Two-directional dendritic macromolecules based on a 3,4-dihydrothiophene *S,S*-dioxide core: synthesis and thermolysis

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This article is dedicated to an old friend, Professor Gurnos Jones, on the occasion of his 70th birthday

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Abstract

It is known that tetranitrile 2 undergoes cheleotropic expulsion of SO_2 to yield the corresponding disubstituted butadiene. We herein expand this process to evaluating the expulsion of SO_2 from *within* the framework of a dendritic macromolecule. First and second tier dendrimers with the core 3,4-dihydrothiophene *S,S*-dioxide were synthesized and their thermolysis was examined. The results were consistent with the facile elimination of SO_2 coupled with an unexpected secondary dehydration processes at the elevated temperatures associated with this procedure.

Keywords: Dendrimers synthesis, 3,4 – dihydrothiophene-S,S-dioxide, dendrimer thermolysis, TGA.

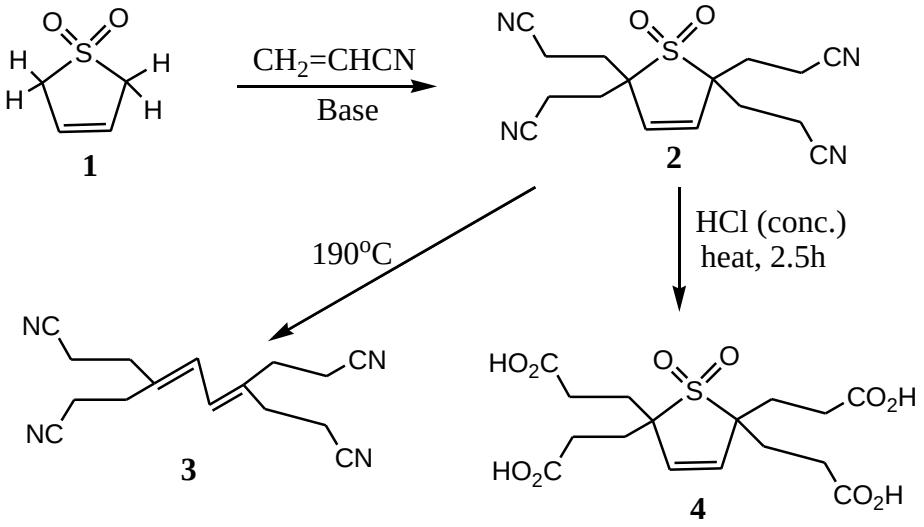
Introduction

The core, 3,4-dihydrothiophene *S,S*-dioxide (1), can be readily synthesized from butadiene and sulfur dioxide but, more importantly, it is commercially available. The facile base-catalyzed addition of four equivalents of acrylonitrile to the 2 and 5 positions of 1, *via* literature procedures,[1,2] gave the desired tetranitrile 2, albeit in low (18-24%) overall conversion (Scheme 1). An interesting property of 2 is, however, found in its thermolysis, in that it undergoes[1] facile cheleotropic expulsion of sulfur dioxide to generate the tetrasubstituted butadiene 3; whereas, hydrolysis of 2 using concentrated hydrochloric acid afforded the corresponding tetraacid 4 in excellent yields by modification of an earlier procedure.[2] Since this tetraacid can now be prepared on large scale in reasonable overall yields, it was interesting to evaluate the expulsion

of SO_2 from within a macromolecular framework, which would afford a two-directional dendritic construction possessing an unsaturated internal functionality at a precise central locus.

Results and Discussion

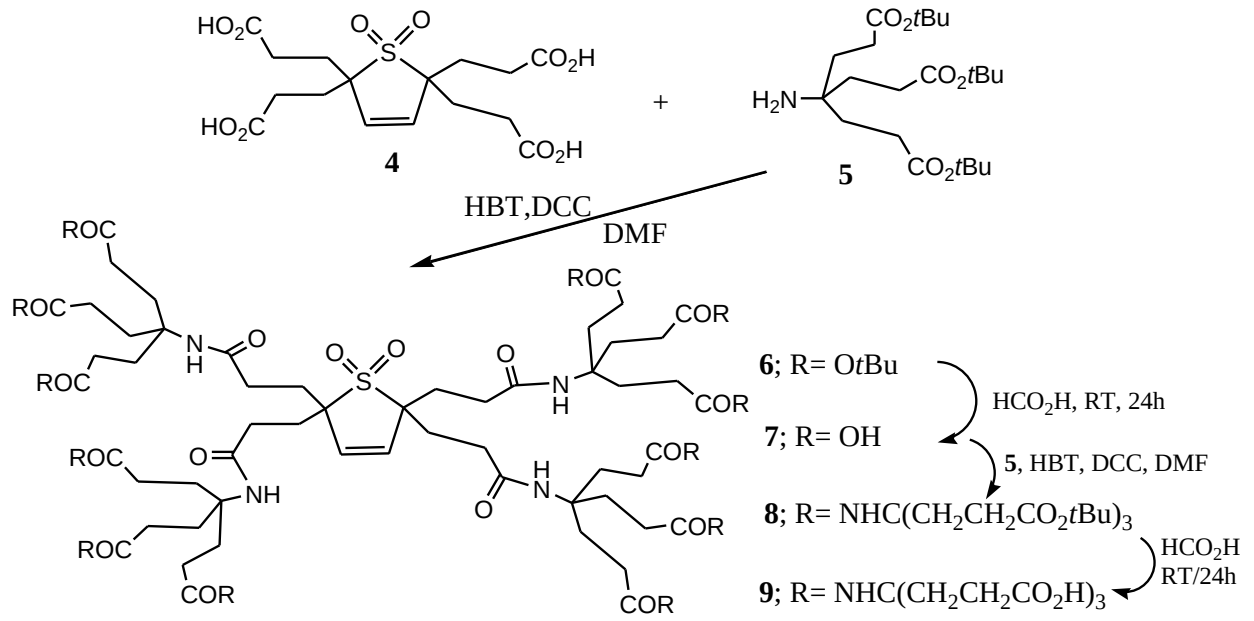
The quantitative hydrolysis of 2 afforded the desired tetraacid 4, whose structure was established by the 4:1 ratio (^{1}H NMR) for the triplet at δ 2.95 (α-C*H*$_2$) to that of the singlet at δ 6.59 assigned to the olefinic protons and the presence of a new peak (^{13}C NMR) at δ 173.6 for the *C*O_2H moiety.



Scheme 1

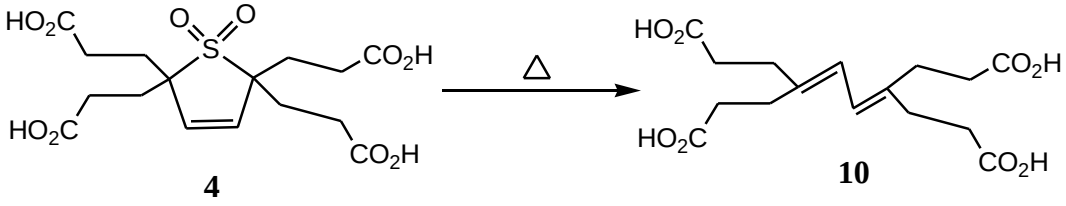
Using the tetraacid 4, as the starting material, its amidation[3,4] with four equivalents of the 1 ⟶ 3 monomer (Beheras amine 5)[5] in the presence of dicyclohexylcarbodiimide (DCC) and *N*-hydroxybenzotriazole (HBT) provided (60%) the desired dodecaester 6. The structure of 6 was established by (^{13}C NMR) in which there appeared two peaks at δ 171.1 and δ 171.4 for the amide and ester carbonyl groups, respectively, as well as the vinyl ring protons (^{1}H NMR) at δ 6.17. Treatment of the dodecaester 6 with formic acid at ambient temperature afforded (92%) the colorless dodecaacid 7, which was characterized (^{1}H NMR) by the disappearance of the peak at δ 1.43 for the *tert*-butyl groups and the proper ratio of vinyl proton (δ 5.98) to NH (δ 7.3) or CO_2H (δ 12.7) of 1:2 or 1:6, respectively.

Construction of the next tier was achieved in the same manner as described above. Formation of the 36-*tert*-butyl ester 8 from dodecaacid 7 was verified by ^{1}H NMR in which a *tert*-butyl signal appeared at δ 1.42 with an expected ratio to =C*H* of 162:1. Conversion of 8 to the corresponding 36-acid 9 afforded a white solid in moderate yield (56%). The identity of the 36-acid 9 was confirmed by the disappearance of the *tert*-butyl signal (δ 1.42) and the appearance of a signal for the acidic CO_2*H* protons at δ 12.05.



Scheme 2

The thermogravimetric analysis (TGA; Figure 1) for tetranitrile 2 showed the expected loss of SO_2 at ca. 222 °C; the experimental mass loss of 18.6% was consistent with the calculated value of 18.9%. The TGA for tetraacid 4 showed a similar expulsion of SO_2 at ca. 219 °C suggesting the formation of the corresponding tetrasubstituted butadiene acid (Scheme 3); the measured weight loss of 16.3% from 4 was in total accord with the calculated value of 15.7% for the desired expulsion of SO_2 thus leaving the diene 10. Figure 1 depicts the TGA data for 2 and 4. There was also notable loss of water of hydration at ca. 100 °C, in that it is difficult to prepare an anhydrous sample. But more interestingly, there was, under these conditions, no evidence for anhydride formation in the case of 4, this must occur at temperatures greater than that for SO_2 expulsion.



Scheme 3

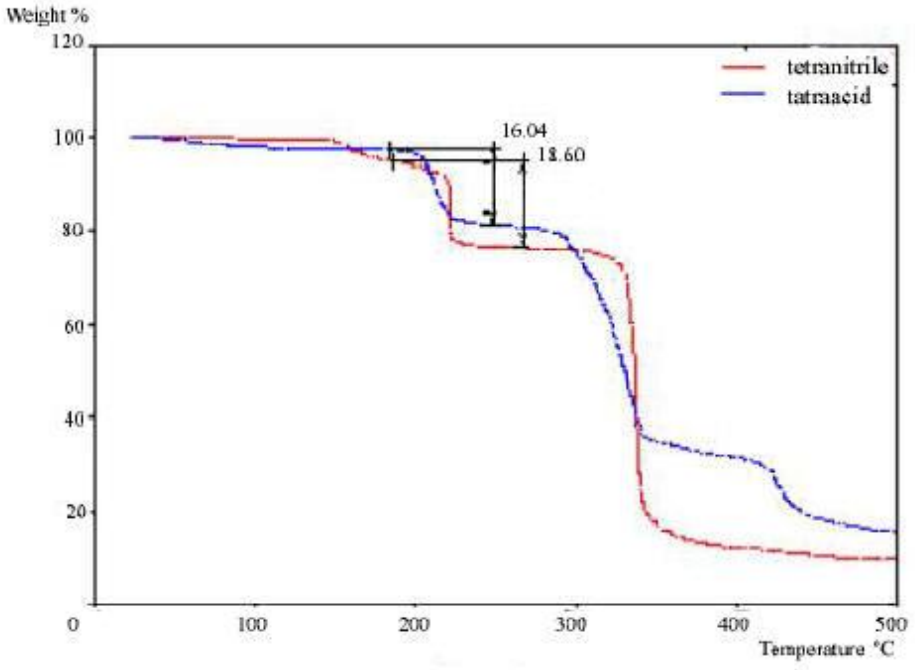


Figure 1. TGA data for tetranitrile 2 and tetraacid 4.

It is well known that thermolysis of simple *tert*-butyl esters results in the corresponding carboxylic acids with the loss of isobutylene at ca. 220 °C.[6] The TGA of the exemplary, simple dendritic dodeca-*tert*-butyl ester (Figure 2) showed a weight loss of 37.9% at ca 220 °C. This corresponds to the expected loss of 12 isobutylene molecules *along with four water molecules*, suggesting the formation of a lactam via an intramolecular cyclization during the thermolysis process. It is noteworthy that the free Beheras amine (5) readily cyclizes at 60 °C to generate the corresponding lactam;[7] thus at 200 °C, the cyclization to the five membered imide appears reasonable.

Thermolysis of dodecaester 6 at 180 °C under vacuum (ca. 1 mbar) for four hours afforded an off-white material that solidified on standing. The resulting product was identified as the corresponding substituted octaacid butadiene 11. Firstly, the disappearance (^{1}H NMR) of the characteristic spike at δ1.42 for C*C*H_3 with simultaneous appearance of the ^{13}C NMR signal for *C*O_2H at δ 174 confirmed the loss of isobutylene. This observation is similar to that made during formic acid hydrolysis. Secondly, the olefinic H*C*=*C*H signal at δ 131.65 disappeared while two new olefinic signals at δ 121.5 and δ 139.0 emerged. This supports the loss of SO_2 and the formation of the diene system. Thirdly, the existence of three C=O peaks at δ 172, 174 and 176 supports the presence of free CO_2H moieties and the intramolecular cyclization process-giving rise to the unwanted lactam product. Although this may be a simple way to remove the amide proton from within the macromolecular construct, we were unsuccessful in retarding this

unfavorable dehydration process. Simpler models are currently being utilized to see if controlled thermolysis can afford the desired conversions.

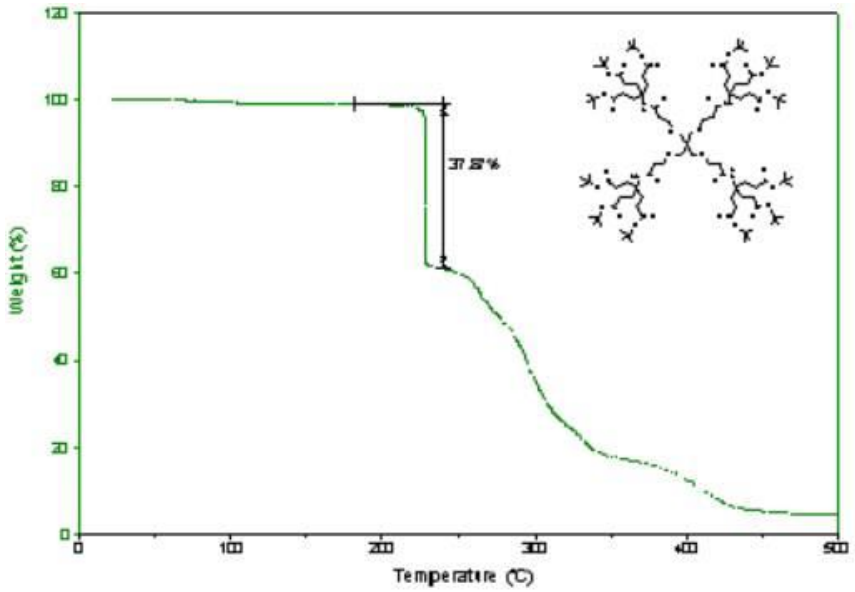
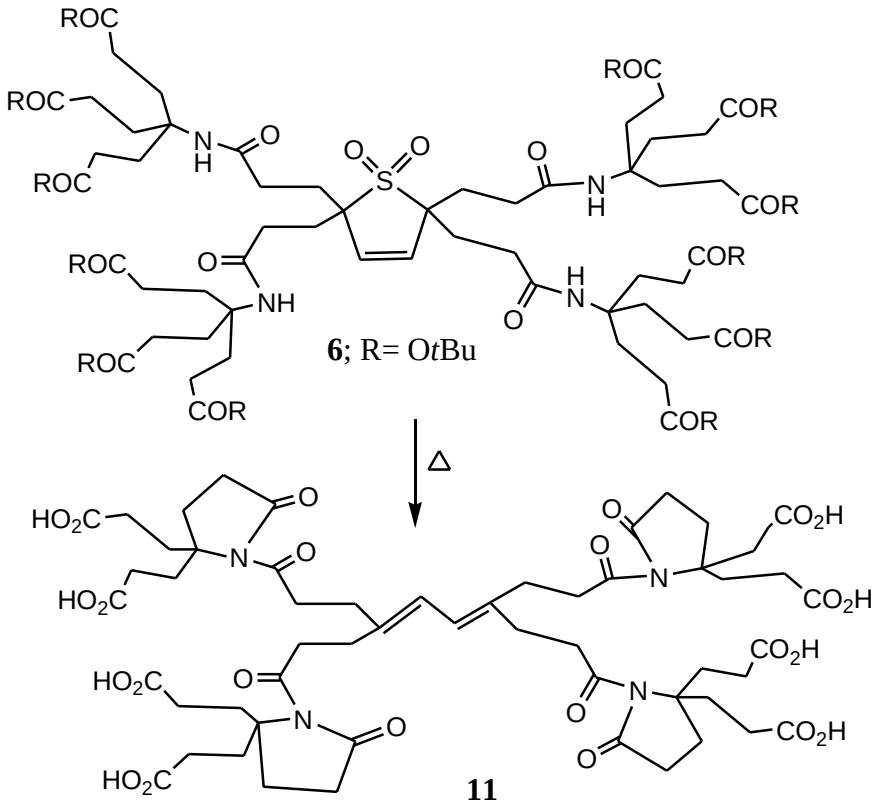


Figure 2. TGA of $C(CH_2OCH_2CH_2CONHC(CH_2CH_2CO_2CMe_3)_3)_4$.



Scheme 4

Experimental Section

General Procedures. All melting points were taken in open capillary tubes and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded at 80.06 and 20.08 MHz, respectively, in $DCCl_3$ solutions, except where noted. Deuterated solvent residues were used as internal solvents [$CDCl_3$: 7.27 (^{1}H) and (77.0 ^{13}C) ppm; DMSO-d_6: 2.49 (^{1}H) and 39.5 (^{13}C) ppm], and the chemical shift values (δ) are recorded in ppm downfield from Me_4Si. Infrared spectra (IR) were recorded on an IBM IR/38 Fourier transform infrared spectrophotometer. M-H-W Laboratories (Phoenix, AZ) conducted the elemental analyses. TGA data were obtained on Hi-Res TGA 2950 Thermogravimetric Analyzer. Unless otherwise noted, all reagents and solvents utilized were of reagent grade and used without further purification.

2,2,5,5-Tetra*kis*(2-cyanoethyl)-2,5-dihydrothiophene *S*,*S*-dioxide(2) was prepared according to a known procedure.[1] Crystallization (MeCN) gave the white crystalline tetranitrile: mp 215 ºC (dec.) (Lit.[1] mp 214-217 ºC); ^{1}H NMR (DMSO-d_6) δ2.50 (t, *J* = 8 Hz, C*H*$_2$, 8H), 2.95 (t, *J* = 8 Hz, C*H*$_2$, 8H), 6.59 (s, C*H*=C*H*, 2H); ^{13}C NMR (DMSO-d_6) δ 12.3 (*C*H_2CN), 28.6 (*C*H_2CH_2CN), 68.0 (*C*SO_2), 119.9(*C*≡N), 130.8 (*C*H=).

2,2,5,5-Tetra*kis*(2-carboxyethyl)-2,5-dihydrothiophene *S*,*S*-dioxide (4). A suspension of 2,2,5,5-tetra*kis*(2-cyanoethyl)-2,5-dihydrothiophene *S*,*S*-dioxide (9.9 g, 30 mmol) in conc. hydrochloric acid (100 mL) was refluxed for 2.5 h. The acid was removed *in vacuo* to afford a residue, which was dissolved in water (300 mL) and reconcentrated *invacuo* to ensure the removal of residual HCl. The residue was extracted with boiling acetone (2 x 200 mL), celite (1g) was added, and the insoluble salts were removed by filtration. The filtrate was evaporated to dryness to give (100%) a white, non-crystalline product. (It required 3 days, until the initial gum-like product became thoroughly solid.): 12.2 g; mp 85-90 ºC (lit.[2] mp 76-79 ºC); ^{1}H NMR (DMSO-d_6) δ 2.35 (t, *J* = 8Hz, C*H*$_2$, 8H), 2.75 (t, *J* = 8Hz, C*H*$_2$, 8H), 6.54 (s, C*H*=C*H*, 2H); ^{13}C NMR (DMSO-d_6) δ 28.4 (*C*H_2CO_2H), 28.9 (*C*H_2CH_2CO_2H), 68.5 (*C*SO_2), 131.5 (*C*H=), 173.6 (*C*O_2H). *Anal*. Calcd. for $C_{16}H_{22}O_{10}S$: C, 47.29; H, 5.46; S, 7.89. Found: C, 47.04; H, 5.67; S, 7.77.

12-Cascade:3,4-dihydrothiophene *S*,*S*-dioxide[2.2.5.5]:(3-oxo-6-oxa-2- azaheptylidyne):*tert*-butyl propanoate (6). Method A. To a solution of 4 (4.06 g, 10 mmol) in DMF (150 mL) was added *N*-hydroxybenzotriazole (HBT; 5.64 g, 42 mmol), followed by dicyclohexylcarbodiimide (DCC; 8.60 g, 42 mmol). After stirring for l h, a solution of di-*tert*-butyl 4-amino-4-[2-(*tert*-butoxycarbonyl)ethyl]heptanedioate (5)[5] (17.34 g, 41.7 mmol) in DMF (60 mL) was added and the solution stirred at 25 ºC for 23 h. The crystals were filtered and washed on the filter with DMF (25 mL). The solvent was distilled at 50 ºC/1mm, and the residual oil was dissolved in ether (600 mL). Crystals were filtered, the ethereal solution was washed successively with 10% HCl (2 x100 mL), saturated $NaHCO_3$ (2 x 100 mL), and brine (2 x 50 mL), then dried (Na_2SO_4). The ether solution was filtered through celite and solvent was then removed *in vacuo* to afford 19.0 g of crude product, which was purified on a silica column eluting with toluene/EtOAc (1:1)

to furnish (60%) the white, non-crystalline 12-ester: 14.0 g; mp 55-60 ºC; ^{1}H NMR δ 1.43 (s, C*H*$_3$, 108H), 1.94-2.28 (m, C*H*$_2$C*H*$_2$, 64H), 5.87 (s, N*H*, 4H), 6.17 (s, C*H*=C*H*, 2H); ^{13}C NMR (DMSO-d$_6$) δ 28.3 (*C*H$_3$), 29.3 (*C*H$_2$*C*H$_2$), 56.8 (*C*NH), 69.0 (*C*SO$_2$), 171.1 (*C*O), 171.4 (*C*O). *Anal.* Calcd for $C_{104}H_{178}N_4O_{30}S$: C, 62.56; H, 8.98; N, 28.06; S, 1.61. Found: C, 62.71; H, 8.85; N, 29.0; S, 1.58.

12-Cascade:3,4-dihydrothiophene*S*,*S*-dioxide[2.2.5.5]:(3-oxo-6-oxa-2-azaheptylidyne) : propanoic acid (7). Method B. A solution of the dodecaester 6 (28.0 g, 14 mmol) in formic acid (400 mL) was allowed to stand at 25 ºC for 24 h. The excess formic acid was removed *in vacuo*, toluene (300 mL) was added to the residue and removed by distillation; this procedure was repeated twice. The glass-like residue was dissolved in water (2 L), decolorized with activated carbon (2 g) with added celite (2 g). After heating to 90-95 ºC for 5 min, the cold solution was filtered through a thin layer of celite and washed with CH_2Cl_2 (100 mL), and then EtOAc (100 mL). Water was removed *in vacuo* to afford (92%) the white, non-crystalline acid: 17.0 g; mp 78-84 ºC; ^{1}H NMR (DMSO-d$_6$) δ 1.8-2.2 (m, C*H*$_2$C*H*$_2$, 64H), 5.98 (s, C*H*=C*H*, 2H); 7.30 (s, N*H*, 4H), 12.07 (br, CO$_2$*H*, 12H); ^{13}C NMR (DMSO-d$_6$) δ 28.19 (CH_2CO_2H), 29.18 ($CH_2CH_2CO_2H$), 30.68 (CH_2CO), 30.69 (CH_2CH_2CONH), 56.67 (HN*C*=), 68.79 (=*C*SO$_2$), 131.65 (*C*H=*C*H), 171.01 (*C*O), 174.58 (*C*O). *Anal.* Calcd for $C_{56}H_{82}N_4O_{30}S$: C, 50.82; H, 6.25; N, 4.23; S, 2.43. Found: C, 50.58; H, 6.19; N, 4.16; S, 2.29.

36-Cascade:3,4-dihydrothiophene dioxide[2.2.5.5]:(3-oxo-6-oxa-2-azaheptylidyne)^2: *tert*-butyl propanoate (8). A solution of the dodecaacid 7 (5.29 g, 40 mmol), BHT (6.70 g, 50 mmol), and DCC (10.22 g, 50 mmol) in DMF (160 mL) was stirred for 1 h. Then, Beheras Amine 5 (20.77 g, 50 mmol) in DMF (100 mL) was added and stirred for 48 h. The work up followed Method A, in which the ether was removed to give a viscous oil, which was stirred in low boiling petroleum ether (100 mL). The insoluble material was removed by filtration and the filtrate was passed through a short basic alumina column. Concentration of the eluent afforded (61 %) the ester, as a white, non-crystalline solid: 15 g; mp 84-86 ºC; ^{1}H NMR δ1.42 (s, CH$_3$, 324H), 1.95-2.20 (m, CH_2CH_2CO, 192H); ^{13}C NMR δ 27.90 [$CCH_3)_3$], 29.97, 31.32, (CH_2CH_2), 57.12 (NC), 80.08 [OC($CH_3)_3$], 172.48 (CO_2). *Anal*. Calcd. For $C_{320}H_{550}NO_{90}S$: C, 63.06; H, 9.10; N, 0.53. Found: C, 62.82; H, 9.74; N, 3.68.

36-Cascade:3,4-dihydrothiophene *S*,*S*-dioxide[2.2.5.5]:(3-oxo-6-oxa-2-azaheptylidyne)^2 : propanoic acid (9). A stirred solution of ester 8 (5.3 g, 8.7 mmol) in formic acid (50 mL) was maintained at 25ºC for 20 h. The work up procedure was detailed for method B affording the title compound as a white solid: 2.0 g (56 %); mp 110-130ºC (dec. temperature 180-200ºC); ^{1}H NMR (DMSO-d$_6$) δ 1.82 (m, CH_2CH_2, 208H), 5.95 (br, CH=, 2H), 7.18 (br, NH, 12H), 7.28 (br, NH, 4H), 12.05 (br, CO_2H); ^{13}C NMR (DMSO-d$_6$) δ 27-31 (CH_2s), 56.2-57.0 (HNC), 131.9 (CH=), 170-172.5 (CONH), 174.7 (CO_2H). *Anal*. Calcd. For $C_{176}H_{262}N_{16}O_{90}S$: C, 51.88; H, 6.48; N, 5.50. Found: C, 51.83; H, 6.67; N, 5.38.

Octaacid 11. A sample of the white non-crystalline solid 6 (107.8 mg, 54.1 μmol) was heated at 175-182ºC *in vacuo* (1.4 mbar) for 4 h to yield an off-white oil that solidified on standing (65.1 mg). The crude was dissolved in water, washed with CH_2Cl_2, and EtOAc then the water

was evaporated to afford the tetralactam 11, as a white non-crystalline solid: ^{13}C NMR (DMSO-d_6) δ 26.3-34.9 (CH_2), 60.2 (ON*C*), 121.5 and 139.0 (*C*H=), 172.1 (*C*ON), 174.4-174.8 (*C*O), 176.5-176.9 (*C*O); ESI-MS (*m/z*): Calcd. for $C_{56}H_{74}N_4O_{24}$ 1186.0, found 1185.0; IR (KBr) 3328 (HC=), 1730 (COOH), 1640 (CON), 1311 (C-O) cm^{-1}.

Acknowledgments

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