]; $[\alpha]_D^{25}$=−167.5 (c 0.0041, MeOH); ν_{max} (film, cm^{-1}) 3600–3050 (br, OH), 3021, 2930, 1685, 1636, 1595, 1553, 1482, 1446, 1408, 1357, 1287, 1254, 1134, 1007, 916; UV (c 3.63 μmol, MeOH), λ_{max} (lgϵ)/nm^{-1} 276.0 (0.215), 365.0 (0.22); δ_H (600 MHz, $CDCl_3$/CD_3OD 1:1, referenced to residual CH_3OH) 7.47 (2H, dd, J=15.0, 11.5 Hz, H-3′, H-5‴), 7.10 (2H, d, J=15.0 Hz, H-2′, H-6‴), 6.66 (2H, dd, J=14.7, 10.9 Hz, H-5′, H-3‴), 6.41–6.35 (2H, m, H-4′, H-4‴), 6.24–6.18 (2H, m, H-6′, H-2‴), 5.98 (1H, dd, J=15.3, 7.9 Hz, H-1‴), 5.89 (1H, dd, J=15.0, 8.1 Hz, H-7′), 5.81–5.78 (1H, m, J=2.2 Hz, H-1″), 5.49 (1H, dd, J=10.1, 2.1 Hz, H-2″), 3.90 (4H, app s, H_a-6, H_a-6⁗, H_b-6, H_b-6⁗), 3.69 (2H, s, H-5, H-5⁗), 3.02 (6H, s, NCH_3, NCH_3⁗), 2.79–2.73 (1H, m, H-3″), 2.23–2.18 (1H, m, H-4″), 2.07 (2H, br s, H_a-6″, H_b-6″), 1.81–1.78 (1H, m, H_a-5″), 1.56–1.48 (1H, m, H_b-5″); δ_C (125 MHz, $CDCl_3$/CD_3OD 1:1, referenced to residual CH_3OH) 194.21 (C-4, C-4⁗), 174.52 (C-2, C-2⁗), 173.02 (C-1′, C-7‴), 145.69, 145.64 (C-3′, C-5‴), 145.48 (C-1‴), 144.66 (C-7′), 144.35 (C-3‴), 144.13 (C-5′), 131.32 (C-6′), 130.58 (C-2‴), 130.36, 130.19 (C-4, C-4‴), 128.74 (C-1″), 128.03 (C-2″), 120.98, 120.87 (C-2′, C-6‴), 101.34 (C-3, C-3⁗), 69.29 (C-5, C-5⁗), 59.13 (C-6, C-6⁗), 45.23 (C-3″), 43.85 (C-4″), 27.69 (C-5″), 26.90 (NCH$_3$, NCH$_3$⁗), 24.41 (C-6″); m/z (ESI) (Found: [M+Na]$^+$, 599.2357. $C_{32}H_{36}N_2O_8$ requires [M+Na]$^+$, 599.2369).

3.1.19. (3*Z*,5*S*,2′*E*,4′*E*,6′*E*,3″*R*,4″*R*,1‴*E*,3‴*E*,5‴*E*,7‴*Z*,5⁗*S*)-5-*tert*-butyldimethylsilyloxymethyl-3-{7′-{4″-[7‴-(5⁗-*tert*-butyldimethylsilyloxymethyl-1⁗-methyl-2⁗,4⁗-dioxo-pyrrolidin-3⁗-ylidene)-7‴-hydroxy-hepta-1‴,3‴,5‴-trienyl]cyclohexen-3″-yl}-1′hydroxy-hepta-2′,4′,6′-trien-1′-ylene}-1-methylpyrrolidine-2,4-dione 23.

A solution of bis-(acetonitrile) dichloropalladium (0.84 mg, 3.2 μmol) in DMF (0.5 ml) was added to a stirred solution of divinyl iodide **21** (25.6 mg, 0.066 mmol) and stannane **2** (106 mg, 0.169 mmol) in DMF (2.5 ml) at room temperature. The reaction was stirred for two h at which point ethyl acetate (50 ml) and water (50 ml) were added. The organic layer was separated, washed with water (4×50 ml) and the solvent removed under reduced pressure. Size exclusion chromatography on Sephadex LH-20 [CH_2Cl_2/MeOH 1:1] then afforded **23** (29.7 mg, 56%) as an orange amorphous solid, mp 89–91°C (dec.); $[\alpha]_D^{25}$=−140 (c 0.05, $CHCl_3$); ν_{max} (film, cm^{-1}) 3100–2390 (br, OH), 2927, 2856 (CH), 1701, 1596, 1555 (C═O, C═C); δ_H (600 MHz, $CDCl_3$) 7.45 (2H, dd, J=14.8, 11.7 Hz, H-3′, H-5‴), 7.12 (2H, d, J=15.1 Hz, H-2′, H-6‴), 6.61 (2H, dd, J=13.4, 11.6 Hz, H-5′, H-3‴), 6.42–6.38 (2H, m, H-4′, H-4‴), 6.22–6.17 (2H, m, H-2‴, H-6′), 5.95 (1H, dd, J=15.0, 7.8 Hz, H-1‴), 5.87 (1H, dd, J=15.0, 8.0 Hz, H-7′), 5.83–5.81 (1H, m, H-1″), 5.51 (1H, d, J=9.5 Hz, H-2″), 3.97–3.92 (4H, m, H_a-6, H_b-6, H_a-6⁗, H_b-6⁗), 3.66 (2H, m, H-5, H-5⁗), 3.03 (6H, s, NCH_3, NCH_3⁗), 2.76 (1H, br s, H-3″), 2.28–2.16 (1H, m, H-4″), 2.09 (2H, br s, H_a-6″, H_b-6″), 1.86–1.76 (1H, m, H_a-5″), 1.65–1.46 (1H, m, H_b-5″), 0.80 (18H, s, SiC(CH_3)$_3$, SiC(CH_3‴)$_3$), [0.03 (6H, s) and −0.01 (6H, s) Si(CH_3)$_2$, Si(CH_3⁗)$_2$]; δ_C (150 MHz, $CDCl_3$) 192.5, 192.47 (C-4, C-4⁗), 174.05 (C-2, C-2⁗), 172.24 (C-1′, C-7‴), 144.15, (C-3′, C-5‴), 143.33 (C-7′, C-1‴), 142.77, 142.57 (C-5′, C-3‴), 130.67 (C-6′), 130.00, 129.91, 129.84 (C-4′, C-4‴, C-2‴), 128.21 (C-1″), 127.56 (C-2″), 120.97, 120.88 (C-2′,

C-6‴), 100.82, (C-3, C-3⁗), 69.71, 68.61 (C-5, C-5⁗), 60.95 (C-6, C-6⁗), 44.52 (C-3″), 43.07 (C-4″), 29.66 (C-5″) 27.06, 26.98 (NCH_3, NCH_3⁗), 25.66 ($SiC(CH_3)_3$, $SiC(CH_3$⁗$)_3$), 24.01 (C-6″), 17.95 ($SiC(CH_3)_3$, $SiC(CH_3$⁗$)_3$), $Si(CH_3$⁗$)_2$); *m/z* (ESI) (Found: $[M+Na]^+$, 827.4099 $C_{44}H_{64}N_2O_8Si$ requires $[M+Na]^+$, 827.4089).

3.1.20.

(3*Z*,5*S*,2′*E*,4′*E*,6′*E*,3″*R*,4″*R*,1‴*E*,3‴*E*,5‴*E*,7‴*Z*,5⁗*S*)-5-hydroxymethyl-3-{7′-{4″-[7‴-(5⁗-hydroxymethyl-1⁗-methyl-2⁗,4⁗-dioxo-pyrrolidin-3⁗-ylidene)-7‴-hydroxy-hepta-1‴,3‴,5‴-trienyl]cyclohexen-3″-yl}-1′-hydroxy-hepta-2′,4′,6′-trien-1′-ylene}-1-methylpyrrolidine-2,4-dione (polycephalin C) 1. A mixture of TFA/water (9:1, 1 ml) was added to **23** (8.5 mg, 10.6 μmol) and immediately removed under reduced pressure. The process was repeated twice and afforded crude polycephalin C. Purification by preparative HPLC then afforded polycephalin C **1** (4.5 mg, 74%) as an orange amorphous solid, t_{ret} 24.5 min, $[\alpha]_D^{25}=-72.5$ (*c* 0.00414, MeOH); ν_{max} (film, cm^{-1}) 3600–3080 (br, OH), 2940, 2922, 1690, 1635, 1590, 1547, 1442, 1404, 1354, 1285, 1256, 1201, 1170, 1132, 1003; δ_H (600 MHz, $CDCl_3/CD_3OD$ 1:1, referenced to residual CH_3OH) 7.47 (2H, dd, *J*=14.7, 11.9 Hz, H-3′, H-5‴), 7.11 (2H, d, *J*=15.0 Hz, H-2′, H-6‴), 6.67 (2H, dd, *J*=14.2, 11.2 Hz, H-5′, H-3‴), 6.45–6.34 (2H, m, H-4′, H-4‴), 6.27–6.17 (2H, m, H-6′, H-2‴), 5.98 (1H, dd, *J*=15.0, 7.8 Hz, H-1‴), 5.89 (1H, dd, *J*=14.9, 8.1 Hz, H-7′), 5.84–5.76 (1H, m, H-1″), 5.49 (1H, dd, *J*=10.0, 1.8 Hz, H-2″), 3.911, 3.909 (4H, 2×s, H_a-6, H_a-6⁗, H_b-6, H_b-6⁗), 3.69 (2H, s, H-5, H-5⁗), 3.02 (6H, s, NCH_3, NCH_3⁗), 2.81–2.72 (1H, m, H-3″), 2.27–2.2 (1H, m, H-4″), 2.08 (2H, br s, H_a-6″, H_b-6″), 1.86–1.75 (1H, m, H_a-5″), 1.56–1.46 (1H, m, H_b-5″); δ_C (125 MHz, $CDCl_3/CD_3OD$ 1:1, referenced to residual CH_3OH) 194.20 (C-4, C-4⁗), 174.56 (C-2, C-2⁗), 173.08 (C-1′, C-7‴), 145.66, 145.61 (C-3′, C-5‴), 145.44 (C-1‴), 144.63 (C-7′), 144.31 (C-3‴), 144.08 (C-5′), 131.36 (C-6′), 130.63 (C-2‴), 130.40, 130.24 (C-4, C-4‴), 128.75 (C-1″), 128.08 (C-2″), 121.06, 120.96 (C-2′, C-6‴), 101.37 (C-3, C-3⁗), 69.34 (C-5, C-5⁗), 59.27 (C-6, C-6⁗), 45.28 (C-3″), 43.89 (C-4″), 27.72 (C-5″), 26.95 (NCH_3, NCH_3⁗), 24.61 (C-6″); *m/z* (ESI) (Found: $[M+Na]^+$, 599.2369. $C_{32}H_{36}N_2O_8$ requires $[M+Na]^+$, 599.2369).

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